Romanian Reports in Physics, Vol. 68, Supplement, P. S847–S883, 2016

RADIOISOTOPE PRODUCTION FOR MEDICAL APPLICATIONS AT ELI-NP

M. BOBEICA[1], D. NICULAE[2,*], D. BALABANSKI[1], D. FILIPESCU[1,2], I. GHEORGHE[1,4], D.G. GHITA[1,2], W. LUO[1,3]

[1]ELI-NP, "Horia Hulubei" National Institute for Physics and Nuclear Engineering, 30 Reactorului Street, RO-077125, Bucharest-Magurele, Romania

[2]"Horia Hulubei" National Institute for Physics and Nuclear Engineering (IFIN-HH), 30 Reactorului Street, RO-077125, Bucharest-Magurele, Romania

[3]School of Nuclear Science and Technology, University of South China, 421001 Hengyang, China

[4]Faculty of Physics, University of Bucharest, 077125, Bucharest, Romania

[*]Corresponding author *E-mail*: dana.niculae@nipne.ro

Abstract. The radioisotope production has a crucial role in medical diagnostic imaging or therapy. Historically, the radionuclides were produced using accelerated beams or nuclear reactors. The radioisotopes are used to precisely localize the pathological process or treat the illness by selectively targeting the site using a bioactive molecule as carrier. The applications of radioisotopes in molecular nuclear medicine require high specific activity, which can be usually obtained using nuclear reactions induced by high intensity accelerated beams of light charged particles or neutrons coming from nuclear reactors. The radioactive element is transmuted from the target isotope and can be separated by chemical procedures. The present Technical Design Report proposes the study of medical radioisotope production using a new route, by γ-induced reaction mechanism where the reaction cross-sections are as low as 0.1 barn. We propose an experimental setup for testing this alternative method using the intense gamma-ray beam at ELI-NP facility, with an irradiation area, a target transport system and a test area. An intensity of 10^{11} γ/s for the new gamma beam at ELI-NP will allow in the first stage the possibility to obtain radioisotopes in quantities and specific activities (1–2 mCi/g) suitable for medical research.

Key words: medical radioisotope, photonuclear reaction, gamma beam facility, radioisotope production.

1. INTRODUCTION

In nuclear medicine, a branch of medicine and medical imaging, radioisotopes are used for diagnostic and therapeutic purposes. In nuclear medicine procedures, radionuclides are combined with compounds or biomolecules to form radiopharmaceuticals. These radiopharmaceuticals, once administered to the patient,

can preferentially localize to specific organs or cellular receptors. This property of radiopharmaceuticals allows nuclear medicine the ability to image the extent of a pathological process in the body, based on the cellular function and physiology, rather than relying on physical changes in the tissue anatomy. Treatment of diseases, based on metabolic or specific uptake, may also be accomplished relying on the tissue-destructive power of high linear energy transfer radiation.

Over 10,000 hospitals worldwide, use radioisotopes in medicine, and about 90% of the procedures are for diagnosis. The most common radioisotope used in diagnosis is technetium-99m, with more than 40 million procedures per year (with 16.7 million in USA in 2012 and 550,000 in Australia), accounting for 80% of all nuclear medicine procedures worldwide. In the USA over 20 million nuclear medicine procedures are performed per year among 311 million people, and in Europe about 10 million among 500 million people. The use of radiopharmaceuticals in diagnosis is growing at over 10% per year.

The global radioisotope market was valued at $4.8 billion in 2012, with medical radioisotopes accounting for about 80% of this, and is poised to reach about $8 billion by 2017. North America is the dominant market for diagnostic radioisotopes with close to half of the market share, while Europe accounts for about 20% (Ref. [1]).

Molecular imaging (MI) has been described in the literature as a multidisciplinary field that combines imaging research, molecular biology, chemistry and medical physics. Molecular imaging is an essential tool in oncological research in cell apoptosis, gene and nucleic acid-based approach, angiogenesis, tumor hypoxia and metabolic imaging and its potential to redirect optimal cancer diagnosis and therapeutics were demonstrated. Although various imaging modalities have been used in molecular imaging, to date the majority of clinical applications are in the field of nuclear medicine. Many diagnostics applications are based on positron-emitters for 3D imaging with PET (positron emission tomography) or gamma ray emitters for 2D imaging with gamma cameras or 3D imaging with SPECT (single-photon emission computed tomography). A high sensitivity of detection systems is the main advantage of nuclear medicine methods using tracers at very low concentrations. With extremely low amounts of radiotracers and single dose administration, any biochemical effect on the organism is not expected. This is desirable in a diagnostic procedure, such that normal body functions are preserved while information is collected. However, the intrinsic advantages of nuclear medicine diagnostics requires that the radiotracers have *relatively high specific activity* such that the injected radiotracer is not accompanied by too many stable isotopes of the same (or a chemically similar) element (see Ref. [2]).

The radioisotopes are used also for therapeutic applications. Targeted systemic therapies are very important in diseases that are non-localized, *e.g.* leukemia and

other cancer types in an advanced state, when already multiple metastases have been created. In the vast majority of cases, there is no curative treatment available for quantitatively large groups of patients with disseminated adenocarcinomas (breast, prostate, colorectal, lung and ovarian tumors), malignant gliomas and melanomas, neuroendocrine tumors and squamous cell carcinomas (lung, esophagus and head-neck tumors). For most of these patients, a palliative effect and/or prolonged survival can at best be achieved with chemotherapy. Other, or complementary, treatment modalities (Fig. 1) seem therefore to be necessary to achieve considerable improvements in the treatment of common types of disseminated malignant diseases, *e.g*. immunotherapy, anti-angiogenesis therapy, gene therapy or radionuclide therapy, in Ref. [3] and [4]. Radionuclide therapy is based on the same effect mechanism as external radiation therapy, namely induction of severe DNA-damage and is therefore a form of radiotherapy. However, radionuclide therapy is placed among the new forms of biology-based therapies (Fig. 2) because it is dependent to a large extent on antigen and receptor expression and the biological factors regulating that, see Ref [5]. Combining a bio-conjugate, which can target the cancer cells with a suitable radioisotope, such as a low-energy electron emitter, allows irradiation and selective destruction of cancer cells, minimizing the side effects that otherwise occur in full body irradiation techniques. When peptides are used as bio-conjugates, the technique is called Peptide Receptor Radio Therapy (PRRT), (see Ref. [6]) or radio-immunotherapy (RIT) if antibodies are used instead (Ref. [7]). The *high specific activities* are required for *carrier-free* radioisotopes used in such therapies to avoid receptors blocking with biomolecules carrying stable isotopes, thus minimizing therapeutic effects. The goal of systemic targeted radiotherapy is to be efficacious, yet determining a minimal toxicity on normal tissue. Its key characteristic is that using a biomolecule (antibody, antibody fragment or peptide) as carrier, a higher amount of a radionuclide can be delivered to cancer cells than to normal tissue. Unlike chemotherapy, systemic targeted radiotherapy is cancer cell specific.

Optimization of the therapy for individual patients remains a goal of clinical practice. Development of new radiopharmaceuticals for both scintigraphic tumor imaging and systemic targeted radiotherapy and their availability are crucial factors influencing the expansion of clinical nuclear medicine, as shown in Ref. [8] and [9]. Radionuclide imaging can identify those patients who may benefit from subsequent targeted therapy by providing regional information on the distribution of the target. An ideal situation may be when the imaging and the therapeutic compounds are the same agent. Theranostics refers to the development of molecular diagnostics and targeted therapeutics in an interdependent, collaborative manner with the goals of individualizing treatment, Ref. [10].

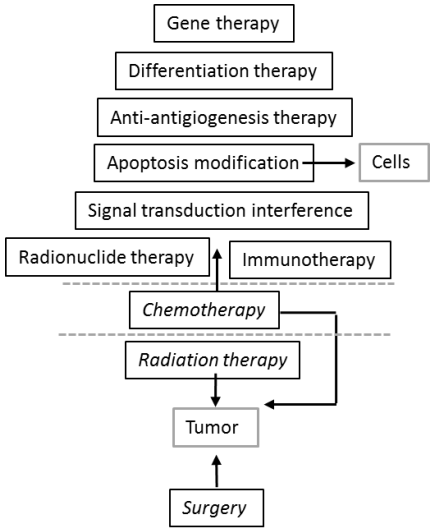

Fig. 1 – Schematic illustration of strategies for tumor therapy. The new approaches are based on biology concepts.

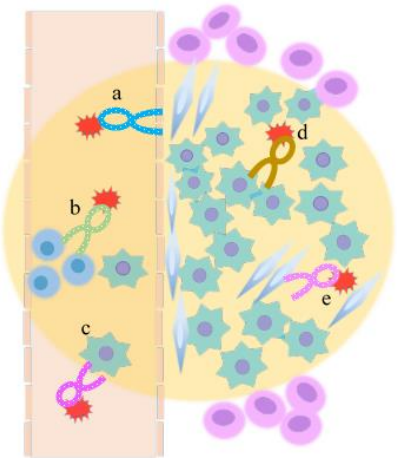

Fig. 2 – Schematic illustration of potential targets for radionuclide therapy in a primary tumor or metastasis area. The radionuclide labelled targeting agents can be used to target cancer-associated blood vessels (a), lymphoma cell associated targets (b), growth factors or receptors on disseminated cells from a solid tumor (c) or on such cells that already have formed metastases (d), or matrix components in the tumor area (e). The red stars indicate radioactive nuclides on the targeting agents (here antibodies).

While it may not be obvious, the choice of radionuclide is a very important decision and depends largely on the clinical utility of radiotracer. The β^- particle emitting radionuclides (*e.g.* ^{67}Cu, ^{90}Y, ^{131}I, ^{177}Lu, ^{186}Re, and ^{188}Re), Auger electron cascades (*e.g.* ^{111}In and ^{125}I) and α-particle emitting radionuclides (*e.g.* ^{211}At, ^{212}Bi, ^{213}Bi, ^{225}Ac, and ^{227}Th), with high linear energy transfer in tissue, are suitable for therapy. Many factors must be considered when choosing a therapeutic isotope and the ideal isotope for one treatment modality may not be appropriate for another. High-energy β^- particles such as ^{90}Y and ^{188}Re are not efficient for killing single disseminated cells or small metastases, since only a small fraction of the electron energy is deposited in such small target Ref. [11] and [12]. Radionuclides emitting low-energy β^- particles such as $^{64/67}$Cu, ^{131}I and ^{177}Lu and α-particle are options, but a large amount of radionuclides per cell is needed, thereby requiring a well-developed targeting process and labeling with high specific radioactivity. The physical half-life of the radionuclides should preferably be in the same order of magnitude as the biological half-life of the radionuclide-conjugate. An overly long physical half-life increases the amount of radionuclides that must be delivered to the tumor cells to achieve the therapeutic levels of decay before excretion. A short half-life may not allow sufficient time for the tumor targeting process to take place, resulting in the majority of the radioactive decays occurring in the vicinity of healthy, and often sensitive, tissues.

Significant advances have recently been made in the characterization of new molecular target structures, cellular processing, pharmacokinetics and modification of radionuclide uptake in targeting agents. There is also improved understanding of the factors of importance of choice of appropriate radionuclides for imaging and therapeutic applications, and the development of theranostics for dual imaging and therapy holds promise for accelerated drug development and translation into clinic. Taken together, this suggests that this field is on the verge of experiencing major advances.

Currently, more than 80% of the medical isotopes are produced by nuclear fission in nuclear research reactors and the rest of them are supplied by particle accelerators, cyclotrons or linacs, or by other methods. Historically, Hevesy first used ^{32}P in 1935 to study phosphorous metabolism in rats. Since that time, the development of cyclotrons, linear accelerators, and nuclear reactors have produced hundreds of radionuclides for potential medical use. The history of medical radionuclide production represents an evolutionary, interdisciplinary development of applied nuclear technology, Ref. [8]. In the last decade however, there has been an acute shortage of fission produced medical radioisotopes with at least six periods of severe disruption since 2007, due to aged and unreliable operation of the reactors, proving that the reactor based method of production is not secure, see Ref. [9]. At

the same time, it is worth noting that all medical radioisotopes were originally manufactured by other mechanisms. In addition, radioisotopes production by other means than by reactor methods can have relevant advantages. For example, the radioisotopes production with cyclotrons offers several significant advantages over nuclear reactors. One of them is that the volume of radioactive waste produced by cyclotrons is much smaller and less hazardous than that resulting from research reactors. Also, the production is decentralized and the cyclotrons can be located near hospitals, which enables easy delivery of pharmaceuticals to patients. In addition, the risk of transport accidents is very low and there is no risk due to nuclear-power accidents, because there is no need for controlled chain reactions.

As an example of the shift in radioisotopes production, after an intense debate in Canada, in May 2008, the Atomic Energy of Canada cancelled the construction of the reactors Multipurpose Applied Physics Lattice Experiment (MAPLE I and II) due to a design fault, and opted for future isotopes production with particle accelerators. More recently, it has been advanced the idea that intense gamma beams can open many new possibilities in nuclear physics and its applications. Such beams can be used to pump a good fraction of the nuclear ground state population via excited levels into an isomeric state. Gamma beams can efficiently excite a nucleon (neutron or proton) into an unbound state leading to photo-dissociation and creation of a new isotope. Using the new beam facilities compact targets could be exposed to the gamma radiation and undergo photonuclear reactions such as (γ, γ'), (γ, n), (γ, p) to form radioisotopes Ref. [13]. After a suitable irradiation time, a radioisotope with high specific activity is produced. After the usual radiochemical steps (such as dissolving the target, thermal separation, chemical purification, pharmaceutical formulation and quality control) a radiopharmaceutical product is created. The produced radioisotope may also be used directly for nuclear medicine applications or it can be used for radiolabeling of biologically active molecules, resulting in radiopharmaceuticals for use in diagnostic or therapeutic nuclear medicine procedures.

Alternative routes for reliable production of emerging radioisotopes will open the way for completely new clinical applications of radioisotopes. For example, ^{195m}Pt could be used to monitor the patient's response to chemotherapy with platinum compounds before a complete treatment is performed. In targeted radionuclide therapy the short-range Auger and conversion electrons resulted from ^{195m}Pt could enable a highly localized treatment. Also, the ^{195m}Pt low-energy γ transition can be used for SPECT imaging. ^{62}Cu, ^{64}Cu, ^{124}I, and ^{68}Ga (also called unconventional isotopes) are recently evaluated for this aim (Ref. [14-18]).

2. PHYSICS CASE

2.1 Demand and supply of currently used radioisotopes

The reactor production of radioisotopes generally leads to neutron excess radionuclides. They mostly decay by β^- emission and are therefore especially suitable for radiotherapy. The cyclotron produced radionuclides are mainly neutron deficient and they decay by electron capture (EC) or β^+ emission. They are particularly useful for diagnostic studies. The positron emitters can be produced only at cyclotrons. For production of some nuclides, both nuclear reactors and cyclotrons are extensively used such that their roles are complementary. Worldwide, there are about 400 research reactors and about 500 cyclotrons. Most of them are at least partially used for production of medically useful radionuclides, Ref. [14].

The most currently used radionuclide in medicine is technetium-99m (^{99m}Tc), the key medical radioisotope. Due to the crisis in 2008 in the supply for molybdenum-99 (^{99}Mo), hundreds of thousands patients were denied diagnostic imaging tests based on ^{99m}Tc. Some of the tests could be performed by alternative techniques such as PET, but at a higher price, others, by using less adapted radioisotopes. Most, however, had to be postponed or cancelled. The demand was high and latest disruptions in supplies as well as the planned closures of nuclear reactors determined the Nuclear Energy Agency (NEA) to become involved in global efforts to ensure a reliable supply of ^{99}Mo and its decay product, ^{99m}Tc.

Until recently, five materials testing reactors (MTRs) produce about 95% of world demand for ^{99}Mo by neutron induced fission of ^{235}U targets highly enriched (HEU): NRU reactor in Chalk River, Canada; HFR in Petten, The Netherlands; BR2 in Mol, Belgium; OSIRIS in Saclay, France and SAFARI in Pelindaba, South Africa. All are older than 40 years. The separation of the ^{99}Mo out of irradiated targets is performed at four centers: AECL separates the ^{99}Mo in Chalk River and MDS-Nordion purifies it in Kanata, Canada; Covidien in Petten, The Netherlands; IRE in Fleurus, Belgium and NECSA-NTP in Pelindaba, South Africa (according to the European Nuclear Society, ENS). The NRU reactor produces about 40% of the required ^{99}Mo. The three European reactors together produce 40–45% and the remaining is produced in South Africa and smaller actors, Ref. [15].

The current status of the above mentioned production facilities in operation is as follows:

- NRU reactor started operating in 1957. The NRU reactor was initially scheduled to close down in 2005. However, it continued to be operated with a number of shutdowns and it is expected to close in 2016.
- OSIRIS (70 MW) will be shut down as of Dec. 31, 2015 date confirmed by the French government.

- BR2 is scheduled to operate at least until 2016 and there is no technical reason to stop its operation before 2020, provided that adequate fuel remains available and that the licensing authorities agree. The BR2 is still one of the most powerful research reactors in the world.
- After having been stopped in 2008 for about six months due to corrosion problems, the High Flux Reactor HFR (located in Petten and operating since 1961) has been authorized by the Dutch regulatory agency to remain operational while a new HFR (*Pallas*) will be constructed according to the Nuclear Research and Consultancy Group (NRG) the company that operates the reactor.

Regarding the secure supply of the most commonly used diagnostic radionuclide ^{99m}Tc, presently produced by fission of highly enriched ^{235}U, it is likely that the industry would modify the industrial production process to be able to cope with the use of low-enriched ^{235}U (thereby reducing the danger of nuclear weapons' proliferation). The dependence on nuclear reactors will however, remain. If at the same time some countries in the OECD-area (Organization for Economic Co-operation and Development area) may decide to utilize a few modern research reactors for production of fission ^{99}Mo, the situation may improve, Ref. [14].

According to NEA, since 2011 the current demand for ^{99}Mo is no longer 12000 6-day curies per week. The temporary reduction in demand occurred as a result of the 2009–2010 supply shortages and adaptive steps including: better use of available ^{99}Mo/^{99m}Tc, more efficient elution of ^{99}Mo generators, substitute diagnostic tests/isotopes, etc. Based on current market practices, market participants have estimated the current demand at between 9,500 and 10,000 6-day curies per week, Ref. [17]. The future demand was estimated by the NEA until 2020, and is expected to increase steadily, while the production capacity is expected to plunge starting in 2016 (see Ref. [18]).

A new perspective of medical radionuclides is emerging through extremely significant developments that are currently taking place in organ imaging. The dynamic and quantitative nature of PET (and recently to some extent also SPECT) is being coupled with X-ray tomography (CT) and magnetic resonance imaging (MRI) to provide a highly powerful combination of systems for organ imaging. The radionuclides of potential interest for the latter combination is ^{64}Cu (a positron emitter) and thus PET and MRI could be advantageously combined. In MRI, the elements Mn and Gd are often used as contrast agents. If a positron-emitting radionuclide is introduced in the system, the high-resolution of MRI and the quantitative nature of PET could lead to very high quality imaging, Ref. [14].

An important application of positron emitters is in quantification of radiation dose, in internal radionuclide therapy. Combining a positron-emitting isotope of an element together with a therapeutic radioisotope of the same element, it is possible to measure the uptake kinetics by PET imaging, thereby allowing an accurate dose calculation related to therapy. A β^- (or Auger electron) and β^+ emitting pair of radionuclides of the same element is now termed as a theranostic pair (for example

^{67}Cu, $T_{1/2}$ = 2.6 d, β^- and ^{64}Cu, $T_{1/2}$ = 12.7 h, β^+). In addition, the isotope ^{67}Cu has shown exceptional potential in the treatment of non-Hodgkin's Lymphoma as well as bladder, colorectal, and ovarian cancers.

Regarding internal radiotherapy, presently a shift is taking place from the use of β^- particle emitters to Auger electron and α-particle emitters which induce more cellular effects.

The isotope ^{195m}Pt (half-life 4 days, decay mode gamma and Auger) could be used towards 2 directions. First direction is to verify the patient's response to chemotherapy [13] by monitoring the drug bio-distribution and metabolism, thus creating an approach to personalized medicine, with evaluation and selection of best treatment before it is completely performed. The second direction is targeted radionuclide therapy using the short-range low energy Auger electrons and radiolabelling platinum complexes, which bind to the DNA. Thus, one can examine the effect of ^{195m}Pt Auger cascades close to the DNA and which are the parameters that enables local treatment. In regards to the alpha-particle emitters, the radionuclide ^{225}Ac (decays through four alpha particles) is very promising. Extensive effort is presently being invested in the development of ^{225}Ac, which could be produced in sufficient quantities for large-scale application in targeted radionuclide cancer therapy, Ref. [13].

2.2 Production of medical radioisotopes *via* (γ, n) reactions

Knowledge of nuclear data plays an essential role in the identification of optimal conditions and of irradiation parameters for the obtaining of medical radioisotopes. Photonuclear reactions with γ-beams allow the production of radioisotopes aimed for medical applications, such as ^{47}Sc, ^{44}Ti, ^{67}Cu, ^{103}Pd, ^{117m}Sn, ^{169}Er, ^{195m}Pt or ^{225}Ac, with expected higher specific activity and/or more economically than by classical methods (Table 1). This route of production will enable further clinical applications of these radioisotopes. For example, ^{195m}Pt can be used for monitoring the chemotherapy with compounds containing platinum. Innovative radioisotopes such as ^{47}Sc, ^{67}Cu or ^{225}Ac, will have a higher availability and could be produced in sufficient quantities for widespread applications in targeted radionuclide therapy (systemic radiation therapy), Ref. [2]. For the new radioisotopes a medical interest must be defined by a more complex characterization, including demand, possible applications, and current production facilities. For radioisotopes that are already in clinical use, it will be needed innovation to improve certain parameters such as: specific activity, production efficiency, radiochemical separation methods, cost, and others. Other radioisotopes are proposed to be added later, after the identification of optimal production methods, purification and testing technologies. The advantage of using γ-beams for production of radioisotopes lies in the high specific activity that can be obtained for isotopes or metastable isomers with major potential in nuclear medicine but which are not available in the quantity or

quality required. The experimental design was based on the scientific case (see Ref. [19] Chapter 5.6.4 and 5.6.5), which selected some of the radioisotopes of interest: ^{195m}Pt, ^{225}Ra (^{225}Ac generator), ^{67}Cu, ^{111}In, ^{103}Pd, ^{99}Mo (for ^{99m}Tc). It aims to accomplish an experimental design for production of medical radioisotopes at Extreme Light Infrastructure-Nuclear Physics (ELI-NP), through photonuclear reactions (γ, n) and radiochemical processing of these isotopes for compliance with the requirements for medical use and demonstrating this usefulness by radiolabeling biomolecules and biological testing of radiopharmaceuticals.

Table 1

Potential radioisotopes produced in (γ, n), (γ, p) or (γ, 2n) reactions. For β and ε decay mode, the emission energy is the mean energy. *Estimated cross sections are marked in italics.

Product isotope	$T_{1/2}$ (day)	Emission energy (MeV)	Target isotope	Reaction type	E_γ (MeV)	σ (barn)	Purpose
^{47}Ca	4.5	0.4 (β), 1.3 (γ)	^{48}Ca	(γ, *n*)	19	0.09	Targeted radiotherapy, SPECT
^{64}Cu	12.7 h	0.28 (ε), 0.191 (β), 0.511 (γ)	^{65}Cu	(γ, *n*)	17	0.09	PET/radiotherapy, as a theranostic, various other applications
^{99}Mo/ ^{99m}Tc	2.8/0.25	0.39 (ε)/0.14 (γ)	^{100}Mo	(γ, *n*)	14	0.16	SPECT
^{103}Pd	17	0.036 (CE), 0.02 (γ)	^{104}Pd	(γ, *n*)	17	*0.05**	Targeted radiotherapy, brachytherapy applications
^{165}Er	10.36 h	0.005 0.038 (Auger),0.05 (γ)	^{166}Er	(γ, *n*)	13	0.3	Tumor therapy
^{169}Er	9.4	0.1 (β)	^{170}Er	(γ, *n*)	12	*0.3**	Targeted radiotherapy
^{186}Re	3.7	0.35 (β),0.14 (γ)	^{187}Re	(γ, *n*)	15	0.6	Bone pain palliation, radiosynovectomy and targeted radiotherapy
^{225}Ra/ ^{225}Ac	14.8/ 10	0.10 (β)/5.8 (α)	^{226}Ra	(γ, *n*)	12	*0.2**	Targeted alpha therapy
^{47}Sc	3.35	0.16(β), 0.16 (γ)	^{48}Ti	(γ, *p*)	19	*0.02**	Targeted radiotherapy, SPECT or camera

^{67}Cu	2.6	0.14 (β),0.18 (γ)	^{68}Zn	(γ, p)	19	*0.03**	Targeted radiotherapy, SPECT or camera
^{44}Ti/ ^{44}Sc	59.1 y 3.97 h	0.07(γ)/ 632 keV (ε), 511, 1157 keV (γ)	^{46}Ti	(γ,*2n*)	27	*0.01**	PET, Compton telescope
^{224}Ra/ ^{212}Pb/ ^{212}Bi	3.7/ 10.64 h/ 60.6 m	5.7 (α)/0.1 (β)/ 6.0 (α), 0.77 (β)	^{226}Ra	(γ,*2n*)	16	*0.1**	Targeted alpha therapy

2.2.1 Simulation of photonuclear (γ, n) reactions at ELI-NP facility

A very brilliant, intense γ-beam of up to 19 MeV, 0.1−0.5 % bandwidth and 10^{11} γ/s will become available at the upcoming ELI-NP facility, allowing the production of radioisotopes for nuclear medicine research. We have investigated the possibility of production of medical radioisotopes via photonuclear reactions with the ELI-NP γ-ray beam by Monte-Carlo (MC) simulation, which is a fundamental tool in nuclear and particle physics, and essential for the advanced applications.

Specific activity for medical radioisotopes: One of the most important quality criteria for radioisotopes production for nuclear medicine research and applications is the specific activity (A/m), usually expressed in mCi/mg or similar units. Here A is the activity and m stands for the mass. The theoretical maximum specific activity for a pure radioisotope without admixture of stable isotopes is given by

$$(\frac{A}{m})_{\max} = \frac{\lambda N_A}{M}, \quad (1)$$

where M is the molar mass (g/mol) of the target isotope, $\lambda = \ln 2 / T_{1/2}$ is decay constant, and N_A = 6.02×10^{23} denotes Avogadro's constant. When an intense γ-ray beam is used to trigger the isotope target into the product of interest, if other reactions (such as destruction of the product by nuclear reactions) do not interfere significantly, the achievable specific activity will be given by

$$(\frac{A}{m}) = \frac{P_0}{m}[1-\exp(-\lambda t_{irr})], \quad (2)$$

where t_{irr} is the irradiation time, and P_0 is production rate of the targeted isotope, triggered by (γ, n) reaction in the irradiation target. We take into account high-energy γ-ray attenuation coefficient and then calculate P_0 to be:

$$P_0 = \int_{E_{th}}^{E_{\max}} \int_0^R \int_0^L \frac{\rho N_A}{M} \sigma(E_\gamma) I(E_\gamma, r) \exp(-\mu x) dE_\gamma dr dx$$
$$= \int_{E_{th}}^{E_{\max}} \int_0^R \frac{\rho N_A}{\mu M} \sigma(E_\gamma) I(E_\gamma, r)[1 - \exp(-\mu L)] dE_\gamma dr \quad (3)$$

where $\sigma(E_\gamma)$ is the cross section of (γ, n) reaction, $I(E_\gamma, r)$ is the γ-ray flux density on the surface of the irradiation target after the polar-angle integration, and its units are photons/s/mm; μ is the linear attenuation coefficient and is converted by mass attenuation coefficient (μ/ρ) by multiplying with the density of the target, R is the target radius, and L is the target thickness with respect to the direction of γ-ray beam propagation. For the latter, we derive the specific activity of the "daughter" radionuclide, ^{99m}Tc from the decay law:

$$(\frac{A}{m}) = \frac{P_0}{m}[1 + \frac{\lambda_1 \exp(-\lambda_2 t_{irr}) - \lambda_2 \exp(-\lambda_1 t_{irr})}{\lambda_2 - \lambda_1}] \quad (4)$$

where λ_1 and λ_2 correspond to the decay constants of the "parent" and "daughter" radioisotopes, respectively. If the generator radioisotope has a smaller decay constant than that of its "daughter" radioisotope, then the final radioactive decay equilibrium will be achieved and hence one could optimize the irradiation time to achieve sufficient specific activities of the radioisotopes.

For some special cases, the "daughter" of the targeted radioisotope rather than itself is of particular interest for medical applications. Generally, the targeted radioisotope is used as a radionuclide generator. The most prominent example is the ^{99}Mo/^{99m}Tc generator; the parent, ^{99}Mo, is usually produced by a neutron-induced fission process, or by photo-neutron reaction and its disintegration, ^{100}Mo(γ, n)^{99}Mo$\rightarrow^{99m}$Tc.

Simulation algorithm: In the previous sections, we have described the principle of the photonuclear reaction to produce medical radioisotope, which provides a basis for the simulation of medical radioisotope production. In the simulation, the following three stages are employed: (1) setting ELI-NP γ-ray beam transport; (2) simulating/preparing reaction cross section and γ-ray attenuation coefficient; and (3) modeling the photonuclear reactions using reject-acceptance methods and then calculating the production rate and specific activity.

(1) ELI-NP γ-ray beam transport

We use the ELI-NP γ-ray beam simulation code (Ref. [20]), integrated with Geant4 toolkit to simulate the MeV-class γ-ray beam generation and transport. A collimator (containing two sets of slots, each set has six slots) with 5 mm aperture is located at approximately 9.5 m downstream of the interaction point (IP) for γ-ray production. The isotope target is located at 9.6 m approximately downstream

of the IP, but at 0.1 m upstream of the collimators. Fig. 3 shows a Geant4-based schematic of the ELI-NP γ-ray beam transport. A circularly polarized laser with a wavelength of 532 nm and a wavelength bandwidth of 0.05%, scattering on a relativistic electron beam (*e*-beam) with an energy spread of 0.04% at a laser incident angle of θ_L =172.5° was used in the Monte Carlo simulation presented below.

Due to the collimator, a large part of the low-energy, Compton-scattered γ-rays are attenuated and only high-energy γ-rays may penetrate the collimator and then arrive at the surface of the irradiation target. For the 5 mm aperture case, the γ-ray survival rate is predicted to be 12–18% depending on the incident *e*-beam energy. Approximately 14.4% of γ-rays scattered by the 650 MeV *e*-beam will reach the surface of the irradiation target. We diagnose the ELI-NP γ-rays by bombarding the isotope target, monitoring their energies, beam fluxes and transverse profiles before they trigger the photonuclear reaction inside the isotope target. Also, this useful information is written into .root files, which will be used in the simulations. Fig. 4 shows the γ-ray beam parameters diagnosed at the surface of the target. For the 650 MeV *e*-beam, the average energy of the transmitted γ-rays is 13.9 MeV and the beam spot size is about 2.5 × 2.5 mm^2. Considering that the total flux of γ-ray produced from the ELI-NP facility is 1.0 × 10^{11} γ/s, the flux of the γ-ray irradiating the isotope target can reach 1.44 × 10^{10} γ/s.

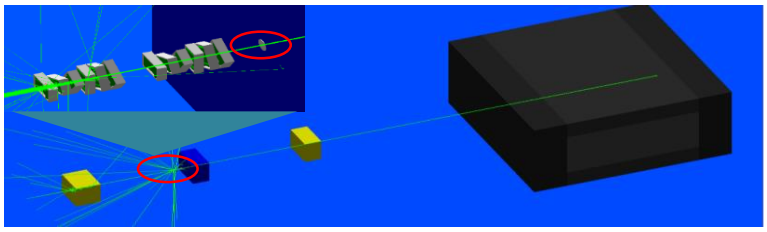

Fig. 3 – The set-up of γ-ray beam transport in Geant4. The inserted figure in the top left corner represents the enlarged collimator and target zone.

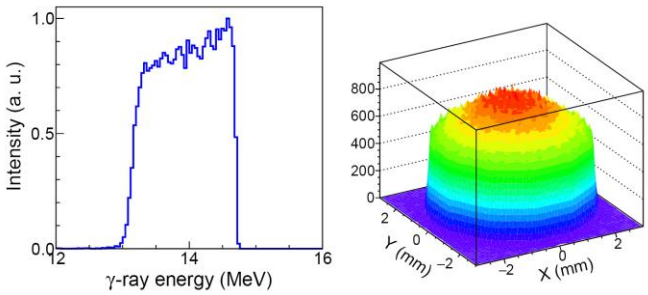

Fig. 4 – A γ-ray beam spectrum (left) and transverse profiles (right) on the surface of the target.

(2) Reaction cross section and γ-ray attenuation coefficient calculation

A reliable and reasonable photonuclear reaction cross section is needed for the calculation of isotope activity. While acquiring the photonuclear reaction from EMPIRE calculation (see Ref [21]), we can also cite the available experimental or theoretical nuclear reaction data from Ref. [22] and [23]. Since the cross section data is crucial to obtain an optimal specific activity by adjusting the irradiation parameters, such as target geometry and incident *e*-beam energy, we will compare the evaluated photonuclear data with the experimental measurements and then implement these data into the simulation as reliable as possible. Fig. 5 shows the results of the simulation of ^{100}Mo(γ, n) reaction and of competing reactions. The experimental cross section is also shown as a comparison.

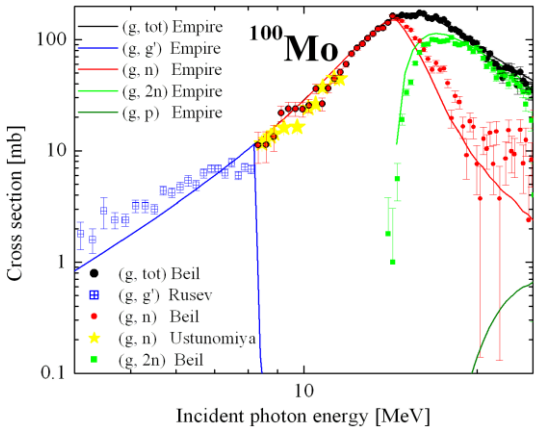

Fig. 5 – Simulation of nuclear reaction ^{100}Mo(γ, n) reaction and of competing reactions. The experimental cross section is also shown for comparison. The maximum (γ, n) reaction cross section is 150 mb corresponding to the incident γ-ray energy, E_γ=14.5 MeV.

The Ref. [24] provides tables of X-ray mass attenuation coefficients and mass energy-absorption coefficients from 1 keV to 20 MeV for elements Z = 1 to 92, from which one can obtain the mass attenuation coefficient for certain isotope target. Since these attenuation coefficients are discrete, we use a linear interpolation method to obtain the attenuation coefficient that corresponds to a given γ-ray energy of interest. As the compounds and mixtures of the isotope targets are employed in the simulation, accordingly we will reprocess the table of attenuation coefficient based on their contents and compositions. As an example, Fig. 6 shows the ^{100}Mo and ^{16}O elements, as a function of photon energy, which will be reprocessed and then used

for the simulation of ^{99}Mo/^{99m}Tc isotope production, since the oxide of ^{100}Mo is employed in this case.

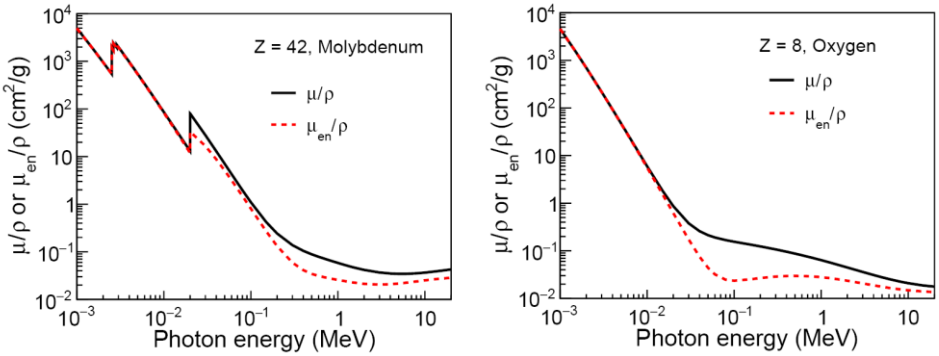

Fig. 6 – The attenuation coefficients of ^{100}Mo and ^{16}O [24]. Since a thick target (molybdenum oxide, *i.e.* MoO_3) would be employed to produce radioisotopes, the attenuation coefficient should be fully considered in the simulation.

(3) Photonuclear reactions simulation

After the photonuclear reaction cross section and the attenuation coefficient are obtained, we use Eq. (3) to model the photonuclear process using high-intensity and small-divergence γ-beams. For a fixed isotope target of radius R and thickness L, we sample a certain γ-ray photon with energy $E_{\gamma,i}$ and position r_i recorded at the surface of the target. Accordingly, the reaction cross section $\sigma(E_{\gamma,i})$ and attenuation coefficient μ_i will be extracted. If the position r_i satisfies $r \le R$, one could calculate the production probability for the i^{th} γ-ray photon interacting with the isotope target

$$p_i = \frac{\rho N_A}{M \mu_i} \sigma(E_{\gamma,i})[1 - \exp(-\mu_i L)]. \tag{5}$$

Thus, one could obtain the production rate as:

$$P_0 = \frac{I}{N} \sum_{i=1}^{N} p_i . \tag{6}$$

Here, N is the sampling number and I is the γ-ray beam flux at the surface of the isotope target, its unit is photons/s. The specific activity of the targeted radioisotope as a function of irradiating time could be obtained by substituting Eq. (6) into Eq. (2) and Eq. (4).

2.2.2 Consideration for production of ^{99}Mo /^{99m}Tc

^{99m}Tc is conveniently obtained in the form of carrier-free (non-carrier added) by eluting the ^{99}Mo generator ($T_{1/2}$ = 66 hours), which can be used for 10 days. Numerous technetium compounds have been developed for various applications in nuclear medicine. Weekly, over 80 kCi (3000 TBq) of ^{99}Mo are generally produced for loading in generators of ^{99}Mo/^{99m}Tc, which are delivered to end users of ^{99m}Tc (especially hospitals and centralized radio-pharmacies). Recently a significant crisis occurred in ^{99}Mo production caused by extensive scheduled closures or emergencies. This has created a growing interest in finding alternative ways for the production of ^{99}Mo/^{99m}Tc (Fig. 7). One of the proposed alternative method is to use the reaction ^{100}Mo(γ, n)^{99}Mo. Production of ^{99}Mo by bremsstrahlung radiation, (Ref [25]) is achieved with limited specific activity that becomes even more difficult to use with currently used generators technology (based on acidic alumina columns). This method of producing radioisotopes with γ beams cannot compete with large-scale production facilities. In spite of the large interest worldwide for production of ^{99}Mo/^{99m}Tc, according to the estimations presented in this paper, ELI-NP will contribute only to research developments. While other facilities do have enough capabilities to decrease the gap between demand and supply chain, at ELI-NP ^{99}Mo/^{99m}Tc will be considered for testing the new production methods, as a standard for research in radioisotope production, since its separation processes and the associated technology is well defined.

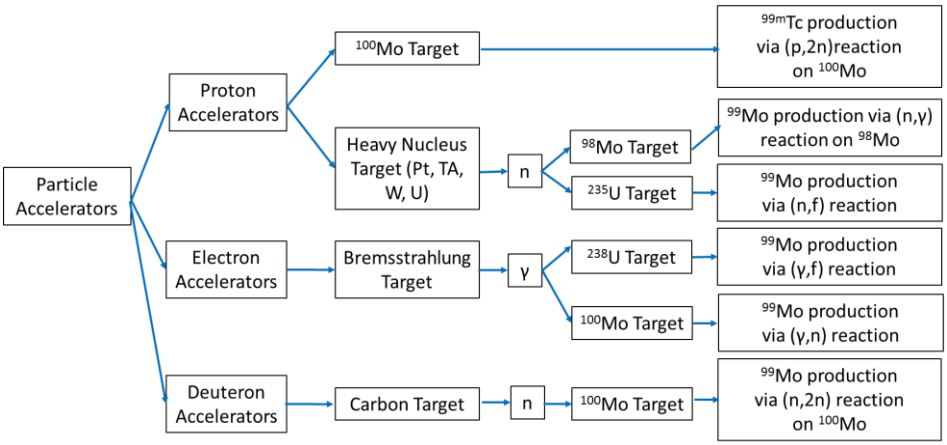

Fig. 7 – Alternative methods of producing Mo-99 using accelerators.

^{99}Mo/^{99m}Tc specific activity: In the simulation, we consider the oxide $^{100}MoO_3$ target as the irradiation target with a density of 4.7 g/cm^3. ^{100}Mo isotope has an extremely long half-life $T_{1/2}^{^{100}Mo}$ =7.3 × 10^{18} years and therefore is considered stable. The isotope ^{99}Mo is a natural beta emitter, decaying spontaneously into ^{99m}Tc, which successively emits 141 keV photons by Internal Conversion into the ground state (see Fig. 8).

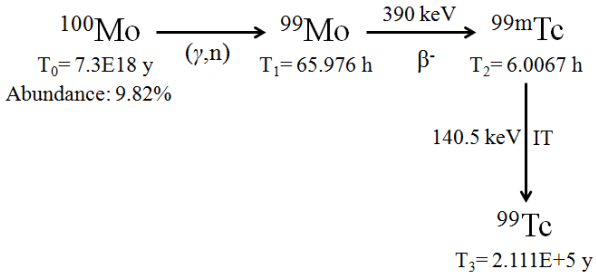

Fig. 8 – Production of ^{99m}Tc via ^{100}Mo(γ, n) reaction and disintegration chain of ^{99}Mo.

Fig. 9 shows the specific activity of ^{99}Mo/^{99m}Tc radioisotopes as a function of irradiating time for different target parameters. The *e*-beam energy is fixed at 650 MeV. The saturation specific activity of the ^{99}Mo/^{99m}Tc generator can reach 1.1 mCi/g, after more than100 h irradiation time.

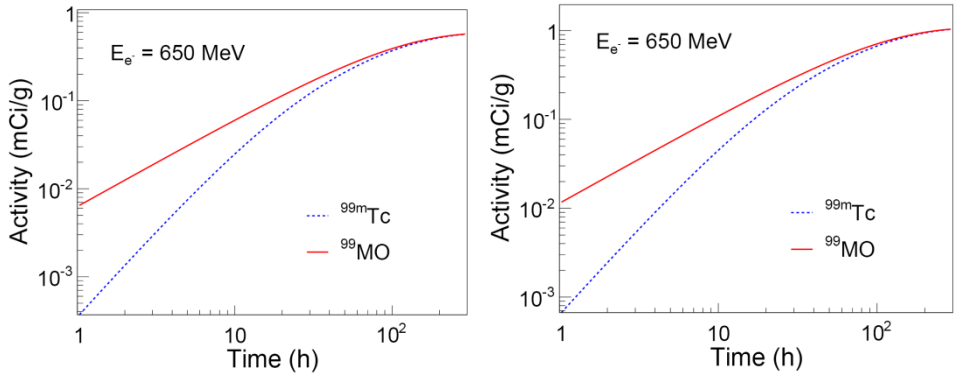

Fig. 9 – The specific activity as a function of the irradiation time. The input target parameters are 2.5 mm radius, and 10 cm thickness (left) and 1.0 cm thickness (right).

Fig. 10 shows the saturation specific activity of ^{99}Mo/^{99m}Tc radioisotopes as a function of the target thickness and radius. It shows also that the specific activity of the radioisotopes is sensitive to the energy of *e*-beam used to produce γ-rays. From Fig. 10 we can conclude that due to the γ-ray attenuation inside the target, a thin target has potential to produce medical radioisotope with high specific activity. For a specific set of parameters for the irradiation target and the *e*-beam, *e.g.* a less than 2.0 mm target radius, 1.0 cm target thickness and 650 MeV electron energy, the saturation specific activity of ^{99}Mo/^{99m}Tc could exceed 1.0 mCi/g.

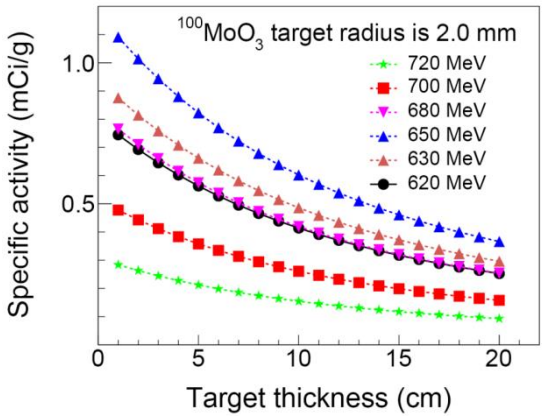

Fig. 10 – Saturation specific activity as function of the target thickness.

Fig. 11 shows that the specific activity of the radioisotopes has a strong dependence on the target radius. In all cases, in principle the specific activity has an inflection point happening at a target radius of 2.5 mm, which matches the γ-ray beam spot size at the surface of the irradiated target. At the right side of the inflection point, the bigger the target radius, the smaller the specific activity is achieved. At the left side of the inflection point, a 680 MeV and higher *e*-beam and a less than 650 MeV *e*-beam cases show very different trends. For the former, the specific activity begins to decrease as the target radius decreases, due to the transmitted γ-rays, with their energies mismatching the peaked photoneutron cross section. For the latter, the specific activity continues increasing as the target radius decreases, but its increase becomes slower compared to that at the right side. For some special cases, the increasing may stop, which will be displayed in the simulation of other radioisotopes production.

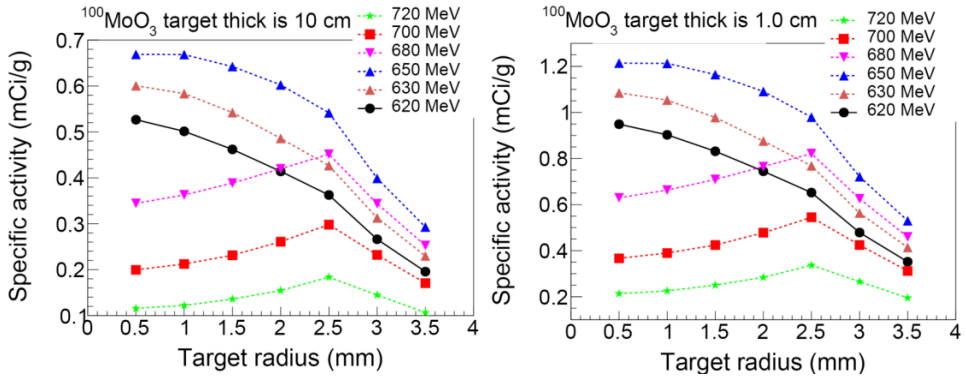

Fig. 11 – Saturation specific activity as function of the target radius while its thickness is 10 cm (left) and 1.0 cm (right), respectively.

It is of great interest to analyze the specific activity of targeted isotopes as a function of the location of the isotope target. Originally, the default location for the MoO_3 target was 9.6 m downstream of the IP. Now we locate the target at 16.4 m downstream of the IP (*i.e.* E7 experimental station) and fix the other geometry parameters. Fig. 12 shows that the specific activity decreases with the increased distance between the IP and the isotope target. For the case of $^{99}Mo/^{99m}Tc$ radioisotopes generation, the specific activity is predicted to be slightly higher than 0.2 mCi/g, only one third of that in the 9.6 m distance case. This results from the decrease of the beam flux density at the surface of the isotope target while increasing the distance between the IP and isotope target and naturally increasing the beam size.

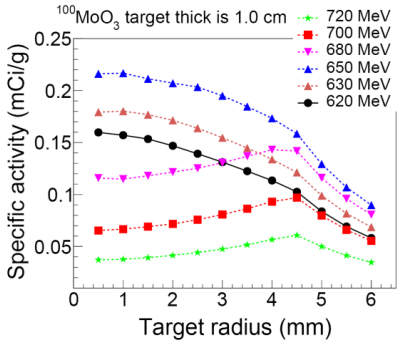

Fig. 12 – Specific activity as a function of target radius for a 16.4 m distance between the IP and the isotope target.

2.2.3 Consideration for production of ^{67}Cu

The radionuclide ^{67}Cu is a beta and gamma emitter (185 keV) with a convenient half-life of 62 h (Fig. 13), all of which are characteristics that makes it very attractive for cancer therapy. In particular, the short path length of β^- particles and the ability to form stable chemical complexes (with antibodies and peptides or other small molecules) make this radionuclide a potential candidate for systemic radiotherapy.

Currently, ^{67}Cu is produced in a cyclotron by the reaction ^{68}Zn(p, 2p)^{67}Cu, at high energy of incident protons, over 30 MeV, or by ^{70}Zn(p, α)^{67}Cu reaction (in Table 2 the cross sections of reactions are presented for the nuclear reactions discussed). Alternatively, we propose to employ the ^{68}Zn(γ, p)^{67}Cu reaction and a competing reaction in the case of natural targets of Zn: ^{66}Zn(γ, d)^{64}Cu.

Proposed targets are cylindrical, 2 × 2 cm, approximately 40–45 g of natural Zn/enriched ^{68}Zn (which could lead to an increase of 40–20 times in the activity). Specific activities relatively small may be obtained (approximately 10 mCi/g) with the main radionuclide impurities isotopes of Zn and ^{64}Cu (whose activity is reduced by 40 % in 2 days of decay), according to Ref. [26]. According to the same source it can be produced around 60–100 mCi/day (Table 3).

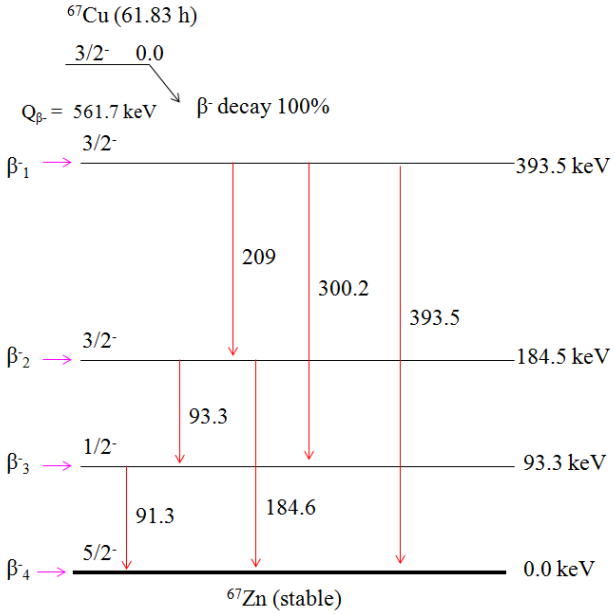

Fig. 13 – Decay scheme of ^{67}Cu.

Table 2

Cross sections of nuclear reactions producing ^{67}Cu

Nuclear reaction	Cross section (mb)
^{68}Zn(p, 2p)^{67}Cu	6 (E_p=30–85 MeV) 24.8 (E_p =130–425 MeV)
^{70}Zn(p, α)^{67}Cu	15 (E_p = 16 MeV)
^{68}Zn(γ, p)^{67}Cu	11 (E_γ=22MeV)

Table 3

The activity of ^{67}Cu obtained by various methods reported in Ref. [27] and reference therein

Target mass (g) / Enrich (%)	Time / current	Energy (MeV)	Reported yield	Adjusted yield (μCi/μAhg)
Zn / 25	2–10 h / 8 –10 μA	25	250 μCi/25 g Zn	0.1
Zn / 100	48 h / 50 μA	35	8.8 mCi/100 g Zn	0.04
ZnO / 90	Several hours / ≤100 μA	130	3×10^5 Bq/μAh/90 g ZnO	0.09
ZnO / 0.025	30 min / 175μA	30–60	0.41–1.29 μCi/μAh/100 mg ^{68}ZnO	4.1–2.9

The radioisotope ^{64}Cu ($T_{1/2}$ = 12.7 h) should not be considered as a radionuclide impurity but as a counterpart (theranostic) of ^{67}Cu, very useful for therapy monitoring. This radionuclide decays via three modes, namely β^- emission (38.4%), β^+ emission (17.8%) and *EC* (43.8%). The β^+ branching and the intensity of the weak 1346 keV γ-ray have been recently determined with higher precision, and the known decay characteristics allow a combination of radio-immuno-therapy and PET, (see Ref. [16]). A simulation was performed (Empire) of the nuclear reaction ^{68}Zn (γ, n) and of the competing reactions (Fig. 14) and the results will be the basis for calculations of the target geometry, the expected activity and the optimum irradiation parameters.

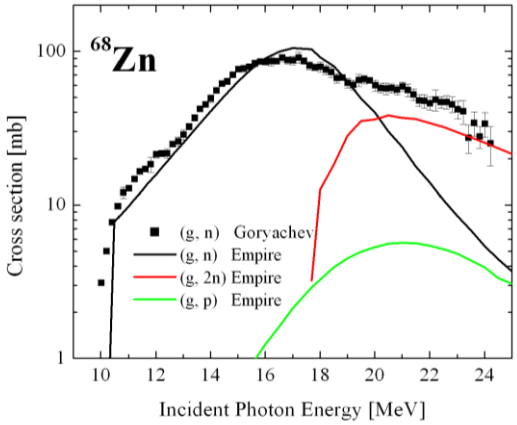

Fig. 14 – Simulation of nuclear reaction ^{68}Zn(γ, n) and of competing reactions.

2.2.4 Production considerations and applications ^{226}Ra/^{225}Ac

Alpha emitters are very promising for therapeutic applications because the emitted alpha particles lay their energy locally (generally having the path length come – one to a few cell diameters) with a large linear energy transfer (LET) causing breakage of DNA double chains. Among the alpha emitters which can be produced at ELI-NP the radionuclide of most interest is ^{225}Ac ($T_{1/2}$ = 14.8 days). It disintegrates to stable ^{209}Bi by a series of four alpha and two beta- decays. The radionuclide ^{225}Ac can be used directly for targeted alpha therapy or as a generator for ^{213}Bi, which in turn is used for targeted alpha therapy. ^{225}Ac is produced by decay of ^{225}Ra (^{235}U chain) or by reaction ^{226}Ra(n, 2n)^{225}Ra → ^{225}Ac. Currently, the ^{225}Ac is available in very small amounts (about 1 Ci = 37 GBq per year), which is very little compared to the need for large scale application. As an alternative, we propose ^{226}Ra(γ, n)^{225}Ra → ^{225}Ac, which decays to ^{225}Ac and is separated chemically from the ^{226}Ra target (generator ^{225}Ra/^{225}Ac) (see Fig. 15). The ^{226}Ra(γ,n) reaction was chosen to produce ^{225}Ra/^{225}Ac radioisotopes due to a considerable photoneutron reaction cross section, approximately 290 mb at a E_γ=12 MeV and it will involve a radioactive target which requires radioprotection measures. We have also checked the ^{229}Th(γ,α)^{225}Ra reaction to produce ^{225}Ra however its reaction cross section value is much lower. Hence, it should be not an effective route for the production of ^{225}Ra/^{225}Ac radioisotopes. To the best of our knowledge, there is also no suitable production route for ^{225}Ra/^{225}Ac radioisotopes by using the photoreactions on ^{228}Th.

The extraction of ^{225}Ac daughter should contribute to cover the demand for ^{225}Ac/^{213}Bi generators. Bismuth can be used for labelling using chelating agents like DOTA (1,4,7,10-tetra-azacyclo-dodecane-1,4,7,10-tetra-acetic acid) but, like all

other "single-alpha" emitters, it is very short lived. These radioisotopes are usually used in combination with peptides with short uptake time and with antibodies seeking blood cancer cells. ^{225}Ac is thus useful in particular in targeted alpha therapy (TAT) but requires a chelating agent to avoid deposition in bones and liver. With a monoclonal antibody that interferes with the HER2/neu receptor has proved effective in: leukemia, lymphoma, breast, ovarian, neuroblastoma and prostate cancers, Ref. [28]. ^{226}Ra targets are difficult to handle because of the alpha radiotoxicity and dose, if their activity becomes significant. Therefore, a high density γ-beam flux is essential to minimize the size of the target and the target activity, maximizing thus the product activity. About 200 GBq can be produced weekly of ^{225}Ac, sufficiently to treat hundreds of patients. High density flux and narrow bandwidth gamma beams will allow the use of smaller ^{226}Ra quantities, allowing the production of tens of GBq of ^{225}Ac per day, using relatively small quantities of ^{226}Ra (order of mg).

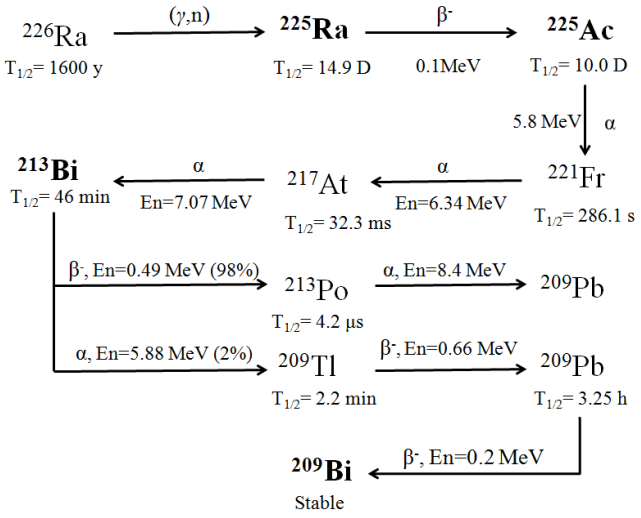

Fig. 15 – The ^{225}Ac radioisotope production and disintegration chain of ^{225}Ra via (γ, n) reaction.

^{225}Ra/^{225}Ac specific activity: The possibility of production of ^{225}Ra/^{225}Ac radioisotopes at the ELI-NP facility is investigated. The metallic ^{226}Ra target with a density of 5.0 g/cm^3 was used in the simulation. It is shown in Fig. 16 that the ^{226}Ra(γ, n) reaction has considerable cross section. The cross section reached a peak at a γ-ray energy of E_γ=12 MeV, which corresponds to a cross section of 290 mb.

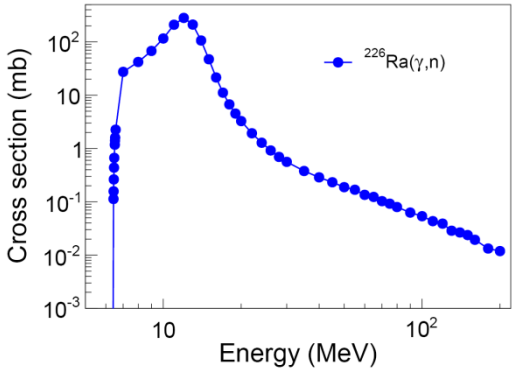

Fig. 16 – Theoretical cross section data for ^{226}Ra(γ, n) reaction from [23].

Fig. 17 shows the specific activity of ^{225}Ra/^{225}Ac radioisotopes as a function of irradiation time. The *e*-beam energy is fixed to 600 MeV. For ^{225}Ra/^{225}Ac radioisotopes, their specific activity will reach a saturation value after a relatively long irradiating time, approximately 70 days, due to a longer half-life, 14.9 days for the isotope ^{225}Ra, and 10.0 days for isotope ^{225}Ac, compared to the half-life of the isotope ^{99}Mo.

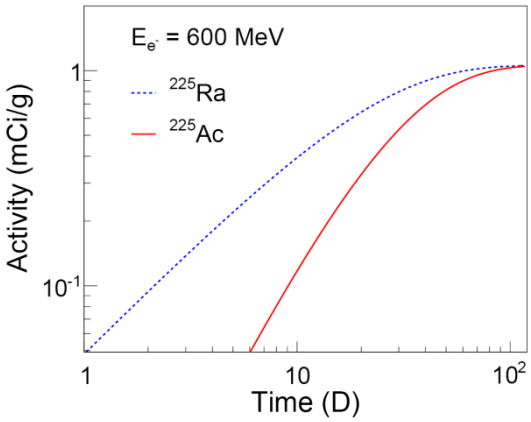

Fig. 17 – The specific activity of ^{225}Ra/^{225}Ac as a function of irradiating time. The target is choose to be 2.0 mm radius and 1.0 cm thick.

Fig. 18 shows the specific activity of ^{225}Ra/^{225}Ac generators as a function of the target thickness and radius. It is shown that a 600 MeV *e*-beam is suitable for triggering indirectly the photoneutron reaction and then generating the highest specific activity of alpha emitters, including ^{225}Ac and its daughter isotopes. For

580 MeV *e*-beam, the saturation specific activity increases as the target radius decreases. Nevertheless, for e-beams of 620 MeV and higher, the highest specific activity will occur at a target radius of 2.5 mm and then decreases as the target radius decreases. It is also shown that if an appropriate irradiation target and *e*-beam parameters (*i.e.* the target radius is smaller than 1.5 mm and the thickness is 1.0 cm) are employed, the saturation specific activity of ^{225}Ra/^{225}Ac could exceed 1.1 mCi/g.

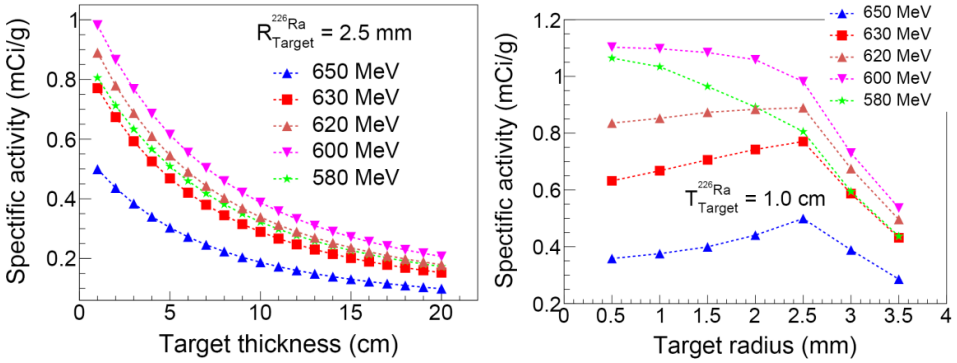

Fig. 18 – Saturation specific activity of the ^{225}Ra/^{225}Ac radioisotopes as function of the target thickness (left) and radius (right) for different *e*-beam energies.

2.2.5 Considerations concerning the production of ^{186}Re

Radionuclide ^{186}Re is a beta and gamma emitter (137 keV) with a convenient half-life of 3.7 day (Fig. 15) all of which are characteristics that make it very attractive for bone pain palliation, radiosynovectomy, and targeted radionuclide therapy.

Fig. 19 shows a schematic of the ^{186}Re radioisotope production via (γ, n) reaction. The metallic ^{187}Re target with a density of 21.04 g/cm^3 was used in the simulation. Fig. 20 shows the experimental cross section for the ^{187}Re(γ, n) reaction, which has as peak at a photon energy of E_γ=15 MeV, corresponding to a cross section of 600 mb.

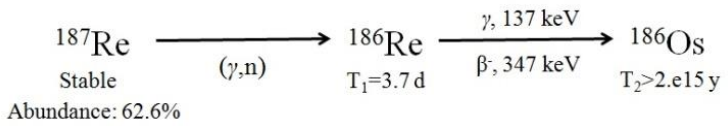

Fig. 19 – ^{186}Re radioisotope production via (γ, n) reaction.

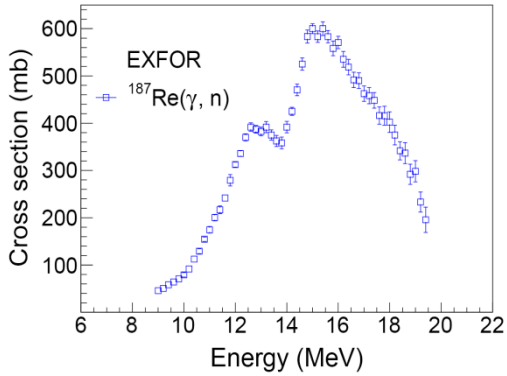

Fig. 20 – Experimental cross section for ^{187}Re(γ, n) reaction.

Fig. 21 shows the specific activity of ^{186}Re radioisotope as a function of irradiating time. The *e*-beam energy is fixed at 680 MeV. It is shown that after nearly 18 days of irradiation, the targeted ^{186}Re isotope production approaches a saturation value of 2.4 mCi/g.

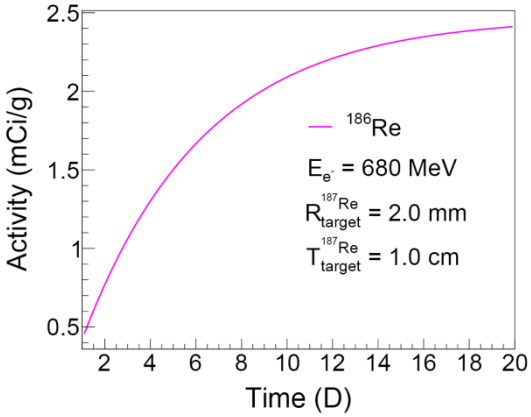

Fig. 21 – The specific activity of ^{186}Re as a function of irradiating time. The target is choose to be 2.0 mm radius and 1.0 cm thick.

The specific activity of ^{186}Re radioactive as a function of the target thickness and the radius is shown in Fig. 22. An optimized radioisotope specific activity occurs for the 680 MeV *e*-beam. In the 650 MeV *e*-beam case, the saturation specific activity continues to increase as the target radius decreases. The other cases show

that the specific activity keeps almost the same value at the left side of the inflection point, at 2.5 mm target radius. The saturation of the specific activity of ^{186}Re will exceed 2.5 mCi/g using an optimized set of parameters, such as a 680 MeV *e*-beam and a target radius equal with or smaller than1.0 mm.

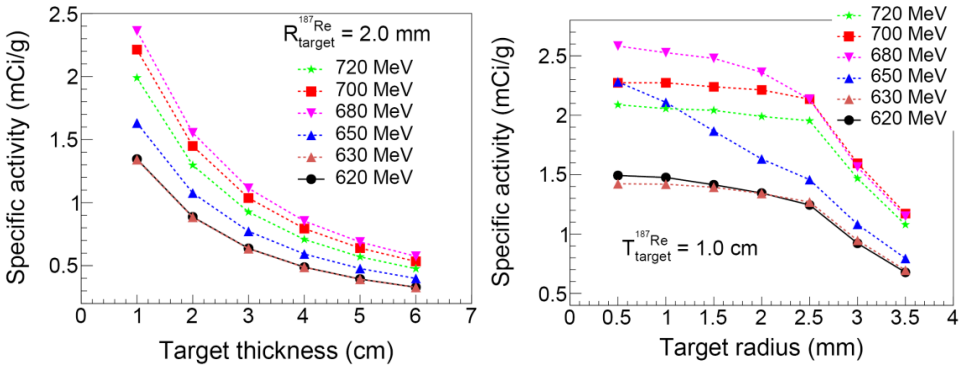

Fig. 22 – Saturation specific activity of the ^{186}Re radioisotope as function of the target thickness (left) and radius (right) for different e-beam energies.

According to our simulations, an intensity of 10^{11} γ/s for the new gamma beam at ELI-NP will allow in the first stage the possibility to obtain radioisotopes in small quantities and specific activities of 1–2 mCi/g. Consequently, ELI-NP may not be envisaged as a production facility for radioisotopes intended for clinical use, but only for research and development purposes, to evaluate the novel production method using small bandwidth γ-beams and thus pave the way towards possible future production facilities.

2.2.6 Other radioisotopes of interest

The production of isomers of interest using (γ, γ') reaction is a very good starting point in the radioisotope production at the ELI-NP γ-beam facility as the day-one experiments exploiting inelastic scattering of low-energy γ-rays (below 3.5 MeV in phase I) to excite isomeric states in ^{195m}Pt and other such isomers (^{115m}In, ^{176m}Lu). The ^{195m}Pt radioisotope can be used in SPECT, to image the distribution of platinum containing anti-cancer drugs, which may bring significant improvement in monitoring of the treatment. Moreover, due to Auger electrons emission, ^{195m}Pt has potential as radiotherapy agent, improving the chemotherapy effect. Further investigation of populating the $13/2^+$ isomer using resonant excitation with small bandwidth gamma beams should be performed, in order to produce higher activities.

In addition, some possible doorway states for the isomers still need to be found. For example, the lower (maybe the lowest) gateway states for ^{87}Sr and ^{115}In was measured to be 1.22 MeV and 1.58 MeV. As a result, another important aspect of this rather new field of radioisotope production with gamma-induced reactions is the investigation of the role played by doorway states in the population of isomers, including ^{195m}Pt, ^{115m}In, ^{176m}Lu and ^{87m}Sr.

Other radionuclides useful in radiotherapy and designated in Ref. [19] are ^{111}In and ^{103}Pd. ^{111}In (half-life of 2.8 days) emits large quantities of Auger electrons and is an isotope that is considered for treatment of metastatic disease. Currently, it is used for labeling of antibodies, isotopic labeling of blood cell components, for localization of inflammation and abscesses using labeled leukocytes. It is also used in diagnostics for rare cancers: carcinoid tumors, paragangliomas, some ectopic pheochromocytomas and other uncommon neuroendocrine tumors. ^{103}Pd **(**half-life of 17.0 days) is extensively used in brachytherapy as a seed or a stent for prostate cancer and uveal melanoma. It decays by electron capture to rhodium-103, emitting X-rays with 21 keV energy which causes the therapeutic effect, see Ref. [14].

2.2.7 Nanodosimetry and Radiation Damage to DNA

As discussed in Ref. [29] of the Physikalisch-Technische Bundesanstalt (PTB) group: "Radiation interaction with matter and namely with living tissue depends on the microscopic details of energy transfer in the micrometer and nanometer range. Since it is not possible to measure with such a high resolution in the condensed phase, various methods have been developed to substitute these measurements: (a) by measurements in low-pressure (tissue equivalent) gases or (b) by simulating the radiation transport through matter by Monte Carlo (MC) models and calculating the deposited energy or the number of ionization events in the volumes of interest". In other words, nanodosimetry in low-pressure tissue equivalent gas serves as a microscope where the energy transfer on the nanometer scale is studied at a few millimeter scale, we refer the reader to Ref. [30] from the Weizmann group for a complete review of the original seminal work in this field.

Time Projection Chamber (TPC) detectors are well suited for nanodosimetry since they register ionizing radiation as high-resolution tracks. TPCs allow the visualization of energy transport in a tissue equivalent gas and thus provide a microscopic picture of energy transport in a (human) cell and the subsequent radiation damage of the DNA molecule. Transmutation of DNA is known as one of the prime factors in creating malignant cancer cells.

The previous studies of nanodosimetry with O-TPC were performed with charged particles, Ref. [29–32], and we propose to study the nanodosimetry with γ-rays using the proposed e-TPC. Since the interaction of γ-rays with matter (*i.e.* via the scattered electron or the e^+ e^- pair creation) is different from the interaction of

ions, it is important to extend the previous studies of nanodosimetry with charged particles to nanodosimetry with γ-rays. The study of nanodosimetry of high energy (above 3 MeV) gamma-radiation will become possible for the first time by employing a low pressure TPC in the γ-beams of the ELI-NP. Such a study will be a continuation of the nanodosimetry studies performed at GSI by the PTB group (Ref. [29–32]). We note that nanodosimetry of gamma radiation can be studied with radioactive sources only at energies up to 2.6 MeV and the high energy γ-beams of the ELI-NP will allow such studies at higher energies above 3 MeV for the first time.

The design Goal (*e*-TPC): O-TPC detectors operating at low pressure (1 Torr) with a tissue equivalent gas (such as the Triethylamine, TEA), have been used in the past for nanodosimetry and assessing the damage to DNA by high-energy charged particles (Ref. [29–32]). The same *e*-TPC detector we propose to develop will also allow us to consider an application to biology by operating the *e*-TPC with a TEA at a very low pressure (even below 1 Torr) and exposing it to high-energy γ-rays from the ELI-NP facility. Our proposed study of nanodosimetry with high intensity γ-ray beam will extend the previous study on nanodosimetry with charged ions, (see Ref. [29–32]). Initially the data collected with our *e*-TPC using tissue equivalent gas (*e.g.* TEA) at very low pressure will be analyzed.

3. TECHNICAL PROPOSAL

The purpose of this technical proposal is to design an experimental set-up dedicated to production of medical radioisotopes: target preparation, irradiation by nuclear reaction (γ, n), methods of isotopes recovery, radiochemical separation, purification and analytical testing. One of the first priorities from a technical point of view is to design a prototype of the irradiation/production unit that will study initially how to produce the isotopes by intense gamma beams and help in the final design of the facility.

The availability of production of certain isotopes with potential medical use is strictly connected with the existence of post-irradiation processing facilities: manipulation of irradiated targets, radiochemical separation, purification, the recovering of the enriched materials and reinsertion in targets, establishing analytical methods for characterization and optimization of radiolabelling of molecules with biological activity. The flow for producing and testing medical radioisotopes comprises the following steps: a) target preparation and characterization, b) transfer and loading, c) irradiation, d) automated unloading and transfer of irradiated target, e) radio-chemical processing and recovery, f) purification, g) radio-analytical, physical and chemical characterization. The process may end with a radiochemical product, or can be supplied to a close or more distant collaborating research laboratory. Depending on the half-life of the radioisotope the chain continues as

follows: h) radiolabeling, i) radiopharmaceutical preparation and quality control, j) preclinical biological testing (*in vitro*, *in vivo*) and, eventually, k) pharmaceutical production for clinical trials in a GMP licensed site. There are important issues necessary to be addressed during the whole flow such as Dosimetry and Safety (radiological and biological) and Quality Management System.

3.1 Targetry and irradiation at ELI-NP facility

At the ELI-NP facility, a number of technical aspects will be addressed as described in the following paragraphs.

Simulations of the nuclear reactions for proposed radioisotopes will be performed, using specific software aiming to estimate the cross sections, yield, efficiency, specific activity, irradiation time, and optimization of dimensions, geometry, composition and mass of the target; based on the results of these simulations the next two steps are designed:

- Targetry consists in design and testing of targets, regarding the geometry, composition and mass of the target, but also physical and chemical characterization of materials used for this purpose.

- Irradiation will be performed either in E7, or in E8 experimental areas, or both, as indicated in Fig. 23. The target could be loaded manually or in an automatic mode (preferably). The latter is preferred to assure the experiments will not interfere with the other ones and do not pose any constrains to the operating personnel. Depending on the radioisotope and the target, the irradiation should last minutes to hundreds of hours, while the resulted activity will be 1–100 MBq/experiment or more, posing radiological safety issues.

If the E7 experimental area is used, an additional beam dump will be needed. It will be mounted at the separation wall between E7 and E8. It will allow doing irradiations at E7 and preparing experiments at E8. The position of the irradiation station should be just before the wall. On the other hand if the irradiations are done in E8, the irradiation station will be mounted in front of the E8 beam dump. It will be used for devoted experiments, or as a parasitic experiment, profiting from the remaining beam from upstream experiments. In this case, the irradiation station should be properly shielded, not to bother the main experiment, producing scattered radiation.

Dosimetry and radiological safety at ELI facility are referring to handling of radioactive irradiated targets and collection and treatment of locally produced radioactive waste. The irradiated targets become radioactive and should be treated accordingly. Proper shielding of irradiation area and local shielding of the transfer system should be calculated and constructed as mobile screens. Calculation depends of expected activity of main radionuclide but also congeners. The target can be placed either in the beam, or in-front of the beam-dumps, where it will run parasitic

to other experiments. In the latter case, one should consider scattered radiation, not to influence the primary experiment, but these simulations can be added later.

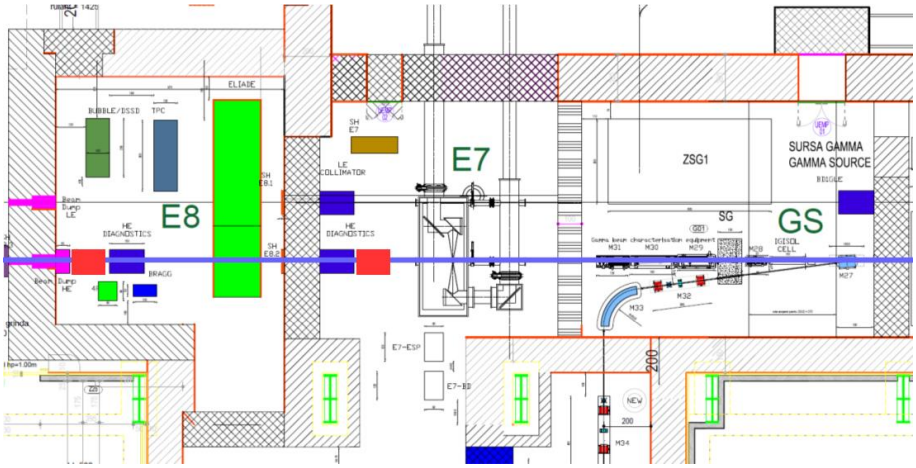

Fig. 23 – Position of the irradiation station for medical isotopes (red rectangular box) at the high-energy γ-beam line (in blue) in E7 and E8 experimental areas.

The exposure dose should be measured based on the worst case scenario and have to comply with nuclear and radiological safety regulations. Again, the automation of loading/unloading processes will greatly contribute to operational safety. The automation could be done using a pneumatic transfer of the target inside the experimental area, in the irradiation position and, when irradiation stops, back to the corridor in a shielded pot/container. This require a trench for a pipe (its diameter should be correlated with target diameter and rabbit dimensions) and a pneumatic system (or equivalent). The automation should be controlled by PLC and software installed on a computer in the control room.

Target transport/transfer issues are referring to containers type, dimensions and weight, lifting equipment, etc. A dedicated flow for radioactive products and also for radioactive waste will be addressed. Other important technical aspects are a remotely controlled sample changing system and in addition a sample transport system that would bring the irradiated material outside the irradiation zone by means of a pneumatic conveyor. Regarding the irradiated target locations inside the irradiation zone and the corresponding conveyor system branches we consider that the design of the conveyor should be done such that the target be moved in any desired location. The associated shielding, control and building safety systems will also be considered.

3.2 Processing of irradiated targets at IFIN-HH

At IFIN-HH, Department of Radioisotopes and Radiation Metrology (DRMR) there are technical capabilities suitable to perform the following tasks:

Processing of irradiated targets – separation of the radioisotope(s) of interest from target involves physical methods such as dissolution, extraction, dry distillation or thermal separation, and chemical purification followed by radioanalytical testing. Target recovery is also envisaged within this stage. These steps, including manipulation of shielded container and irradiated target can be performed at DRMR-CPR using existing facilities, see Fig. 24 (hot cells with telepliers, chemical equipment, preparative HPLC). Small laboratory equipment such as furnace with remote control, reactors, shakers and heater controllers dedicated to a certain process/radioisotope are needed.

Radiochemical processing is in certain cases necessary to prepare a radioisotope in a radiochemical form, needed for potential medical application. These include the development of an in-house generator for ^{99}Mo/^{99m}Tc or other chemical means to separate the ^{99m}Tc from ^{99}Mo in the pertechnetate form. A bigger separation column mounted in a dedicated hot-cell will be installed for preparation of pertechnetate solution, which can be sent for further investigations to distant laboratories. All the radiochemicals intended for radiolabeling of small or biologically active molecules, resulting in radiopharmaceuticals should be well characterized.

Analytical testing (quality control) of radiochemicals and radiopharmaceuticals–fully physical and chemical characterization (radionuclide purity, chemical and radiochemical purities, specific activity, residual solvents and others) will be done. A range of analytical equipment is available: HPLCs with UV/radiodetection, radio-TLC, gamma-spectrometers, dose calibrators, IR, NMR, ICP- AAS GC, and others.

Radionuclide metrology laboratory will contribute to establish nuclear data for the medical radioisotopes, to prepare calibration sources and standards, and to calibrate the equipment for radiation measurements.

Dosimetry and safety issues refer to handling of highly radioactive open sources, transport, automation of radiosynthesis, management of locally produced radioactive waste, hot cells, HVAC, filters, environmental and personnel monitoring, including licenses for radioactive sources manipulation. Dosimetry measurements will be conducted during operations and transport of irradiated targets. Radioactive waste produced at ELI-NP will be managed at ELI-NP while the radioactive waste produced at DRMR-CPR will be managed at the CPR facility. The relevant dosimetry and safety measures at the CPR as well as Quality assurance will supervise and guide the initial implementation of similar measures and systems at ELI-NP after which ELI-NP will independently oversee them. In the case of radiobiology

experiments using certain tumor cell lines and animal models, the biological safety and ethics committee approval will be considered.

Quality management system (QMS) related to the above processes, will assure compliance to the applicable regulations and traceability. At DRMR department all the activities regarding radiochemical preparations and services to external users are under the ISO certification. The certified activities also cover the exploitation of the radiological installations, hot cells and their manipulation. The new activities will be designed to comply with the quality assurance criteria. Standard operating procedures (SOP) will be defined for each process while the equipment used will be qualified and the methods validated. The QMS also implies that the operating personnel will be trained and qualified.

Targetry – some of the experiments related to target development, preparation and testing could be made under a collaboration agreement at IFIN-HH by targetry lab at Department of Tandem Accelerators (DAT) and AFM lab at Department of Applied Nuclear Physics (DFNA).

3.3 Radiolabeling and preclinical testing of radiopharmaceuticals

The radiolabeling of molecules with biological activity or other small molecules will be performed, obtaining potential radiopharmaceuticals and tested pre-clinically (biological *in vitro, ex vivo* and *in vivo* evaluation, using animal models and tumor cell lines). Radiosynthesis and/or radiolabeling are to be performed at IFIN-HH DRMR or at distant collaborating laboratories, if the half-life of radioisotope is long enough. The carriers are to be selected from bioactive molecules, which specifically target pathological processes or are involved in biochemical pathways (antibodies, antibody fragments, peptides or other small molecules).

Preclinical and clinical evaluations of radiolabeled agents are further steps towards demonstration of the potential of a radiopharmaceutical and its application. Then, depending on the results, technology transfer for radiopharmaceutical preparation in a GMP licensed site and clinical testing can be done locally or externalized.

The experimental set-up for radiosynthesis and biological evaluation depends on each team methodology and usually include cell biology lab, animal models, imaging devices, GMP compliant facility, microbioloby lab, radio-analytical equipment and fully- or semi-automated synthesis units. All of these facilities are available and operating at IFIN-HH with the exception of imaging devices (SPECT/PET/CT for small animals) and some upgrades to be made at animal housing for immunosuppressed models.

In order to design and to demonstrate the viability of the proposed solutions, we proposed the production of radioisotopes from the above list in set-ups capable of producing optimal amounts of these nuclides for experimental studies. Even if the targets and the nuclear reactions are not the same, the radiochemical processing may

be similar. After preparing a suitable target and irradiation parameter settings, the irradiation process must be optimized. This is especially important if targets have more than one stable isotope that can be the basis of a nuclear reaction that produces additional radioactive isotopes, other than the one desired.

The QMS is a key issue to be considered. When a radiochemical is produced at IFIN-HH, intended to be tested in distant laboratories (physical, chemical and/or preclinical testing) the quality is assured by a certified QMS (ISO 9001), as described above. When a radiopharmaceutical intended for clinical evaluations is prepared, the QMS should comply with pharmaceutical preparation regulations, namely Good Manufacturing Practice (GMP).

A GMP compliant laboratory is to be licensed for radiopharmaceutical preparation at IFIN-HH, DRMR but other laboratories or medical/industrial community can access to radiochemicals, to use them in their clinical studies. Magurele High Technology Cluster strongly activates in this direction.

Fig. 24 – Some of the hot cells and radiochemistry hoods installed at IFIN-HH.

4. ESTIMATE OF COUNT RATES/FEASIBILITY OF PROPOSED DEVICES

The irradiation setup: The irradiation station is placed in the beam dump of the gamma beam and consists of a target holder and a customized automated target loading/unloading system. The system will allow for target positioning, irradiation and withdraw of irradiated target independently to other experiments. The control unit is to be located on a PC, outside experimental area (control room). The automated irradiation station should be customized although there are many similar systems installed at cyclotrons/linear accelerators sites, and therefore not posing a risk of accomplishing. The main difference is target geometry and facility particularities.

The measurement setup for characterization of the irradiated samples consists of a shielded HPGe detector and associated electronics suited for measuring the activities of the irradiated samples and local spectrometry. Gamma spectrometry systems are available both in IFIN-HH DRMR and ELI-NP laboratories, and can be used in the first phase, before acquiring a dedicated one, which is foreseen to be used on irradiation site to detect the ultra-short lived radioisotopes. It will have use also for environmental and air samples radiation measurements as part of the radiation monitoring system. Radiation area monitors (flowmeters), with visual and acoustic alarm levels has to be installed and interlocked with doors. Radiation monitoring system is the general one; it should be completed with interlocks, local alarms and remote readers.

Small laboratory equipment such as furnace with remote control, reactors, shakers and heater controllers dedicated to a certain process/radioisotope are needed. They are usually radiochemistry equipment used for targets post-processing.

Containers for transfer of radioactive irradiated targets, made of tungsten, lead or similar materials are to be designed according to the target transfer system. Four containers are sufficient for starting.

Shielding for irradiation station and target transfer system should be designed and constructed. The ideal solution will be mobile shielding screen, customized according to geometrical particularities and estimations of produced radioactivity of desired radioisotopes, congeners and backside radioactive products.

All devices is to be commissioned after building is finished and should installed by qualified personnel and tested (factory acceptance test, FAT and site accepting test, SAT).

5. SAFETY REQUIREMENTS

The safety requirements mainly refer to radiological safety but should also refer to occupational safety at work, physical protection and environmental protection. The risks are coming from radiation hazard, working with heavy loads and producing radioactive sources. All the activities should be planned and effectuated according to approved standard operating procedures, as part of the Quality Management System in order to minimize the risks and comply with specific regulations.

The radiological safety requirements ask for monitoring the environmental radioactive dose in the experimental rooms and adjacent areas, monitoring of the dose to exposed personnel, monitoring the public areas (around buildings and working places of exposed professionals), separate flows for radioactive products and radioactive waste. A risk assessment and a plan to assure the compliance with specific requirements should be made and approved prior operation. The radiological safety planning will determine the high risk area and places which should be monitored. This should be a part of the general safety plan.

The physical components of the radiological safety system are (at least) the following: a) local shielding of the transfer system and irradiation unit (calculation depends of expected activity of main radionuclide but also congeners); b) gamma radiation area monitor(s) with visual and acoustic alarm levels, interlocked with experimental rooms doors and connected to the computer in the control rooms; c) shielded containers for transfer of radioactive irradiated targets; d) collection of radioactive waste.

Acknowledgements. M.B., D.B., D.F., I.G., D.G.G., and W.L. were supported by the Project Extreme Light Infrastructure - Nuclear Physics (ELI-NP) - Phase I, a project co-financed by the Romanian Government and European Union through the European Regional Development Fund.

REFERENCES

1. World Nuclear Association, *Radioisotopes in Medicine*, Information Library, Nov (2014). Updated 24 September 2015.
2. D. Habs, P. G. Thirolf, C. Lang, M. Jentschel, U. Köster, F. Negoita, V. Zamfir, *Proc. SPIE **8079**, Laser Acceleration of Electrons, Protons, and Ions; and Medical Applications of Laser-Generated Secondary Sources of Radiation and Particles*, 80791H, (2011).
3. J. Carlsson, T. Stigbrand, G.P. Adams, "*Targeted Radionuclide Therapy", Biological Aspects*, Springer, ISBN 978-1-4020-8695-3, 2008.
4. J. Carlsson, A. E. Forssell, S.O. Hietala, T. Stigbrand, J. Tennvall, Radiother. Oncol. **66**, 2, 107 (2003).
5. G.P. Adams, L.M. Weiner, Nat. Biotechnol. **23**, 9, 1147 (2005).
6. J.C. Reubi, H.R. Macke, E.P. Krenning, J. Nucl. Med. **46**, 67S (2005).
7. S.A. Jacobs, Comm. Oncology **7**, 1, 7 (2010).
8. R.D. Ice, Health Phys. **69**, 5, 721 (1995).

9. Nuclear Monitor, *Medical isotopes production without a nuclear reactor*, No **710/711**, June 2010.
10. NuPECC Report, *Nuclear Physics for Medicine*, European Science Foundation, www.nupecc.org, 2014.
11. I. Velikyan, "*The diversity of ^{68}Ga-based imaging agents, theranostics, gallium-68, and other radionuclides: a pathway to personalized diagnosis and treatment"*, Ed. R.P. Baum and F. Rosch, Springer, 2013.
12. P.J. Riss, S. Lu, S. Telu, F.I. Aigbirhio, V.W. Pike, Angew. Chem. Int. Edit. **51** (11), 2698 (2012).
13. D. Habs and U. Koster, Appl. Phys. B **103**, 501(2011).
14. S.M. Qaim, Radiochim. Acta **100**, 635 (2012).
15. M. Frontera, Aaron Bernstein, Tomas Eriksson, Mathilde Figon, Karin Granath, Martin Orbe, Charlie Shanks, Erik Stromqvist, Julie Woodland, Peter Zavodszky, Uno Zetterberg, *Future Supply Options of ^{99}Mo and ^{99m}Tc*, Mo-99 2014 Topical meeting on molybdenum-99 technological development, June 24-27 (2014).
16. S.M. Qaim, F. Tárkányi, R. Capote, *Nuclear data for the production of therapeutic radionuclides*, Technical Reports Series No. 473, International Atomic Energy Agency IAEA (2011).
17. OECD-NEA, Organization for Economic Co-operation and Development – Nuclear Energy Agency, *A supply and demand update of the Molybdenum-99 market* (2012).
18. OECD-NEA, Organization for Economic Co-operation and Development – Nuclear Energy Agency, *Medical isotope supply in the future: production capacity and demand forecast for ^{99}Mo/^{99m}Tc market 2015-2020* (2014).
19. White Book - ELI-NP, http://www.eli-np.ro/documents/ELI-NP-WhiteBook.pdf.
20. I. Gheorghe *et al.*, *"Laser Compton scattering simulation code"*, private communication.
21. M. Herman, R. Capote, B.V. Carlson, P. Obložinský, M. Sin, A. Trkov, H. Wienke, V. Zerkin, *EMPIRE: Nuclear Reaction Model Code System for Data Evaluation*, *Nuclear Data Sheets* **108**, 2655-2715 (2007); *www-nds.iaea.org/empire/index.html.*
22. IAEA Nuclear data services, *https://www-nds.iaea.org/.*
23. TENDL-2009, *http://www.talys.eu/tendl-2009/.*
24. NIST X-ray Attenuation Databases, *http://physics.nist.gov/PhysRefData/XrayMassCoef/tab3.html*.
25. A.V. Sabelnikov, O.D. Maslov, L.G. Molokanova, M.V. Gustova, and S.N. Dmitriev, Radiochemistry **48**, 91 (2006).
26. N.I. Ayzatskiy, N.P. Dikiy, A.N. Dovbnya, Y.V. Lyashko, V.I. Nikiforov, A.E. Tenishev, A.V. Torgovkin, V.L. Uvarov, B.I. Sharmenko, D. Ehst, Probl Atomic Sci Technol **3**, 49, 174 (2008).
27. N.A. Smith, D.L. Bowers, D.A. Ehst, App. Radiat. Isotopes **70**, 10, 2377 (2012).
28. A.M. Ballangrud, W-H. Yang, St. Palm, R. Enmon, P.E. Borchardt, V.A. Pellegrini, M.R. McDevitt, D.A. Scheinberg, and G. Sgouros, Clin. Cancer Res. **10**, 4489 (2004).
29. U. Titt, V. Dangendorf, B. Großwendt, H. Schuhmacher, Nucl. Instr. Meth A**, 477,** 536 (2002).
30. S. Shchemelinin, G. Garty, A. Breskin, R. Chechik, Nucl. Instr. Meth. A, **477**, 527 (2002).
31. H. Schuhmacher, V. Dangendorf, Radiat. Prot. Dosim. **99**, 317 (2002).
32. Gabor Laczkó, Ph. D Thesis, University of Frankfurt, Germany, 2007; available at http://jinst.sissa.it/jinst/theses/2007_JINST_TH_001.jsp