THE ISOLPHARM PROJECT FOR THE PRODUCTION OF HIGH SPECIFIC ACTIVITY RADIONUCLIDES FOR MEDICAL APPLICATIONS*

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Abstract

ISOLPHARM is a branch of the INFN-LNL SPES project, aimed at the production of radioisotopes for medical applications according to the ISOL technique. Such an innovative method will allow to produce carrier-free radionuclides, useful to obtain radiopharmaceuticals with very high specific activities. In this context a primary proton beam, extracted from a cyclotron will directly impinge a target, where the produced isotopes are extracted and accelerated, and finally, after mass separation, only the desired nuclei are deposed on a secondary target.

This work is focused in the design and study of the aforementioned production targets for a selected set of isotopes, in particular for ^{64}Cu, ^{89}Sr, ^{90}Y, ^{125}I and ^{131}I. ^{64}Cu will be produced impinging Ni targets, otherwise the SPES UC_x target is planned to be used. Different target configurations are being studied by means of the Monte Carlo based code FLUKA for the isotope production calculation and the Finite Element Method based software ANSYS ® for the temperature level evaluation.

An appropriate secondary target substrate for implanting the produced isotopes is under study.

INTRODUCTION

SPES (Selective Production of Exotic Species) is a project aiming at the construction of an ISOL facility (Isotope Separation On-Line) at INFN-LNL (Istituto Nazionale di Fisica Nucleare – Laboratori Nazionali di Legnaro) for the production of radioactive ion beams of neutron rich nuclei with high purity, with mass ranging between 80 and 160 amu [1].

In this framework the ISOLPHARM project is devoted to the application of the SPES technologies for the production of innovative radiopharmaceuticals.

Radiopharmaceuticals are drugs capable of delivering a predefined dose of radiation to a biological target tissue for diagnostic or therapeutic purpose. They are usually composed by a "radioactive core" and a "carrier system" that allows to deposit radiation selectively onto the malignant tissue avoiding the compromising of healthy cells.

Since the ISOL technique allows the on-line production of high intensity and high quality radioactive ion beams [2], it might be an efficient way to produce radionuclides for radiopharmaceuticals with specific activity close to its theoretical value. The higher is the specific activity, the more effective is the radionuclide for the radiolabeling of compounds.

ISOLPHARM project will mainly deal with two aspects: the isotope production according to the ISOL technique and the radioPHARMaceuticals labelling with the produced nuclei, after the radionuclide purification.

Radionuclides will be produced by impinging a dedicated target with a primary proton beam extracted from SPES cyclotron (up to 70 MeV 350 μA). The production target will be held at high temperature (up to 2200-2300°C), thus allowing the migration of the produced nuclei towards the ion source thanks to the diffusion and effusion processes [1]. After ionization a radioactive ion beam will be extracted with a potential difference up to 40kV. Mass separation will provide the desired single-mass nuclide beam which will be deposed in an appropriate collection target. Since the collected isotopes are characterized by a single mass number, the subsequent chemical separation will provide the desired single isotope for the radiopharmaceuticals labelling. After pharmaceutical processes high specific activity drugs will be available for diagnosis and therapy (Fig. 1).

The radioisotopes interesting from a radiopharmaceutical point of view are: ^{89}Sr, ^{90}Y, ^{125}I, ^{131}I, ^{133}Xe [3, 4, 5, 6, 7], which can be produced through fission using the SPES uranium carbide target, and ^{64}Cu [8] produced through spallation on a dedicated nickel target. Different production target configurations are described in this work.

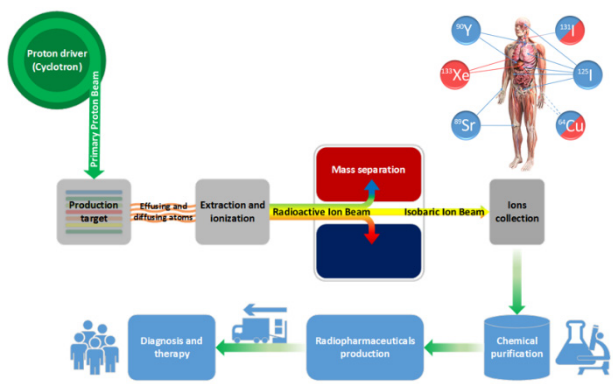

Figure 1: Overview of the ISOLPHARM project, grey balloons concern the isotope production aspects, blue balloons deal with the chemical and pharmaceutical aspects. On the top right are indicated the first planned isotopes for radiopharmaceutical labelling.

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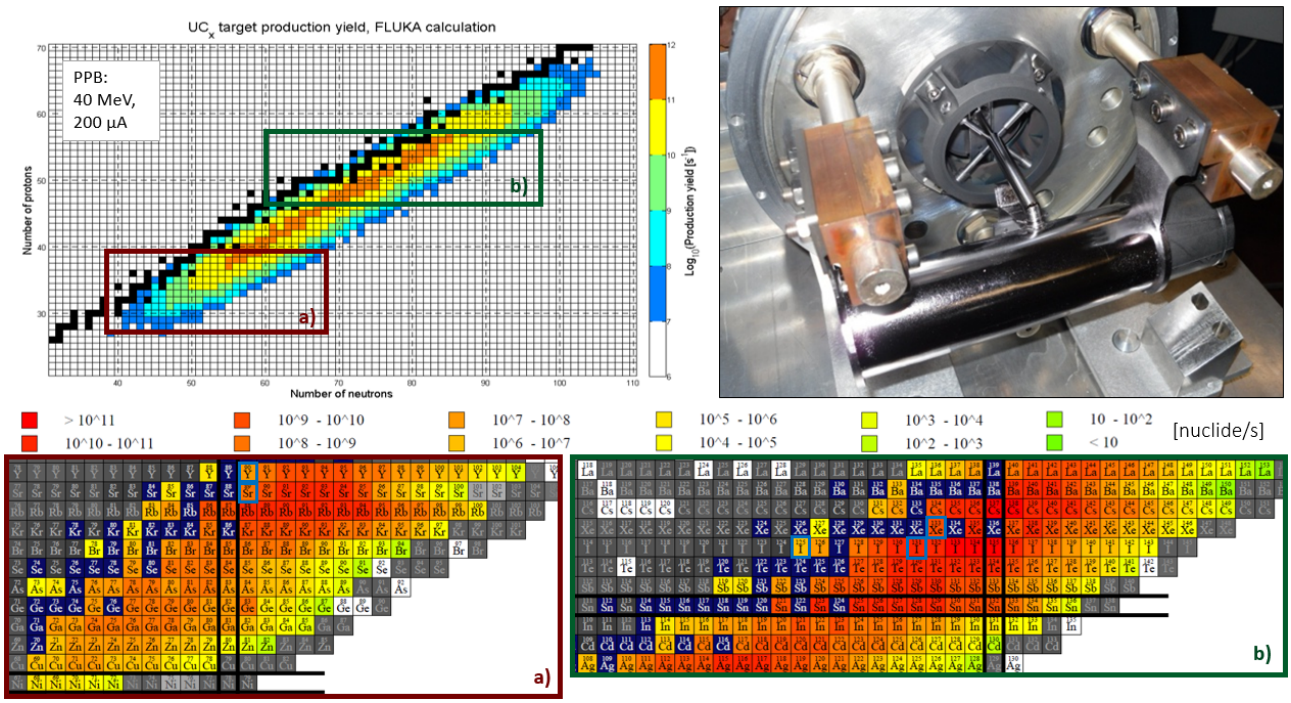

Figure 2: the production spectrum of SPES target according to FLUKA simulations, with focus on ^{89}Sr, ^{90}Y (a) and ^{125}I, ^{131}I, ^{133}Xe (b). On the top right a picture of the existing SPES target prototype, used for off-line tests.

THE UC$_X$ TARGET

In the framework of the SPES project a multi-foil uranium carbide target has been designed with the capability of generating approximately 10^{13} fissions when impinged by a 40 MeV 200 μA proton beam [9, 10].

The SPES production target is composed by 7 uranium carbide disks, characterized by a diameter and a thickness of 40 and 0.8mm, inserted opportunely spaced in a tubular graphite box. One of its extremities is closed with a thin graphite windows (0.2 mm thickness), which hinders the migration of the produced nuclei outside from the target, being alongside transparent to the proton beam. At the other side three dumping disks characterized by a thickness of respectively 0.8, 0.8 ,1 mm are capable to stop all the residual proton beam. (Fig. 3a)

The target complex is inserted into a tubular tantalum heater which provides both heat by Joule effect (heating current up to 1300 A) for target conditioning and the proper alignment to beam during irradiation. A tubular transfer line provides allows the migration of the produced isotopes towards the ion sources.

The design of such a target was developed making use of massive amount of numerical simulations, used for the estimation of both the production yields and the proton beam power deposition in the desired energy range, alongside with calculations for radioprotection purposes.

MCNPX and FLUKA are fully integrated Monte Carlo packages for the simulation of the transport and interaction of particles and nuclei with matter, which were used for these purposes. According to this numerical models SPES target production ranges between 80 and 160 amu (Fig. 2). The aforementioned models were also experimentally validated with appropriate tests at ORNL.

Table 1 summarizes the numerical results for the nuclides of medical interests (^{89}Sr, ^{90}Y, ^{125}I, ^{131}I, ^{133}Xe), which are produced by ^{238}U fission in SPES target, and have a validated medical application.

Table 1: SPES Target Production Yields - for nuclide of medical interest according to the two different codes, with a 200 μA 40 MeV proton beam

Isotope	FLUKA Calculated Yield
^{89}Sr	2.191*10^{9} nuclei/s
^{90}Y	3.458*10^{8} nuclei/s
^{125}I	2.47*10^{7} nuclei/s
^{131}I	1.027*10^{11} nuclei/s
^{133}Xe	6.143*10^{10} nuclei/s

According to the ISOL technique the migration of the produced nuclei towards the ion source is due to effusion and diffusion processes (Fig. 1), as a consequence high target temperatures are required in order to gain a sufficient release rate. In particular, SPES target was designed to work at temperatures above 2000°C, allowing the extraction of the majority of the produced nuclei (the extraction of highly refractory elements is not possible).

Thermal simulations of the target behavior were performed using the Finite Element Method software ANSYS®, considering as input the proton beam power deposition calculated with FLUKA.

The mechanical design of the target was consequently optimized in order to be capable to maintain the desired temperature level (2200-2300 °C), with the sole heating

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power coming from the proton beam. Figure 3b shows the calculated temperature field of the target when impinged by the proton beam.

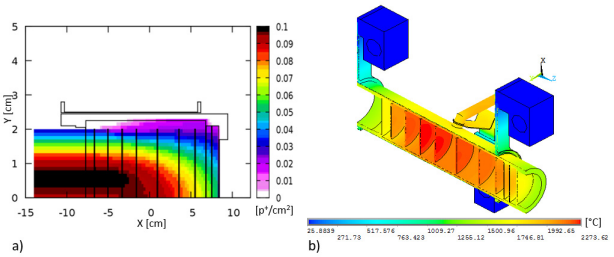

Figure 3: on the left (a) the plot of a FLUKA simulation, showing that the proton beam is entirely stopped in the target; on the right (b) the temperature field calculated with ANSYS® when the target is impinged by the proton beam.

A model for the description of the diffusion and effusion processes is being defined, taking into account the ANSYS® calculated temperatures, using Geant4, a Monte Carlo toolkit. It may lead to further optimization of the target design and to better knowledge of the overall isotope production efficiency.

THE NICKEL TARGET

^{64}Cu is a promising radioisotope currently under preclinical studies for theragnostic applications. It is commonly produced with medical cyclotrons impinging a proton beam on a nickel target via the ^{64}Ni(p,n)^{64}Cu reaction.

The production of high specific activity ^{64}Cu using the innovative ISOL technique may contribute significantly to this research activity, however, since SPES target will not produce copper isotopes, a new target concept is required.

An ISOL nickel target is currently under preliminary studies. Three different target layouts are being considered:

- a graphite foam target coated by thin layers of ^{64}Ni;
- a metallic foam nickel target, using natural nickel, which includes less than 1% of ^{64}Ni;
- a metallic foam nickel target, using enriched ^{64}Ni (around 99% of the total Ni mass used).

Foam targets were preferred because of the lower density, which may lead to a more spread proton beam power deposition, preventing the unwanted target local melting; and to shorter diffusion mean free paths, increasing the release efficiency.

The graphite foam target was soon discharged because of expected manufacturing complexity and lower calculated production.

Table 2 summarize the FLUKA calculated ^{64}Cuproduction for the three concepts, considering a 40 MeV 100μA proton beam entirely dumped in the production target.

As expected, the higher is the ^{64}Ni amount in the target, the higher is the ^{64}Cu production, however such an enriched ^{64}Ni production target is prohibitively costly.

Considering that the peak of the cross section for the ^{64}Ni(p,n) ^{64}Cu reaction is around 10 ÷ 12 MeV [11], a new target concept is being developed. It will combine a first section of natural nickel metallic foam for the degradation of the beam energy up to the preferable range, followed by a thin layer of ^{64}Ni where the beam energy is around 10 MeV, with another subsequent natural nickel section for beam stopping, thus exploiting the whole beam energy available.

Table 2: FLUKA Production Yields for ^{64}Cu - with a 100 μA, 40 MeV proton beam on different target concepts, considering 0.5 days of irradiation

Target Concept	FLUKA Calculated Yield
Natural Ni metallic foam	2.85*10^{14} nuclei/s
^{64}Ni enriched metallic foam	3.26*10^{16} nuclei/s

In addition, some tests are currently being performed for the evaluation of the optimal copper release temperature, with the aim to determine the target working temperature range.

THE SECONDARY TARGETS

A subsequent important issue is the definition of appropriate substrates for the development of the secondary target, where the extracted nuclei are implanted. The aforementioned substrates have to be capable of collecting the largest amount of the impinging radioactive ions and to release them with appropriate chemical dissolution processes.

In the framework of the preliminary tests for the ISOL-PHARM project, beams of stable isotope of strontium, yttrium and iodine were extracted for evaluating the efficiency of the secondary target. For strontium and yttrium sodium chloride substrates were used, whereas iodine was deposed on activated carbon targets (Fig. 4). Since the deposition efficiency is dependent only from the chemical properties of both the extracted element and the target substrate, the obtained results are valid also in case of radioactive isotopes.

Table 3 summarizes the deposition efficiencies obtained during the aforementioned tests. Other tests are being performed with the aim to increase the deposition efficiency.

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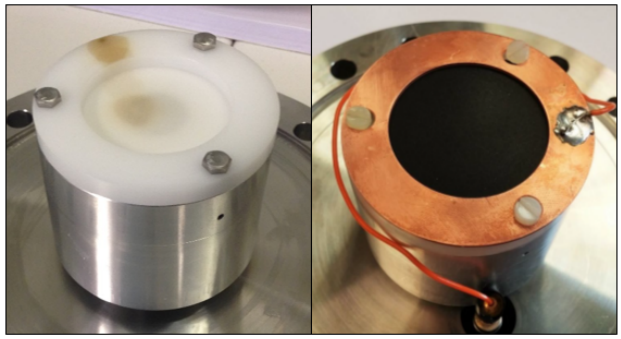

Figure 4: on the left a sodium chloride substrate for the deposition of strontium and yttrium, on the right (b) the activated carbon secondary target designed for iodine beams.

Table 3: Deposition Efficiencies Obtained in the Off-line Test Bench using Stable Isotopes Beams

Extracted Element	Secondary Target Substrate	Deposition Efficiency
Strontium	NaCl	41%
Yttrium	NaCl	55%
Iodine	Activated carbon	23%

CONCLUSIONS

It hasn't been possible yet to perform tests with RIBs since SPES facility is currently under construction.

Numerical simulations and first tests showed preliminary promising results. A large amount of the extracted ions was collected on the secondary target substrate, and chemical purification techniques are currently under investigation.

As first step this project will be focused on radionuclides which are already used or planned to be implemented in nuclear medicine. However, the ISOLPHARM method will afterwards explore the possibility of the application in nuclear medicine of further radionuclides, which were not possible to produce with the traditional techniques.

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