

The SPES_MED project

This is a pre print version of the following article:

Original:

Pupillo, G., Andrighetto, A., Arzenton, A., Ballan, M., Barbaro, F., Belcari, N., et al. (2026). The SPES_MED project. JOURNAL OF RADIOANALYTICAL AND NUCLEAR CHEMISTRY [10.1007/s10967-026-11169-4].

Availability:

This version is available <http://hdl.handle.net/11365/1328654> since 2026-10-03T10:51:23Z

Published:

DOI: <http://doi.org/10.1007/s10967-026-11169-4>

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The SPES_MED project

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Research Article

Keywords: Medical radionuclides, Cross-section measurements, ISOL-production, Nuclear modeling

Posted Date: July 8th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10055208/v1>

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Journal of Radioanalytical and Nuclear Chemistry on September 18th, 2026. See the published version at <https://doi.org/10.1007/s10967-026-11169-4>.

Title page

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Title: The SPES_MED project

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The SPES_MED project

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Abstract

The production of medical radionuclides is one of the research activities carried out in the framework of the SPES (Selective Production of Exotic Species) project under the completion stage at the Legnaro National Laboratories of the National Institute for Nuclear Physics (INFN-LNL). This work outlines the main goals of the “SPES_MED” project, funded for the 2025-2027 years, aiming at research activities to produce medical radionuclides exploiting both the direct activation method and the ISOL technique at SPES. Results obtained during the first year of the project, regarding recent nuclear cross section measurements, ISOL-production and nuclear modelling, will be described.

Keywords

Medical radionuclides, Cross-section measurements, ISOL-production, Nuclear modeling

Introduction

As underlined during the 12th International Conference on Isotopes (12ICI) [1, 2], radionuclides and radiopharmaceuticals are fundamental tools in nuclear medicine, by enabling imaging and treatment in tens of millions of procedures performed yearly worldwide. Over the years, the number of radiation applications in nuclear medicine has experienced a rapid increase and a diversification in many directions (e.g. theranostics, bimodal imaging, targeted radiotherapy), requiring many novel radionuclides with different chemical and physical characteristics [3]. The production of emerging medical radionuclides is therefore a key aspect in the development of innovative radiopharmaceuticals. The availability of new research infrastructures dedicated to this goal is thus crucial for Europe. For such a reason, in 2021 the PRISMAP consortium was established and in 2026 the following PRISMAP+ project was funded by the European Commission, to gather the European research community working in this field and to provide high-purity grade radionuclides for research purposes [4]. The INFN-LNL takes part in the PRISMAP consortium as an emerging facility, including both the direct activation method (LARAMED project, acronym for Laboratory of Radioisotopes for MEDicine) [5] and the ISOL (Isotope Separation On-Line) technique (ISOLPHARM project, acronym for ISOL technique for radioPHARMaceuticals) [6] within the SPES project [7]. Indeed, the SPES main goal is the realisation of an advanced ISOL facility to produce re-accelerated exotic ion beams (RIBs) for fundamental nuclear physics studies, but the cyclotron double-beam extraction system also

allows to simultaneously carry out applied research, such as radionuclides production for medicine. The Commissione Scientifica Nazionale 3 (INFN-CSN3) funded the SPES_MED project for the 2025-2027 years, whose main objectives are: 1. Perform measurements of nuclear cross sections aiming at the optimization of medical radionuclides production, also using nuclear modelling tools to find out the best irradiation conditions; 2. Provide a precise measurement of the ISOL production yields originating from SiC and TiC targets; 3. Compare the produced data with the existing simulation libraries, with the purpose of providing an experimental benchmark when the theoretical predictions fail. The project is thus structured considering 3 work packages (WP) and, in addition to INFN-LNL, it involves the INFN divisions of Milano (MI), Padova (PD), Pavia (PV) and Pisa (PI). This work is focused on the experimental results and recent installations realized by the SPES_MED collaboration during the first year of the project.

SPES infrastructures

The SPES_MED project exploits the infrastructure at SPES described in the following paragraphs, focusing both on the ISOL and direct techniques dedicated to medical radionuclides production. The heart of SPES is a dual-extraction 70 MeV proton cyclotron, capable of providing intense beams up to 700 μA (max 500 μA allowed at each beam port) [8].

The ISOL facility

The ISOL technique is an established RIB production method which features high intensity, good ion optical quality and the possibility of selecting a desired radionuclide species [9]. At SPES a cyclotron is used to provide proton beams with energy up to 40 MeV and current up to 200 μA . The proton beam impinges on a thick target to produce radioactive nuclei, and different target materials can be used to produce different RIBs. Three materials are considered: SiC, TiC and UCx; in particular, the latter enables the production of neutron rich radionuclides generated by the proton-induced fission of the Uranium nuclei. Each target is realized as a set of 7 disks; by keeping them at high temperature (2000 $^{\circ}\text{C}$) the diffusion of the products is promoted. A transfer line connects the target to the ion source, where the neutral radioactive nuclei are ionized to a 1+ charge state, and accelerated through a static electric field [10]. To maximize the elemental purity of the extracted RIB, laser resonant photo-ionization technique can be employed [11]. A mass separation stage with a mass

resolution of about 1/300 is used to provide a single-mass beam to the low-energy experimental area [12].

For the specific case of medical radionuclides production, the ions are collected at the ISOLPHARM Radionuclide Implantation Station (IRIS), an experimental setup where the ions are implanted on a suitable substrate [13]. Currently, the substrates consist of tablets with diameter 13 mm and thickness of 1.1 mm (see Fig. 1); they are realized by pressing organic powder with a manual press. Sorbitol and hypromellose are used as starting material, to easily recover the implanted radiometals.

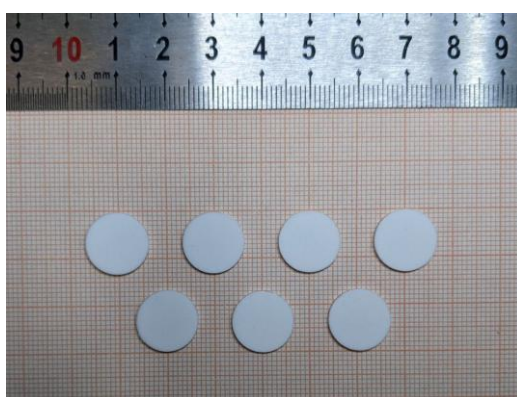


Fig 1. Hypromellose tablets used for the implantation of RIBs

The SPES Laser Ion Source (SPES-LIS) has recently been commissioned using stable samarium beams. The ionization method employed in this kind of ion source is the laser resonant stepwise photoionization. During commissioning, a two-step excitation scheme was implemented, consisting of an initial resonant transition followed by excitation to an autoionizing state. Both transitions were driven using the same laser wavelength of 435.706 nm (in vacuum), which had been previously validated with the SPES-LIS at the ISOLDE Offline 2 laboratory as part of preparatory studies and source characterization [14]. Solid-state Sirah Credo Ti:Sa lasers operating at a repetition rate of 10 kHz are used to generate the required wavelengths in the SPES laser laboratory [15], and the laser beams are subsequently transported to the ion source cavity located approximately 18 meters from the laboratory. With the successful commission of SPES-LIS, the facility can now produce other elements of interest to SPES_MED, such as ^{111}Ag with high efficiency and low isobaric contamination.

The LARAMED facility

The LARAMED infrastructures within the SPES building have been already described [16–18]. The main implementation is the target station designed and realized at the INFN-LNL, temporarily installed in the ISOL-2 bunker for the commissioning activities carried out in spring 2024. The target station is shown in Fig. 2, including the details of the diagnostic chamber to monitor the proton beam, an external graphite collimator (9 mm diameter, red squared detail) to avoid activation of the target holder, the target holder (12 mm diameter, yellow squared detail) and the graphite beam stopper behind it (green squared image).

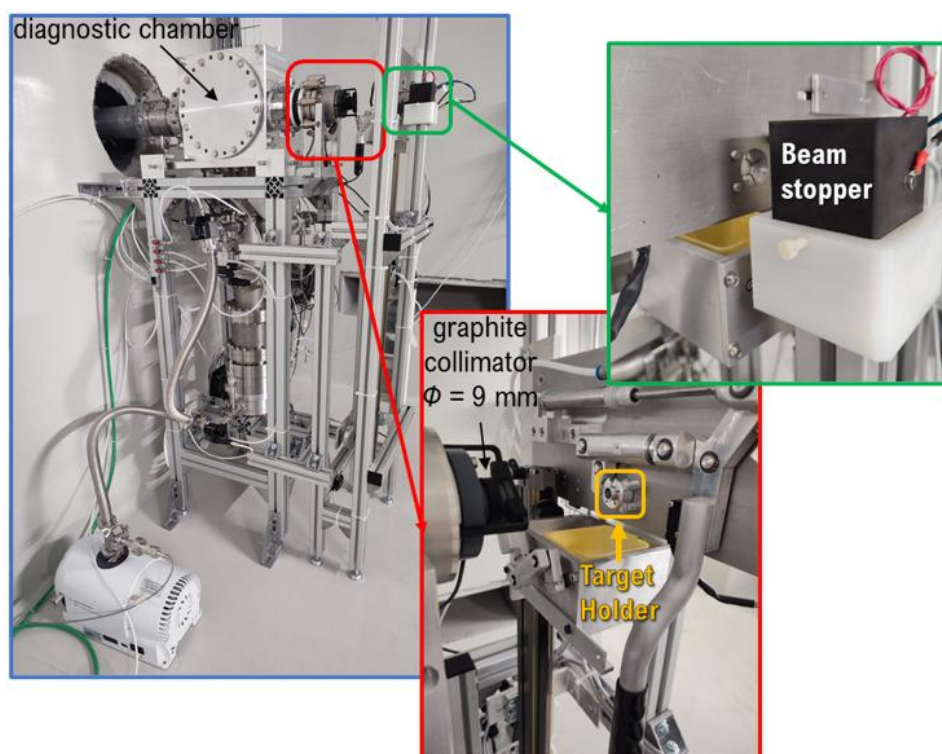


Fig. 2 Target station dedicated to nuclear cross section measurements at SPES

After the irradiation, the target foils are automatically recovered from the target station within a lead pot to be safely moved. The produced activity is then measured by γ -spectrometry using a HPGe detector with low background lead shield and integrated cryocooling system (Ametek Ortec, measured resolution FWHM 1.6 keV, efficiency 30% at 1.33 MeV).

At the second floor of the SPES building, the laboratories dedicated to target manufacturing [19–21] and radiochemical process for radionuclides extraction and purification are under completion.

A target station devoted to high intensity irradiations will be established in a dedicated bunker for medical radionuclides production. In addition to R&D activities, collaborations with private partners are foreseen for the next years.

SPES_MED goals and results

The project aims at attaining a deeper knowledge on the properties of promising radionuclides, in particular ^{28}Mg , ^{43}K , $^{43,44,47}\text{Sc}$, ^{51}Cr , $^{64,67}\text{Cu}$, ^{111}Ag and $^{149,152,155}\text{Tb}$, from the following points of view:

WP1: the measurement of unexplored nuclear reactions, considering the production of both the radionuclides of interest and their contaminants, to find out the best irradiation parameters for each specific case;

WP2: the precise evaluation of the production yield of several medical radionuclides applying the ISOL technique to targets of interest for the SPES project;

WP3: the possibility to employ the new experimental data to improve both the nuclear data libraries and theoretical models, particularly in the low- and intermediate-energy regions which are so crucial for radionuclide production. Different tools for Monte Carlo simulations are employed to optimize performances of ISOL-based SiC and TiC production targets.

In the following paragraphs, the results obtained by each WP during the first year of SPES_MED are presented.

Nuclear cross section measurements (WP1)

Accurate nuclear cross-section data are essential for the optimized production of medical radionuclides and for the assessment of radionuclidic purity. During 2025, the SPES_MED team has been focused on ^{47}Sc and Terbium isotopes. The results provide valuable input for nuclear databases and support optimized production routes for emerging medical radionuclides.

Measurements of the $^{49}\text{Ti}(d,x)^{47}\text{Sc}$ reaction

^{47}Sc is one of the theranostic radionuclides of interest of SPES_MED and its production has

been investigated considering deuteron beams and enriched ^{49}Ti targets [22]. Additional information on targets realization by High Vibrational Powder Plating (HIVIPP) technique and their characterization can be found elsewhere [23–25]. Irradiation runs have been carried out at GIP ARRONAX [26], exploiting the tunable deuteron beam available (energy range 16 - 35 MeV) and the well-known stacked-foils target method. A typical stacked target was composed by about $1 \div 2 \mu\text{m}$ enriched ^{49}Ti targets (enrichment level 96.25%) deposited on $25 \mu\text{m}$ $^{\text{nat}}\text{Al}$ backing layers, $25 \mu\text{m}$ $^{\text{nat}}\text{Ni}$ foils to monitor beam flux, $10 \mu\text{m}$ $^{\text{nat}}\text{Al}$ foils to monitor recoil atoms, and thicker ($50 \div 300 \mu\text{m}$) $^{\text{nat}}\text{Al}$ foils to decrease the beam energy through the stack. After irradiation, the foils have been measured by γ -spectrometry using two HPGe detectors, previously calibrated with ^{152}Eu and ^{241}Am sources. The decay of the produced radionuclides (i.e., ^{47}Sc and all contaminants) has been followed for the next 5 days after the End of Bombardment (EOB) to check eventual interferences in the γ -lines and improve the final cross section uncertainty. Fig. 3 shows the obtained results for ^{47}Sc and ^{46}Sc , the main radioisotopic impurity since it has a longer half-life (83.79 d) than ^{47}Sc (3.3492 d) [27].

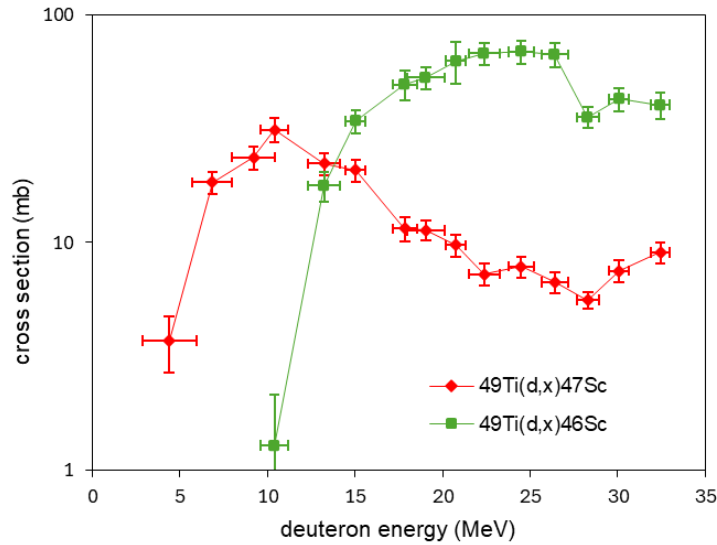


Fig. 3 Measured nuclear cross section of the $^{49}\text{Ti}(d,x)^{47}\text{Sc}$ (red dots) and ^{46}Sc (green dots)

Measurements of the $^{\text{nat}}\text{Eu}(\alpha,x)$ reactions and optimization of ^{155}Tb production

Tb-isotopes have recently attracted increasing interest due to their potential use in diagnostic, therapeutic, and theranostic applications. Despite this interest, experimental data for charged-particle-induced reactions on gadolinium and europium targets remain incomplete, especially

at intermediate energies. Moreover, uncertainties in decay data, such as branching ratios of metastable states, can strongly affect the interpretation of experimental results. Within the SPES_MED framework, a systematic experimental program was undertaken to address these issues, also with a focus on the experimental determination of a key branching ratio of ^{154}Tb . Natural gadolinium and europium targets were prepared using standard techniques suitable for activation experiments. For optimization studies, isotopically enriched ^{153}Eu targets were supposed.

Alpha-particle irradiations were carried out up to 65 MeV, while proton irradiations on $^{\text{nat}}\text{Gd}$ covered energies between 60 and 68 MeV. Beam parameters were monitored to ensure reproducibility and reliable dose determination. After irradiation, induced activities were measured by high-resolution γ -ray spectrometry using calibrated HPGe detectors. Peak analysis and efficiency corrections were applied following standard procedures. Production cross sections were derived using the activation method, taking into account decay during irradiation, cooling, and counting. Uncertainty propagation included contributions from beam current measurements, detector efficiency, target thickness, counting statistics, and nuclear decay data.

Eighteen production cross-section points were measured for the $^{\text{nat}}\text{Eu}(\alpha, x)$ reaction between 20 and 65 MeV, covering $^{149-156}\text{Tb}$ and $^{153,159}\text{Gd}$ [28]. Fig. 4 shows the experimental results of the $^{\text{nat}}\text{Eu}(\alpha, x)^{149}\text{Tb}$, ^{152}Tb and ^{155}Tb reactions, respectively represented with blue triangles, red circles and black squares.

A numerical optimization approach based on genetic algorithms was applied to simulate ^{155}Tb production on enriched ^{153}Eu . The optimization variables included beam energy, target thickness, irradiation time, and cooling time. Pareto-optimal solutions were obtained by simultaneously maximizing ^{155}Tb yield and radionuclidic purity. A perturbation analysis confirmed that the optimal solutions are stable against moderate variations of the input parameters [28].

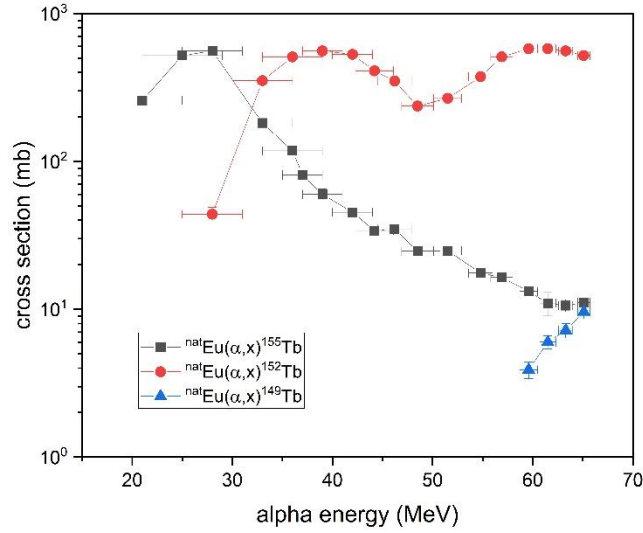


Fig. 4 Nuclear cross sections of the $^{\text{nat}}\text{Eu}(\alpha, x)^{149}\text{Tb}$ (blu triangle), ^{152}Tb (red circle) and ^{155}Tb (black square) reactions

The lack of reliable decay data for the ^{154}Tb isomeric triplet represents a significant source of uncertainty in ^{155}Tb purity evaluations. An experimental branching ratio for the dominant internal transition ($^{154\text{m1}}\text{Tb} \rightarrow ^{154\text{g}}\text{Tb}$) was determined by fitting experimental decay curves of the ground state using Bateman equations. The preliminary value obtained, $\sim 8\%$, is substantially lower than the evaluated literature value of $21.8 \pm 0.7\%$ [26].

Data evaluation for the $^{\text{nat}}\text{Gd}(p, x)$ and the $^{\text{nat}}\text{Gd}(\alpha, x)$ reactions for the production of $^{149-156, 160, 161}\text{Tb}$, $^{153, 155, 157, 159}\text{Dy}$, and ^{153}Gd are ongoing, and additional irradiations are planned to improve energy coverage and statistical reliability.

ISOL yield measurements and installations (WP2)

The IRIS system for radionuclides collection was recently installed in a dedicated beamline of the SPES low-energy experimental hall. Fig 5 shows the setup: the RIB comes from the right-hand side of the picture, and it is dumped on the tablets within the IRIS chamber; the lower part of the setup hosts the γ -ray spectrometry system, which analyze each tablet after irradiation. Two detectors are available: an HPGe with electrically refrigerated cryostat and a LBC inorganic scintillator; both of them were extensively described in a previous work [29]. The setup was tested offline, with particular attention to the venting and evacuating procedures, which are of paramount importance to recover the radioactive material.

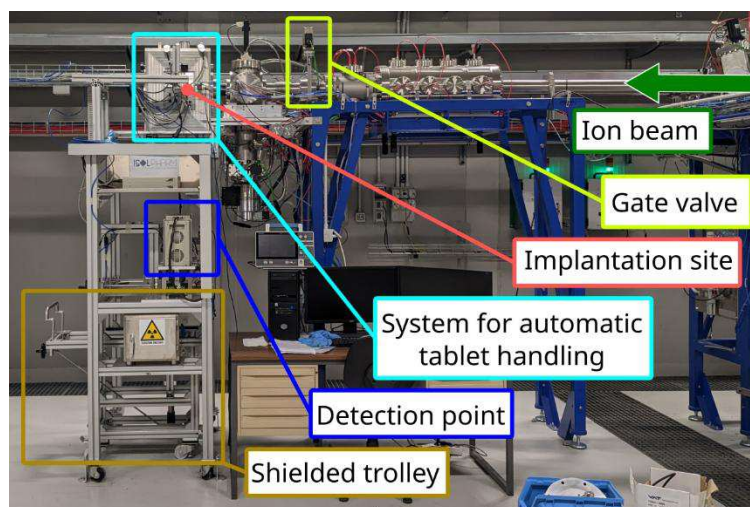


Fig 5. Picture of the ISOLPHARM Radionuclide Implantation Station (IRIS) at SPES

Recently, Ag stable beam ionization and extraction was also carried out at the SPES offline front-end. The aim of the ionization tests with stable beams is to identify the optimal conditions for the efficient ionization of elements of interest. These tests were performed at the SPES offline front-end, which reliably reproduces the corresponding online machine. The FEBIAD ion source was adopted [30], and neutrals were injected exploiting the well-established Mass Marker technique [31]. As an example, Fig. 6 shows the selected $^{107}\text{Ag}^+$ ion current during one experimental run. The setup proved to be a viable option for the future ionization efficiency tests planned within the project.

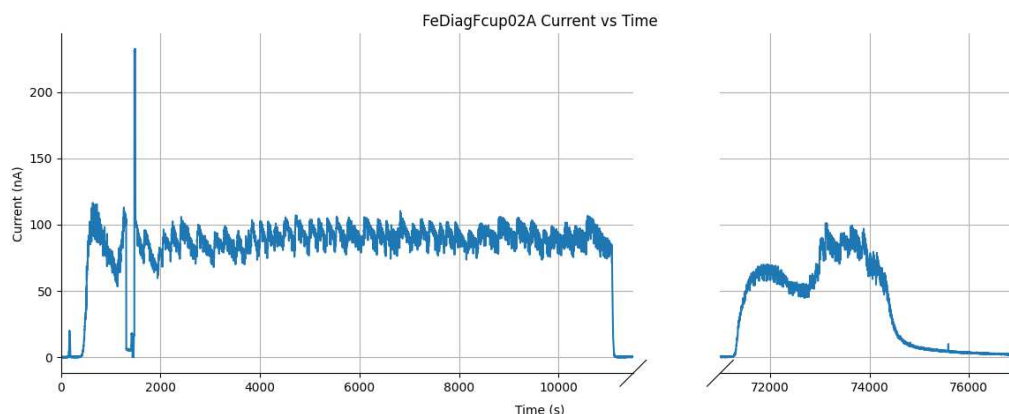


Fig 6. Extracted $^{107}\text{Ag}^+$ ion current as a function of time

In addition to the aforementioned research activities, WP2 also focused on a new low uncertainty measurement of the ^{111}Ag half-life. This activity followed a discrepancy observed between the presently recommended 7.45(1) days (1σ) ^{111}Ag half-life and the two most recent values reported in literature. A new determination was carried out by measuring the decay of

a ^{111}Ag sample using state-of-the art γ -detection systems fully characterized for their long-term efficiency stability. The resulting 7.4236(11) d (1σ) value is not in agreement with the recommended value and confirms the observed discrepancy [32]. In addition, a computational notebook was developed to process experimental data collected with a γ -detection system for the determination of the activity value of a radionuclide including an uncertainty budget compliant with the Guide to the expression of Uncertainty in Measurement (GUM) [33].

Nuclear modeling and Monte Carlo simulations (WP3)

WP3 of SPES_MED project is devoted to simulations: on one hand, for nuclear cross sections and the optimization of theoretical models employing the new experimental data from WP1; on the other hand, for the ISOL production, using simulations to optimize the production steps described in WP2.

Genetic algorithm optimization of the $^{49}\text{Ti}(p,x)^{47}\text{Sc}$ production

Figure 7 summarizes the TALYS parameter optimization based on a genetic algorithm (GA), carried out within WP3 for the $^{49}\text{Ti}(p,x)$ production route of ^{47}Sc . The procedure optimized 12 level-density parameters across six compound nuclei and nine reaction channels, using Latin Hypercube Sampling, tournament selection, single-point crossover, and adaptive mutation. The root mean square error (RMSE) comparison shows that the GA-optimized calculation provides a consistently more reliable description of the measured cross sections than the default TALYS model, supporting the use of GA-based optimization as an effective tool for improving nuclear reaction simulations relevant to medical radionuclide production. These results are based on the work reported in [34].

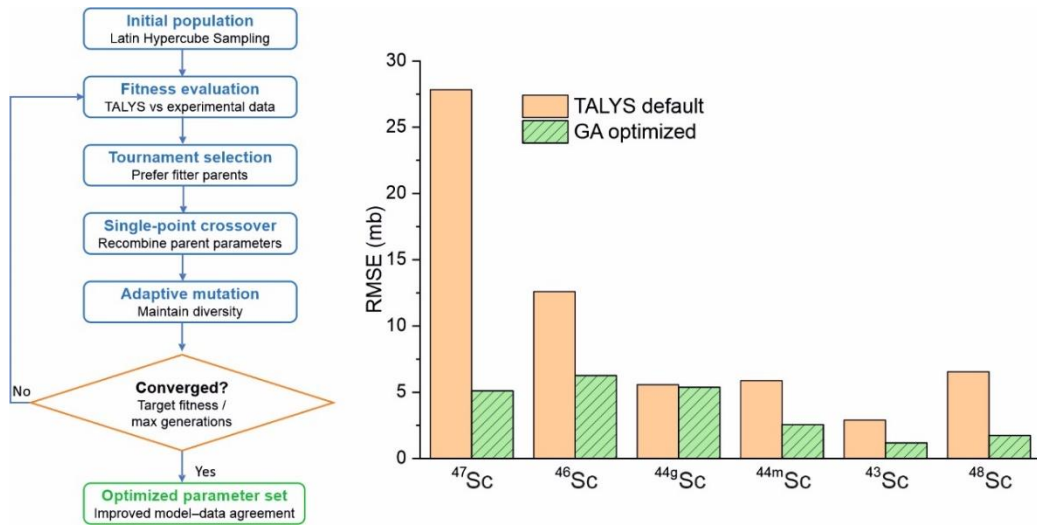


Fig. 7 Workflow of the GA-based TALYS parameter optimization. Left panel: schematic workflow of the genetic-algorithm procedure. Right panel: RMSE comparison between the default TALYS model and the GA-optimized calculation for selected $^{49}\text{Ti}(p,x)$ reaction channels

Monte Carlo optimization of SiC and TiC targets

Regarding the theoretical analysis of the ISOL production steps, the first task is the simulation of the diffusive processes in the target box through a Geant4 Monte Carlo routine. Silicon carbide (SiC) target configurations with different size and density are implemented in the code (see Fig. 8), and the mean escape time for the nuclides generated by proton-induced reactions can be computed under each condition. Preliminary tests with magnesium isotopes were performed [35]. Contextually, the intrinsic efficiency of possible photoionization schemes suitable for the SPES Laser Ion Source (LIS) is studied for four elements of biomedical interest: magnesium, scandium, gallium and silver. The considered schemes, which can start either from the ground state or from a thermal state populated at the SPES-LIS temperature (up to 2000°C, depending on the thermal resistance of the target), are mainly taken from the literature and, in certain cases, developed by the SPES_MED WP3 group. This leads to the optimization of the resonant laser parameters (especially power) for every scheme, the selection of the best scheme for each element and the prediction of the ion yield mediated by pure laser-atom interaction within a single pulse. For certain elements, results have already been published elsewhere [36, 37]. Finally, in the advanced stage of the project, the focus will be on in-target production modeling; to do this, the latest version of

the FLUKA Monte Carlo code will be used to calculate a dataset of production rates (nuclide per proton) using silicon, titanium and uranium carbide targets.

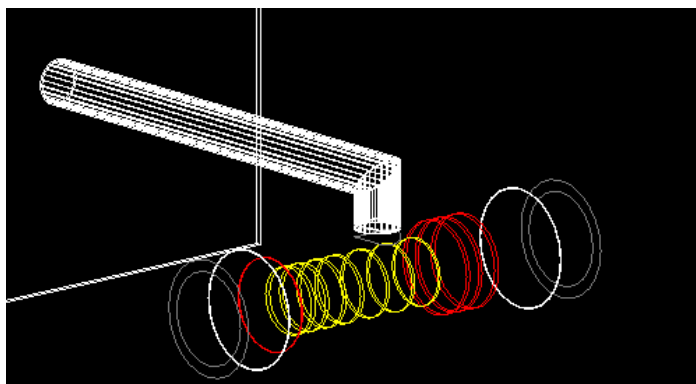


Fig. 8 Geometry of the SiC target configuration in the Geant4 user interface. The seven SiC disks are in yellow, the beam dumpers are in red and the target box limits are in grey.

The tube above is the transfer line, which drives the atoms to the hot cavity [36]

A computational study using FLUKA and PHITS tools for Monte Carlo simulations is also currently underway, to investigate the production of isotopes from titanium carbide (TiC), an excellent target material for operation at for high-power proton irradiation facilities. High performance multi-foil TiC targets are in fact employed at the SPES-ISOL facility, for production of medical ^{43}Sc , ^{44}Sc and ^{47}Sc radioisotopes of strategic relevance within the PRISMAP consortium [38].

Calculations of proton induced nuclear cross sections for production of the scandium isotopes of interest will allow physical models implemented in the Monte Carlo codes to be benchmarked on experimental production data at SPES.

Furthermore, using innovative additive manufacturing technologies, SPES is designing complex targets with high surface-to-volume ratios [39]. These types of targets will improve heat dissipation, thereby allowing for an increase in the energy and intensity of the proton beam compared to what is achieved with a multi-foil TiC target.

Discussion and Conclusions

Regarding WP1, the present results extend the experimental database for alpha- and deuteron-induced reactions on europium and ^{49}Ti targets, respectively, which are of direct relevance for medical radionuclide production for terbium isotopes and ^{47}Sc . The optimization study demonstrates the potential of combining experimental nuclear data with advanced numerical techniques to improve production yields and purity. The large discrepancy observed for the

$^{154m1}\text{Tb} \rightarrow ^{154g}\text{Tb}$ branching ratio suggests that revised decay data may be required and highlights the importance of dedicated experimental studies of nuclear decay schemes, since they have direct consequences on purity assessment. Ongoing and future measurements will further refine these results and contribute to improved nuclear data evaluations. The cross section investigation of the $^{49}\text{Ti}(\text{d},\text{x})^{47}\text{Sc}$ nuclear reaction highlighted a valid production route exploiting low-energy deuteron beams, which, hereafter, needs to be deepened from a dosimetric point of view. A work analyzing the results to establish the production constraints for the utilization in preclinical studies of ^{47}Sc obtained through this pathway is under review [22].

Focusing on WP2, the IRIS system for radionuclides collection was recently installed in a dedicated beamline of the SPES low-energy experimental hall and tested offline, with particular attention to the venting and evacuating procedures. Ionization tests with stable Ag beams to identify the optimal conditions for an efficient ionization were performed at the SPES offline front-end, which reliably reproduces the corresponding online machine. Following the successful commissioning of the SPES Laser Ion Source, the range of isotopes that can be produced with high efficiency and purity has been significantly expanded.

Main results from WP3 regard the use of genetic algorithm (GA) to optimize the description of the $^{49}\text{Ti}(\text{p},\text{x})^{47}\text{Sc}$ reaction with the TALYS modeling code. The RMSE comparison shows that this GA-optimized calculation provides a consistently more reliable description of the measured cross sections than the default TALYS model, supporting the use of GA-based optimization as an effective tool for improving nuclear reaction simulations relevant to medical radionuclide production. In addition, Monte Carlo optimization of SiC and TiC targets have been performed with Geant4 and FLUKA and PHITS respectively, to optimize the production of medical radionuclides using the ISOL technique. Contextually, the intrinsic efficiency of possible photoionization schemes suitable for the SPES-LIS has been studied for Mg, Sc, Ga and Ag, four elements of biomedical interest. This leads to the optimization of the resonant laser parameters (especially power) for every scheme, the selection of the best scheme for each element and the prediction of the ion yield mediated by pure laser-atom interaction within a single pulse.

The 12ICI was a perfect framework to present the first results of the SPES_MED community, providing fruitful discussions with the international colleagues working in this field.

Acknowledgements

SPES_MED is funded by Istituto Nazionale di Fisica Nucleare – Commissione Scientifica Nazionale 3 (INFN-CSN3) for the 2025-2027 years.

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