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Development of targets for the production of radionuclides of medical interest according to the ISOL technique

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Abstract

Radiopharmaceuticals, namely drugs having as core a radiation emitting nuclide, are one of the fundamental tools of nuclear medicine, being employed for both therapeutic and diagnostic procedures. The aforementioned radionuclide is bound to ligand that selectively accumulates into a target tissue, thus allowing a focalized treatment or precise imaging.

Research in the radiopharmaceutical field involves on one side the development of new ligands for specific cellular targets on the other side the discovery of the potential medical uses of innovative radionuclides. However, the widespread of novel medical nuclides is often limited by the lack of a suitable production technique, able to ensure a radionuclidic purity or a specific activity acceptable for the labelling of a pharmaceutical compound.

Thus, along with the development of conventional production routines, mostly accelerator – based or reactor – based, new approaches are emerging, such as MEDICIS at CERN and ISOLPHARM at INFN-LNL, both based on the use of electromagnetic mass separators to increase the achievable radionuclidic purity.

The main focus of this thesis is ISOLPHARM (ISOL technique for radioPHARMaceuticals), a project devoted to the discovery and development of high purity radiopharmaceuticals exploiting the radionuclides producible with the future SPES (Selective Production of Exotic Species) ISOL (Isotope Separation On-Line) facility at INFN-LNL. According the ISOLPHARM approach, a proton beam (up to 70 MeV), extracted from SPES cyclotron will directly impinge a primary target, inducing nuclear reactions. The so-produced species are then released from the target thanks to its high working temperature (2000°C), ionized with suitable ion sources, extracted into a beam and accelerated. Finally, thanks to the use of an electromagnetic mass separator, only the nuclei characterized by a given mass number are deposed on a secondary target. After the dissolution of the latter, a chemical purification step allows to recover among the collected isobars only the desired nuclides, thus without any isotopic contaminants that decrease their specific activity.

The strength point of such production method is the capability to produce a wide set of intrinsically carrier-free nuclides with high flexibility, since different radioisotopes can be extracted separately from the same production target by simply adjusting the settings of the

electromagnetic separator. In particular, ISOLPHARM could have the capability to provide never studied nuclides with medically relevant decay properties, such as ^{111}Ag, or isotopes for which there is a very limited availability with conventional techniques, such as ^{43}Sc, ^{47}Sc, ^{67}Cu, ^{149}Tb, ^{152}Tb and ^{155}Tb, once a suitable production target is identified.

In the presented work Uranium Carbide (UC_x) is proposed as production target for ^{111}Ag, Zirconium Germanide (ZrGe) for ^{67}Cu, along with ^{64}Cu, Titanium Carbide (TiC) or Titanium Boride (TiB_2) for ^{43}Sc and ^{47}Sc, and Gadolinium Boride (GdB_4) for ^{149}Tb, ^{152}Tb and ^{155}Tb. The feasibility of the production of the desired nuclides was subsequently evaluated by means of Monte Carlo codes, in particular FLUKA and Geant4, and promising yields were calculated. Furthermore, in the case of the ZrGe target, provided the lack of experimental measurements on the ^{nat}Ge(p,X)^{64}Cu and ^{nat}Ge(p,X)^{67}Cu reactions, dedicated nuclear cross section studies were performed.

In addition to the numerical evaluation of the produced in-target amounts, the feasibility study included also the performance of tests with stable counterparts of the desired nuclides, aimed to investigate the capability of SPES technologies to ionize, accelerate and selectively collect single isotopes of the elements of interest. Thus, at SPES offline laboratories it was possible to successfully ionize and collect stable beams of Silver and Copper, and the efficiencies of such processes were measured. In addition, preliminary ionization tests with Scandium and Terbium were performed.

Finally, a complex model with Geant4 was developed with the aim to simulate the release of the produced species and their migration towards the ion source, processes dominated by the effusion and diffusion phenomena, and preliminary run were performed. However, being such model computing intensive, an adequate IT (Information Technology) infrastructure was developed in CloudVeneto, a Cloud service of the IaaS (Infrastructure as a Service) family owned by INFN and UNIPD.

Riassunto

I radiofarmaci, ossia formulazioni mediche che includono un radionuclide, sono uno degli strumenti fondamentali della medicina nucleare, impiegati sia per le applicazioni diagnostiche, sia per quelle terapeutiche. In essi, il radionuclide è veicolato da un ligando, una molecola che si accumula selettivamente in un tessuto target, consentendo quindi un'azione terapeutica mirata o un imaging accurato.

La ricerca nel campo dei radiofarmaci ha come obiettivo da un lato lo sviluppo di nuovi ligandi per target cellulari specifici, dall'altro la scoperta del possibile uso in medicina di radionuclidi innovativi. Tuttavia la diffusione di tali nuovi isotopi di interesse medico è spesso limitata dalla mancanza di una tecnica di produzione adeguata, in grado di garantire un grado di purezza radionuclidica o un livello di attività specifica idonea per la radiomarcatura di composti farmaceutici. Pertanto, in aggiunta alle procedure convenzionali di produzione, per lo più basate sull'uso di acceleratori o reattori, nuovi approcci stanno emergendo, come quello proposto al CERN con la facilty MEDICIS o il progetto ISOLPHARM presso INFN-LNL, entrambi basati sullo sfruttamento di separatori di massa elettromagnetici per aumentare la purezza radionuclidica ottenibile.

Questo lavoro di tesi è principalmente focalizzato su ISOLPHARM (ISOL technique for radioPHARMaceuticals), un progetto che ha come obiettivo lo sviluppo di nuovi radiofarmaci, estremamente puri, sfruttando i nuclidi producibili a SPES, (Selective Production of Exotic Species), una futura facility ISOL (Isotope Separation On-Line) in costruzione presso INFN-LNL. Secondo il metodo ISOLPHARM, un fascio di protoni con energie fino a 70 MeV, estratto dal ciclotrone di SPES, viene inviato su un bersaglio solido, inducendo reazioni nucleari. Si producono così un set di radionuclidi, che sono poi rilasciati, grazie alle elevate temperature del bersaglio (2000°C), ionizzati con opportune sorgenti di ionizzazione, estratti in un fascio e accelerati. Infine, mediante l'utilizzo di un separatore di massa elettromagnetico, solamente i nuclidi caratterizzati da un determinato numero di massa sono raccolti in un target secondario. Dopo lo scioglimento di quest'ultimo, uno step finale di purificazione chimica consente di estrarre tra gli isobari raccolti esclusivamente i nuclidi di interesse, senza gli eventuali contaminanti che ne riducono l'attività specifica.

Il punto di forza di questo metodo è la capacità di produrre una grande varietà di radionuclidi intrinsecamente carrier-free in modo flessibile, dal momento che diversi isotopi possono essere estratti separatamente dallo stesso target di produzione, variando semplicemente le impostazioni del separatore di massa. In particolare, il metodo ISOLPHARM potrebbe essere usato per fornire nuclidi mai studiare, ma con proprietà di decadimento promettenti per la medicina nucleare, come ^{111}Ag, o isotopi le cui disponibilità con le tecniche convenzionali è molto limitata, come ^{43}Sc, ^{47}Sc, ^{67}Cu, ^{149}Tb, ^{152}Tb e ^{155}Tb, dopo aver identificato un opportuno bersaglio di produzione.

In questo lavoro si propone il Carburo di Uranio (UC_x) come target per la produzione di ^{111}Ag, il Germaniuro di Zirconio (ZrGe) per il ^{67}Cu, assieme al ^{64}Cu, il Carburo di Titanio (TiC) o il Boruro di Titanio (TiB_2) per ^{43}Sc and ^{47}Sc, e il Boruro di Gadolinio (GdB_4) per ^{149}Tb, ^{152}Tb and ^{155}Tb. La fattibilità della produzione dei nuclidi di interesse è stata quindi valutata per mezzo di simulazioni con codici Monte Carlo, in particolare FLUKA e Geant4, ottenendo rese promettenti. Inoltre, nel caso particolare del target in ZrGe, verificata la mancanza di misure sperimentali per le reazioni ^{nat}Ge(p,X)^{64}Cu e ^{nat}Ge(p,X)^{67}Cu, le sezioni d'urto in esame sono state studiate.

In aggiunta alle valutazioni numeriche circa le quantità di nuclide d'interesse prodotte nei diversi target, lo studio di fattibilità ha riguardato anche l'esecuzione di test con le controparti stabili dei nuclidi di interesse, volti a verificare l'effettiva possibilità di ionizzare, estrarre e collezionare selettivamente singoli isotopi degli elementi selezionati, sfruttando le tecnologie di SPES. Presso i laboratori offline di SPES, è stato quindi possibile ionizzare e raccogliere fasci stabili di Argento e Rame, e le efficienze coinvolti in tali processi sono state misurate. Inoltre, test preliminari sulla ionizzazione dello Scandio e del Terbio sono stati eseguiti.

Infine, un complesso modello Geant4 è stato sviluppato con l'obiettivo di simulare il rilascio delle specie prodotte nel target e il loro spostamento verso la sorgente di ionizzazione, processi regolati dai meccanismi di diffusione ed effusione, e alcuni run preliminari sono stati eseguiti. Tuttavia, trattandosi di simulazioni richiedenti grandi risorse di calcolo, si è reso necessario lo sviluppo di un'adeguata infrastruttura di IT (Information Technology), basata su CloudVeneto, un servizio Cloud della famiglia IaaS (Infrastructure as a Service) di proprietà di INFN e UNIPD.

Introduction

"Δοκεῖ δὲ αὐτῶι τάδε ἀρχὰς εἶναι τῶν ὅλων ἀτόμους καὶ κενόν, τὰ δ'ἄλλα πάντα νενομίσθαι."

"The first principles of the universe are atoms and empty space; everything else is merely thought to exist."

Diogenes Laërtius (biographer of the Greek philosophers, fl. 3rd century AD), *Democritus*, Vol. IX, 44

It is difficult to conceive modern medical procedures without the ability to visually access any bone, any soft tissue and potentially any part of the human body. Such practice was not possible until the end of 19th century, when radiography was fortuitously discovered by Wilhelm Conrad Röntgen in 1895 [1]. In the 20th century the discoveries of different forms of radioactivity and the existence of unstable nuclei further promoted and boosted new lines of research. In example Marie Curie encouraged the use of radioactive radium to treat a wide range of diseases, from cancer to nervous illnesses [2], thus preparing the ground for modern nuclear medicine. Nowadays nuclear medicine is a fundamental branch of medicine for diagnosis and treatment of tumor diseases.

As fundamental tool for nuclear medicine procedures, radiopharmaceuticals are unique medicinal formulations containing radionuclides, and are used in various clinical areas for diagnosis and/or therapy. Such radionuclides are bound to a ligand, which selectively accumulates into a target tissue allowing either a precise imaging or a focalized treatment.

Therefore, progress in the research in the radiopharmaceutical field can be accomplished on one side by the discovery of the potential medical uses of innovative radionuclides on the other side by the development of new ligands.

In such framework, ISOLPHARM is a multidisciplinary project, aiming on one hand to study a new and unconventional method for the production of pure radionuclides based on the ISOL (Isotope Separation On-Line) [3], [4]technique, on the other hand to develop a new generation of ligands. As one of the applications of the SPES project (Selective Production of Exotic Species), ISOLPHARM will exploit the Radioactive Ion Beams (RIBs) produced in the future ISOL SPES facility at the Legnaro National Laboratories (LNL) of the Italian National Institute for Nuclear Physics (INFN) [5].

According to the ISOL technique, radioisotopes are produced by impinging a target with a primary beam, and are subsequently released thanks to the high working temperatures (generally 2000°C). The produced species migrates towards an ion source where they are ionized and extracted forming the aforementioned RIB. Such beam is accelerated and mass separated thus obtaining an isobaric beam, which can finally be collected into a dedicated deposition target. After the dissolution of the latter, a final step of chemical purification can be performed in order to harvest selectively only the desired isotope, hence collecting a "carrier-free" product, namely free from any isotopic contaminant. Such purity should be regarded as particularly relevant because it can be achieved easily and inexpensively thanks to the aforementioned mass separation step.

"Carrier-free quality" radionuclides are remarkably sought as radiopharmaceuticals precursors. Indeed, in the last decades of research in radiopharmaceutical sciences, efforts were made for the development of new receptor targeting radiometal labelled pharmaceuticals [6]. Such radiopharmaceuticals are essentially composed by a biomolecule linked to a radiometal. The biomolecule acts as vector, since it exhibits molecular complementarity with a membrane protein that is overexpressed on the surface of cancer cells, allowing consequently the accumulation of the radiation in the tumor tissue. Since the binding with the aforementioned cell receptors can be easily saturated, the efficacy of the radiopharmaceutical is affected if it is diluted with cold compound. As a consequence, biomolecules labelled with "carrier-free" radionuclides can optimize the accumulation of radiation to the target organs [7].

Thanks to its intrinsic flexibility, the ISOL technique allows the production of a wide range of Radioactive Ion Beams, which, if opportunely collected with an appropriate deposition target, can provide amounts of "carrier free" radiometals. At INFN-LNL, depending on the primary target, and consequently on the induced nuclear reactions, several radioisotopes of medical interest can potentially be produced. In addition to the nuclides with applications already in clinical stage, as in example ^{89}Sr [8], ^{125}I [9], ^{131}I [10], ^{90}Y[11], and ^{177}Lu [12], many other innovative isotopes can be harvested, such as ^{111}Ag [13], ^{43}Sc, ^{47}Sc [14], ^{64}Cu [15], ^{67}Cu [16], ^{149}Tb [17], ^{152}Tb [18] and ^{155}Tb [19].

Because of its founding multidisciplinary, many competences are involved in the ISOLPHARM project [20]. Nuclear physics studies on the expected nuclear reactions, material science and engineering developments of the desired production targets, accelerators physics as well as mechanical implementation of the beam lines are essential ingredients for the RIBs production. Afterwards, for the collection of such RIBs on the deposition targets and the subsequent desired isotopes harvesting, chemical and pharmaceutical developments are required. Subsequently, pharmaceutical studies are necessary for the radiolabelling of biological vectors for the production of a radiopharmaceutical, aiming to the optimization of the ligands characteristics to improve the diagnostic and therapeutic features. Finally, biological studies aiming to verify the receptor-affinity and the cell internalization, measure the pharmacokinetic properties and minimize the side effects are part of the development of a radiopharmaceutical.

In this work the potential use of the SPES ISOL facility under construction at LNL for the production of medical radionuclides is presented into detail.

Chapter 1 presents the current state-of-art of the medical application of radionuclides, along with the conventional production routines. In particular, SPECT (Single Photon Emission Computed Tomography) [21] and PET (Positron Emission Tomography) [22] are the main diagnostic medical procedures involving radiopharmaceuticals, whereas Targeted Radionuclide Therapy (TRT) [23] is regarded as the most promising therapeutic application. Concerning the radionuclides production procedures, the routinely used methods are the production in nuclear reactors, especially for therapeutic radioisotopes, the accelerator- based techniques, used mainly in Small Medical Cyclotrons (SME) for the production of diagnostic nuclides, and the extraction from generators, that exploit the decay of a long-lived parent nucleus.

Along these conventional techniques, together with the increasing interest in emerging radionuclides, other unconventional methods are being explored. Such approaches, based on the electromagnetic mass separations for the achievement of a carrier-free production, are being developed at CERN, where the newly built MEDICIS facility [24] has been operating as a spin-off of ISOLDE [25], and at LNL-INFN, where the SPES-ISOLPHARM project is being studied.

Chapter 2 is devoted in particular to the detailed description of the SPES facility and the innovative patented ISOLPHARM project. Since according to the ISOLPHARM method al large variety of nuclides is easily producible in carrier-free form, a new generation of radiopharmaceuticals can be developed, by employing nuclides that were less studied, since conventional techniques were not capable to provide them with reasonable radionuclidic purity. That is the case of ^{111}Ag, a promising therapeutic nuclide. In such framework, the collaboration project ISOLPHARM_Ag is aimed to evaluate the feasibility of radiopharmaceutical labelled with such radiometal, considering both the estimation of the producible amounts at SPES and

the design of proper pharmaceutical compounds for its administration. In particular, regarding the achievable production of ^{111}Ag, a feasibility study was performed and is summarized in chapter 3. Indeed, such nuclide can be produced with the SPES multi-foil UC_x target, and Monte Carlo simulations were used to calculate the in-target yields. Furthermore, as foreseen by the ISOLPHARM technique, the capability of SPES technologies to extract, transport and collect ^{111}Ag had to be carefully evaluated, thus offline tests performing the ionization and collection of stable Silver beams were performed.

Among the other radionuclides of medical interest that could be produced with the ISOL technique, ^{64}Cu and ^{67}Cu are a promising theranostic pair [26], being the first suitable for PET applications and the latter a promising therapeutic nuclide, whose production with conventional techniques is extremely challenging. Therefore, as reported in chapter 4, a preliminary study was performed to evaluate its feasibility at ISOLPHARM [27]. In particular, ZrGe was proposed as ISOL target material, and the expected yields were calculated with Monte Carlo codes. Given the lack of reference experimental data for the nuclear reactions ^{nat}Ge(p,X)^{64}Cu and ^{nat}Ge(p,X)^{67}Cu, various models were considered to evaluate the reliability of the calculated yields. Furthermore, the feasibility foresaw also the ionization and collection of stable Copper beams with the SPES technology, to evaluate the efficiency of such processes, as done for Silver.

Chapter 5 was focused on the evaluation of the possibility to produce with ISOLPHARM the theranostic pair ^{43}Sc, ^{47}Sc [14] for which difficulties to develop an accelerator-based production were highlighted. In such case Titanium Carbide or Titanium Boride were proposed as target, and the production yields were calculated with Monte Carlo simulations. Very preliminary ionization tests with stable Scandium were also performed.

In addition to the already presented nuclides, among the radiolanthandes a unique quadruplet of Terbium radionuclides, namely ^{149}Tb, ^{152}Tb, ^{155}Tb and ^{161}Tb are extremely interesting and were tested *in vivo* with promising results [28]. However, with exception of the latter, their production with traditional techniques is not feasible. Thus, as reported in chapter 6, a preliminary study for the ISOLPHARM production of ^{149}Tb, ^{152}Tb and ^{155}Tb from a Gadolinium Boride target was performed. As in the other cases, Monte Carlo simulations were used to estimate the in-target yields and the capability to ionize stable Terbium with the SPES technologies was tested.

The ISOL technique is a complex method, as declared in chapter 7. Indeed, the desired nuclides are firstly generated in target through nuclear reactions induced by the primary beam, subsequently they diffuse through the target material and then effuse in vacuum towards the ion source. There they are ionized, extracted and then mass separated, and finally transported as a

beam to the desired experimental hall. Whereas the yields are normally calculated with dedicated Monte Carlo codes, and the ionization and transport of the desired nuclides can be evaluated with offline test with their stable counterparts, the diffusion and effusion processes, namely the release, are difficult to predict. Thus, a complex model with Geant4 [29] was developed with the aim to estimate the release efficiency, and first run were performed. However, being computing intensive, an adequate IT infrastructure was developed for it in CloudVeneto, a Cloud service of the IaaS (Infrastructure as a Service) family owned by INFN and UNIPD.

Finally, appendix A includes a list of the ISOL nuclides of possible medical interest, appendix B describes the apparatus developed for the collection targets for ISOLPHARM, whereas appendix C provides more detail on the numerical study of the cross sections for the $^{nat}Ge(p,X)^{64}Cu$ and $^{nat}Ge(p,X)^{67}Cu$ reactions.

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Chapter 1

Radionuclide production for applications in nuclear medicine

“Ἐς δὲ τά ἔσχατα νοσήματα αἱ ἔσχαται θεραπεῖαι ἐς ἀκρίβειαν κράτισται.”

“For extreme diseases, extreme methods of cure, as to restriction, are most suitable.”

Hippocrates of Kos (Greek medic, c. 460 – c. 370 BC), *Aphorisms*, I, 6

1.1 Introduction

The accidental discovery of radiography, performed in 1895 by the German scientist Wilhelm Conrad Röntgen [1.1], is nowadays considered a turning point for the modern medical procedures. Indeed, thanks to such invention it was possible for the first time to visually inspect interior organs, thus providing fundamental information for the choice of the most suitable treatment. Such discovery rapidly spread out worldwide and several medical radiographs had been made in Europe and the United States, which were used by surgeons to guide them in their work, thus representing the first application of radiation in medical procedures.

In the 20th century subsequent discoveries led to a better comprehension of radioactive phenomena, since the different radiation types were identified, and radioactive decay models were theorized and experimentally verified. Furthermore, the discovery of a wide range unstable nuclei and the invention of technologies for their artificial production further promoted and boosted new lines of research in many fields of science. Marie Skłodowska Curie, for example, was one of the first promoters of the medical application of unstable nuclei. Indeed, she encouraged the administration of drugs based on radioactive radium, discovered by herself and her husband Pierre Curie in 1898, to improve the health status in case of in case a wide

range of ailments, including nervous illnesses. She also observed the benefits of radium salts based treatments in case of various cancerous diseases [1.2], thus preparing the ground for modern nuclear medicine procedures.

Nowadays nuclear medicine is a fundamental branch of medicine, with significant applications in both diagnosis and treatment of tumor diseases. In such framework, radiopharmaceuticals are one of the fundamental tool for nuclear medicine procedures. Indeed, such unique medicinal formulations containing radionuclides are nowadays used in various clinical areas for diagnosis and/or therapy, thanks to their capability to selectively accumulates into a target tissue allowing either a precise imaging or a focalized treatment.

The production of radioisotopes, which are the radioactive "core" of radiophanrmaceuticals, is a very crucial step, since it can affect the quality of the radiopharmaceutical, and consequently the efficacy of the diagnosis and/or treatment.

In the following chapter radiopharmaceuticals are presented in detail along with the state-of-art of the main production routes of medical isotopes.

1.2 Radiopharmaceuticals: radionuclides for diagnosis and therapy

As previously introduced, radiopharmaceuticals are a type of pharmaceutical drugs, which include a radiometal, whose emitted radiation can be exploited for diagnostic and therapeutic purposes. Typically, the structure of a radiopharmaceutical includes three functional components, a chelator, a linker and a targeting agent, as schematized as showed in figure 1.1. The chelator is a molecule capable of carrying the selected radioisotope, usually a metal, thanks to coordination bonds. Such bonds have to be stable after administration, in order to avoid the so-called transchelation phenomenon, meaning that the nuclide is released and substituted by other ions normally present in human body, thus affecting the efficacy of the drug since radiation is not delivered to the disease site. The linker is a molecule capable to bind the chelator with the targeting agent. It is called also spacer because it acts as separation between the latter two, avoiding their reciprocal influence that might affect their effective *in-vivo* behaviour.

The targeting agent is a molecule developed to interact with the cancer cells according to the lock and key model [1.3], meaning that it is selectively recognized by specific cellular receptors, normally present on the cellular membrane and over expressed only by disease cells. Since such cellular target might be easily saturated, the effectiveness of the radiolabelling of the radiopharmaceutical can significantly affect the efficacy of the diagnosis or treatment. The radiolabelling of the drug molecules is more efficient if highly pure radionuclides are used.

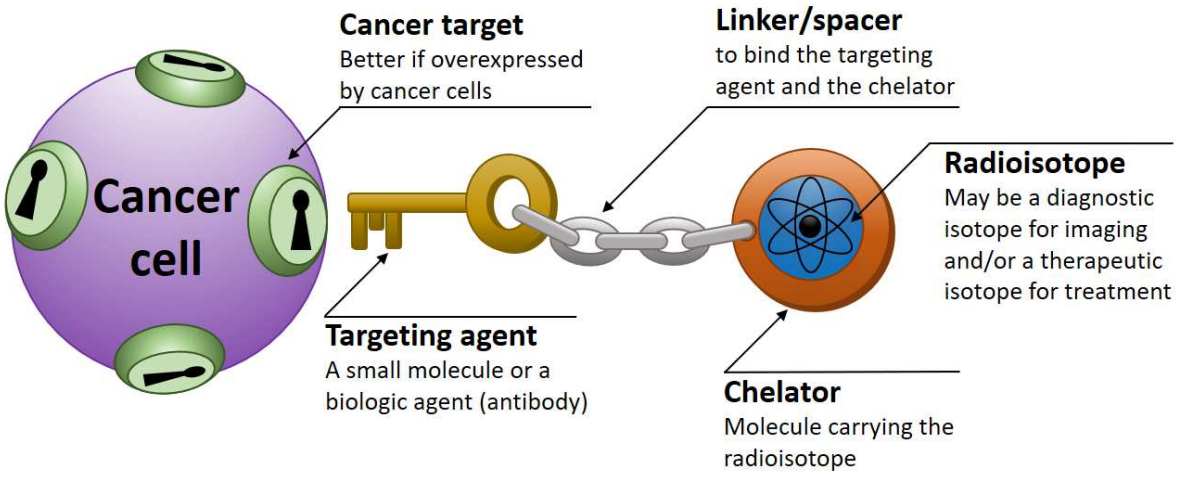

***Figure 1.1**: Schematic representation of a radiopharmaceutical according to the lock and key model*

Generally, the medical radionuclides should meet specific requirements to be clinically employed [1.4]:

- Suitable physical properties for its application in terms of half-life ($t_{1/2}$), decay mode, emission energy;
- Suitable chemical properties for labelling processes, with high radiochemical yields;
- Acceptable dose delivered to the patient, considering the needed image quality or therapeutic effect;
- A reasonable price.

In addition to such requirements, high quality nuclides are the most desirable radiopharmaceutical precursors. For such reason, the quality of the radionuclides is normally evaluated by means two properties: the specific activity and the radionuclidic purity.

The specific activity of a radioisotope is defined as the ratio between the activity of the radioisotope (MBq) and the mass of the element (mg). Such concept important, since the radionuclide of interest might be diluted by mixtures of other "cold" isotopes of the same element often, coming from the adopted production routine, and, being stable, do not exert any effect. Radioisotopes with high specific activities are referred as "carrier-free" and are fundamental for radiolabeling of ligands that target easily saturable tumor markers on cells. Differently, those diluted by cold mixtures of the same element are defined as "carrier-added", and have low specific activity.

The second essential parameter to control the quality of the radiopharmaceutical is the radionuclidic (defined also as radioisotopic) purity. It is defined as the ratio between the activity of the desired radionuclide and total activity of a radioactive compound, and thus it is referred to the presence of other radioactive species within the pharmaceutical preparation. A compound has absolute radionuclidic purity if it contains no radionuclide other than the one of interest.

In the following paragraphs the diagnostic and therapeutic use of radiopharmacuticals will be discussed in detail.

1.2.1 The diagnostic applications of radiopharmaceuticals: SPECT and PET

The most common diagnostic applications of radiopharmaceutical compounds are the Single-Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). Such diagnostic procedures are fundamental tools not only for early diagnosis but also for prognosis and monitoring of progress, regression or stagnation of a certain disease upon application of a particular therapy [1.5].

SPECT has been available since 1980, and is currently widely employed for detecting molecular changes in cardiovascular, neurological and oncological diseases [1.6]. Furthermore, the interest in SPECT has currently grown, since advances in the detectors technologies allow to increase the accuracy of the obtained images.

The SPECT imaging technique requires the delivery to the patient of a γ emitter nuclide, in the form of a biomolecule or a radiopharmaceutical, normally through the injection into the bloodstream. The out-coming radiation is successively detected through SPECT-cameras (large scintillation crystals connected to Photo-Multiplier Tubes, PMTs), and the resulting signals are further elaborated thus obtaining a 3D image of the distribution of the radionuclide within the patient body [1.6].

Generally, the suitable nuclides are selected according to their half-lives and radiation properties, and the ideal radiation energy range should be chosen according to the application. As general principle, the γ ray energy should be high enough to emerge from the patient's body but low enough to be fully absorbed by medium-size crystals, whereas the radiation intensity should be as high as acceptable in order to increase the imaging accuracy. In addition, the nuclides that emit exclusively radiation within the application range are strongly recommended, in order to reduce the dose delivered to patients.

SPECT-cameras are normally provided with collimators, that selectively absorb almost all γ rays coming from any direction different than the chosen one. Such filtering of the out-coming radiation is indeed necessary to allow the reconstruction the spatial distribution of the injected radiopharmaceutical. By acquiring many views of patients from different angles, it is then possible to reconstruct the complete 3D distribution of the employed radionuclide.

The speed of acquisition may have an important effect on the quality of the resulting image: indeed, the unavoidable motion of the patient himself or of his organs influences the effectiveness of the merging of scans from different angles. In some cases, in order to increase

the speed of acquisition, multi-headed cameras are used, thus partially attenuating the aforementioned problem.

An additional recent improvement, is the fusion of CT (Computed Tomography) with SPECT, allowing thus to combine the functional information of the cellular metabolism coming from SPECT with the tissues and organs morphological information coming from CT [1.6]. Furthermore, the recent advances in collimator design and in the software and reconstruction algorithms, together with the replacement of the sodium iodine (NaI) crystals with the more effective cadmium zinc telluride (CZT) detectors, confirmed SPECT as a fundamental technology in diagnosis procedures [1.6].

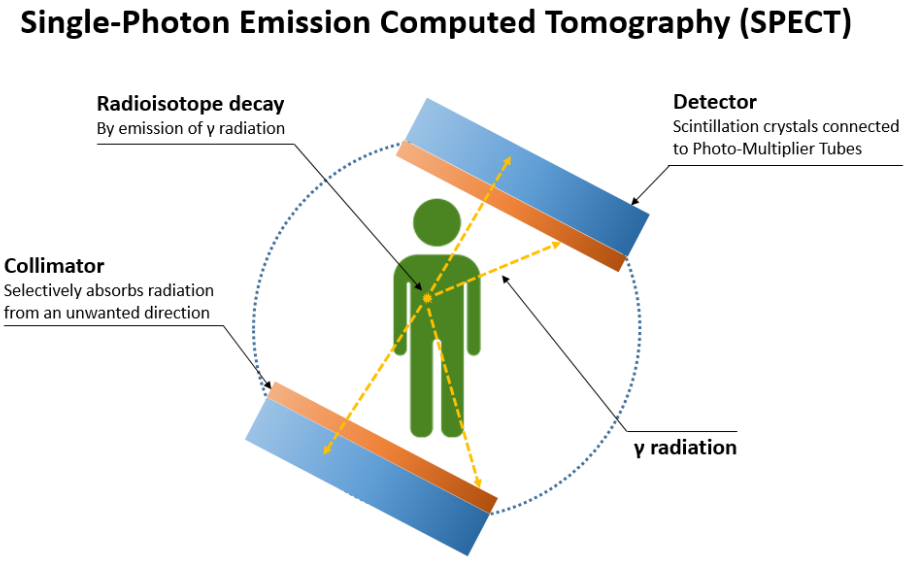

Figure 1.2: *schematic principle of SPECT*

The SPECT commonly used radiotracers have relatively long half-lives from a few hours to a few days (^{99m}Tc $T_{1/2}$ = 6.0 h; ^{111}In $T_{1/2}$ = 67.3 h; ^{123}I $T_{1/2}$ = 13.3 h; ^{201}Tl $T_{1/2}$ = 72.9 h) and their employment can be adapted to the specific application being investigated. However, ^{99m}Tc is still the most commonly used SPECT radionuclide [1.7], employed for approximately 30 million diagnostic procedures worldwide each year [1.8]. Indeed, it emits mostly 140.511 keV photons (I = 89%), thus in the ideal energy range, and causing the least dose to the patients. In addition, the use of the ^{99}Mo/^{99m}Tc generator systems makes it available even in structures not equipped with a nuclide production facility and the versatile complex formation chemistry of Technetium allowed the development of various different compounds, thus targeting almost all the major body organs like brain, liver, bone, lungs, kidney, heart.

PET applications foresee the exclusive employment of radiopharmaceuticals labelled with a β^+-emitter. The emitted β^+ particle is indeed unstable and annihilates with an electron in few millimeters from the emission point, generating two quasi-opposite 511 keV -rays. PET cameras working principle is similar to SPECT; but in such case the PMTs are not equipped

with collimators, since the detection in coincidence of both -rays simply define their Line Of Response (LOR). Indeed, all signals not having an opposite counterpart are neglected when the PET image is reconstructed by the software.

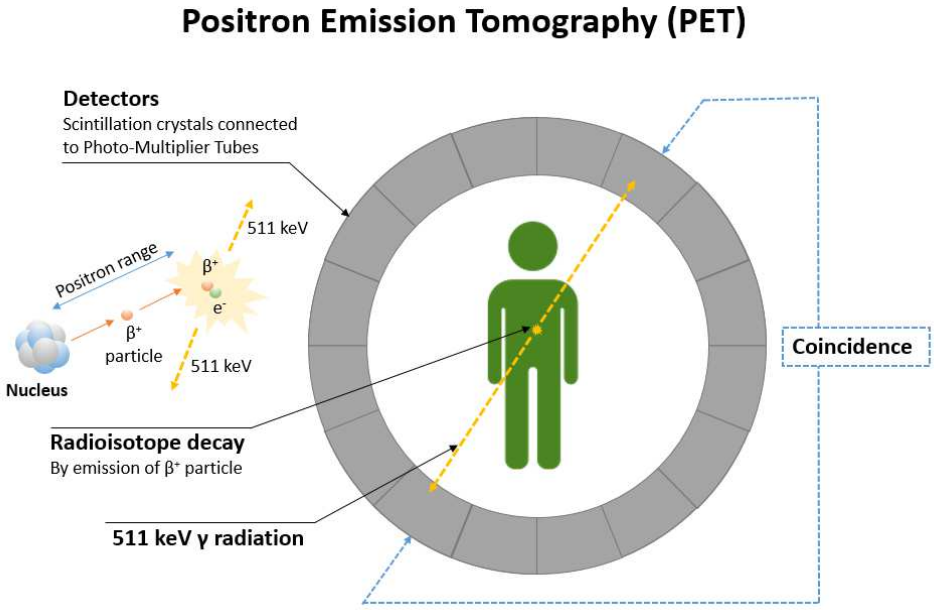

Figure 1.3: *schematic principle of PET*

The most used nuclide for PET applications is ^{18}F ($T_{1/2}$ = 109.77 min), normally produced in small size hospital cyclotrons. The use of PET was indeed boosted in the mid-1970s with the development of ^{18}F-deoxyglucose (FDG), allowing the generation excellent quality PET images of the brain, the heart and tumours [1.9]. Anyway, in addition to ^{18}F, many other radionuclides are nowadays used in PET, such as ^{11}C ($T_{1/2}$ = 20.334 m), ^{13}N ($T_{1/2}$ = 9.965 m) and 68Ga ($T_{1/2}$ = 67.71 m), as well as other non-standard positron emitters, under development [1.10, 1.11].

As in the case of SPECT/CT, even for PET combined imaging methods were developed, in particular PET/CT and PET/MRI (Magnetic Resonance Imaging). Such solutions allowed to significantly improve the quality of PET images, since the functional PET information is merged and compared to the anatomical image. In particular, for oncology applications, PET/CT has completely replaced PET, whereas clinical applications of PET/MRI are currently under development, since such technology is not yet fully mature [1.12].

Thanks to the very high sensitivity of modern SPECT and PET cameras, diagnostic procedures require an extremely small amounts of radiopharmaceuticals to be injected in a living organism. However, since the resolution of these cameras is in the range of mm, the accuracy of the functional image is limited. As a general consideration PET, that relies on a monochromatic radiation, allows better quantification than SPECT, that has some limitation in resolution linked to the strong attenuation of the 140 keV -line and to the collimator size.

Research towards the physically possible limits for scintillation cameras can overcome the limitations in resolution of current devices, and ensure a constant improvement. However, in case of PET the achievable spatial resolution is limited by the fact that the β^+ particle annihilation occurs in about few millimeters around the emission point.

1.2.2 The therapeutic application of radiopharmaceuticals: Targeted Radionuclide Therapy and Theranostics

Various therapeutic strategies involve the use of radiation, either administrated from external sources, or delivered internally into the human body by inserting radionuclides.

Radiation therapy, in example, can be performed thanks to the irradiation of the targeted organ with electron beams [1.13], x-rays and γ-rays from radioactive sources (such as ^{60}Co) [1.14], high-energy γ-rays from accelerators or hadrons as neutron, protons and heavy ions (in such case the treatment is referred as hadron therapy) [1.15]. In the case of brachytherapy, instead, a liquid (conglomerates or colloids) or solid (as seeds) radiation source is surgically inserted directly into the targeted organ, and is left in the patient's body in order to exert the desired therapeutic effect [1.16].

The less invasive and one of the most promising therapeutic application of radiation is the Targeted Radionuclide Therapy (TRT) [1.17], that consists in the selective delivery of a radionuclide in proximity of a certain tumor, performed thanks to a biological vector, thus a radiopharmaceutical. The transported radionuclide emits energetic particles (α, β^- or Auger electrons) towards the targeted cell, inducing damage, thus, ideally, TRT delivers a high amount of radiation dose selectively to cancer cells, sparing therefore other healthy tissues.

Depending on the size, type and position of the tumor, the radionuclide used in TRT has to be chosen considering both its half-life, that has to be compatible with the biological half-life of the chosen vector, and its emitted radiation. As an example, nuclides that decay emitting β^- particles with energies up to 1 MeV, are suitable to treat macro-clusters cells, since such radiation is dissipated over 1 to 10 mm, having low Linear Energy Transfer (the cross-fire effect is often exploited, to damage the less accessible core of the cancerous cluster) [1.18], whereas, up to 6 MeV energy α particles emitters are more appropriate for isolated metastatic cells or micro-clusters, since such radiation has high Linear Energy Transfer (LET) and is absorbed within 0.1 mm [1.19]. Finally, Auger electron emitters are generally used to label molecules, such as monoclonal antibodies, that are internalized by tumor cells, where the emitted low-energy electrons can reach the nuclear DNA of the only hosting cell, thus sparing the surrounding healthy tissues, thanks to their very short path length [1.20].

As the integration of therapy and diagnosis, theranostics is an evolving new approach, with potentiality to increase the efficacy of the treatment. Indeed, it foresees the use of the same bio-vector, labelled either with a nuclide, such as ^{67}Cu, that emits radiation both suitable for therapy (such as α or β^- particles) and diagnostics (as γ radiation), or with pairs of isotopes of the same element, such as ^{44}Sc/^{47}Sc, ^{64}Cu/^{67}Cu, ^{124}I/^{131}I, being the first one suitable for diagnostics applications and the second one adapt for therapy, but sharing the same chemical properties [1.21]. In such way it is possible to perform preliminary dosimetry studies, to evaluate in advance the patient response by observing the bio-distribution of the selected targeting agent and finally monitor the efficacy of the treatment.

1.2.3 Commonly used radionuclides in nuclear medicine

As already introduced, some radionuclides have interesting decay and chemical properties that make them suitable either for diagnostics or therapy.

Regarding the diagnostic applications, the fundamental principle is that the radiation dose to the patient has to be as low as possible, compatible with the required quality of imaging and the diagnostic advantage in comparison to other non-radioactive methods. In addition, nuclides with half-life of order of magnitude of hours are generally preferred.

Considering such requirements, the most used nuclei in Single Photon Emission Computed Tomography (SPECT), are the γ-ray emitting ^{99m}Tc ($T_{1/2}$ = 6.0 h), ^{123}I ($T_{1/2}$ = 13.2 h) and ^{201}Tl ($T_{1/2}$ = 3.06 d) [1.22]. In Positron Emission Tomography (PET), on the other hand, short-lived β^+-emitting radionuclides find often application, and among those ^{11}C ($T_{1/2}$ = 20.4 min), ^{13}N ($T_{1/2}$ = 10.0 min), ^{15}O ($T_{1/2}$ = 2.0 min), ^{18}F ($T_{1/2}$ = 110 min), ^{68}Ga ($T_{1/2}$ = 68.3 min) and ^{82}Rb ($T_{1/2}$ = 1.3 min) are the most common, with are either in-situ produced or available through the generator system. [1.23]

Regarding therapeutic applications, the variety of commonly used radionuclides is wider. In particular, as already clarified, radionuclides emitting low-range highly-ionising radiation, such as α or β^- particles, conversion and/or Auger electrons, are mostly used, since the radiation dose has to be localised and limited to the malignant or inflammatory tissue. The half-life of such nuclides is generally longer, coherently to the biological half-life of the employed targeting agent. Among the β^- emitters, the most commonly used radionuclides ^{32}P ($T_{1/2}$ = 14.3 days), ^{89}Sr ($T_{1/2}$ = 50.5 days), ^{90}Y ($T_{1/2}$ = 2.7 days), ^{131}I ($T_{1/2}$ = 8.0 d), ^{153}Sm ($T_{1/2}$ = 1.9 d), ^{169}Er ($T_{1/2}$ = 9.4 d), ^{177}Lu ($T_{1/2}$ = 6.7 days) and ^{188}Re ($T_{1/2}$ = 17.0 h) [23]. Regarding α-emitting radionuclides, several nuclei are in development phase, anyway existing radiopharmaceuticals with ^{211}At ($T_{1/2}$ = 7.2 h) and ^{223}Ra ($T_{1/2}$ = 11.4 days) are currently used. Concerning Auger electron and X-ray emitters, at the moment only ^{125}I ($T_{1/2}$ = 59.4 days) and ^{103}Pd ($T_{1/2}$ = 17.0

days) are widely used, whereas the radionuclide ^{131}Cs ($T_{1/2}$ = 9.7 days) is also finding increasing application [1.23].

1.2.4 Emerging radionuclides for a potential medical application

In order to expand the medical radionuclides availability and variety, recent research has been carried out mainly in two directions [1.23]:

- Development of novel positron emitters
- Development of novel highly-ionising radiation emitters for internal radiotherapy

The need of novel non-standard positron emitters is indeed related the growing significance of PET in diagnostic nuclear medicine, especially for studying slow metabolic processes and for quantification of targeted therapy, thus in the framework of theranostics.

In such framework, in example, β^+ emission intensities were accurately determined for ^{120}I ($T_{1/2}$ = 81.6 min) [1.24], ^{124}I ($T_{1/2}$ = 4.18 days) [1.25], ^{64}Cu ($T_{1/2}$ = 12.7 h) and ^{76}Br ($T_{1/2}$ = 16.0 h) [1.26], and several other nuclides, listed in table 1.1 , [1.23].

Table 1.1: *Some novel positron emitters for medical applications* [1.23]

Radionuclide ($T_{½}$)	Major production route	Energy range (MeV)	Application[a]
^{55}Co (17.6 h)	$^{58}Ni(p,\alpha)$	15 → 7	Tumor imaging; neuronal Ca marker
	$^{54}Fe(d,n)$	10 → 5	
^{61}Cu (3.3 h)	$^{61}Ni(p,n)$	15 → 7	Immuno-PET
	$^{64}Zn(p,\alpha)$	18 → 11	
^{64}Cu (12.7 h)	$^{64}Ni(p,n)$	14 → 9	Radioimmunotherapy
^{66}Ga (9.4 h)	$^{66}Zn(p,n)$	13 → 8	Quantification of SPECT-pharmaceuticals
^{72}As (26.0 h)	$^{nat}Ge(p,xn)$	18 → 8	Tumour imaging; immuno-PET
^{76}Br (16.0 h)	$^{76}Se(p,n)$	15 → 8	Radioimmunotherapy
^{82m}Rb (6.2 h)	$^{82}Kr(p,n)$	14 → 10	Cardiology
^{86}Y (14.7 h)	$^{86}Sr(p,n)$	14 → 10	Therapy planning
^{89}Zr (78.4 h)	$^{89}Y(p,n)$	14 → 10	Immuno-PET
^{94m}Tc (0.87 h)	$^{94}Mo(p,n)$	13 → 8	Quantification of SPECT-pharmaceuticals
^{120}I (1.3 h)	$^{120}Te(p,n)$	13.5 → 12	Iodopharmaceuticals
^{124}I (4.18 d)	$^{124}Te(p,n)$	12 → 8	Tumour targeting; dosimetry

Produced at a small cyclotron ($E < 20$ MeV) using mostly highly-enriched target material

[a] Each application involves PET imaging

In addition, ongoing research is focussed on several other potentially useful positron emitting radionuclides, such as ^{44}Sc ($T_{1/2}$ = 3.9 h), ^{45}Ti ($T_{1/2}$ = 3.1 h), producible with cyclotrons with energy up to 20 MeV, or ^{52}Fe ($T_{1/2}$ = 8.3 h), ^{73}Se ($T_{1/2}$ = 7.1 h), ^{77}Kr ($T_{1/2}$ = 1.2 h) and ^{83}Sr ($T_{1/2}$ = 32.4 h), that demand a high intensity cyclotron or accelerator to be produced.

Regarding the potentially interesting therapeutic radionuclides, their number is very large [1.7]. However, as mentioned above, recent research is focussed mainly on low-range but highly-ionising radiation emitters. Table 1.2 summarizes some example of novel interesting medical nuclides for Targeted Radionuclide Therapy.

Table 1.2: *Some important emerging therapeutic radionuclides and their related decay characteristics* [1.23]

Radionuclide	$T_{½}$ (days)	Radiation of interest (%)	End point energy (keV)
^{67}Cu	2.58	β^- (100)	577
^{186}Re	3.78	β^- (92.2)	1,070
^{225}Ac	10.00	α (100)	5,830
^{117m}Sn	13.61	IT (100)	161
		Conversion electrons	
^{193m}Pt	4.33	IT (100)	135
		Auger electrons	
^{195m}Pt	4.02	IT (100)	130
		Auger electrons	

Among the presented nuclides, ^{67}Cu ($T_{1/2}$ = 2.58 days) is gaining increasing significance as a theranostic pair of the β^+emitter ^{64}Cu, and several production routines are being investigated [1.27, 1.28]. ^{186}Re ($T_{1/2}$ = 3.78 days) [1.29] is attractive for internal radiotherapy since the chemistry of Rhenium is similar to that of Technetium and since a large number of Tc-compounds are already used in nuclear medicine. Great attention is paid also one α- emitter nuclides, in particular on ^{225}Ac ($T_{1/2}$ = 10.00 days), that is useful both in itself and as a generator for ^{213}Bi ($T_{1/2}$ = 46 min; Eα = 5900 keV) [1.30].

^{117m}Sn ($T_{1/2}$ = 13.61 days) is a low-lying isomeric state of the stable ^{117}Sn that decays by heavily converted isomeric transition to the ground state. Thus, it emits conversion electrons with energies about 160 keV, that are ideally suitable for therapeutic applications. Because of such interesting characteristics. such nuclide has been studied for more than three decades [1.23].

Finally, ^{193m}Pt ($T_{1/2}$ = 4.33 days) and ^{195m}Pt ($T_{1/2}$ = 4.02 days) are isomeric counterparts of the very long lived ^{193}Pt ($T_{1/2}$ = 50 years) and the stable ^{195}Pt, respectively, and are pure X-ray and Auger electron emitters. For such nuclei, each decay leads to more than 30 secondary electrons, with energies ranging between 10 and 130 keV, thus extremely interesting for Auger therapy. In addition, Platinum based complexes have been developed and used as proficient anti-tumour agents for a long time [1.31]. However, the remarkable drawback so far, is their limited availability and the difficulties in increasing their specific activity to acceptable levels.

As general consideration, many other nuclides have the potentiality to become proficient tools for labelling new generation radiopharmaceuticals, however their further study and widespread is limited by the lack of suitable production routines, able to ensure both quantity in terms of available activities to the end users, and quality, in terms of radionuclidic purity, at a reasonable price. For some of the listed nuclides, a remarkable research effort is nowadays focussed on the

investigation of the most proficient nuclear reactions having them as product, as well as on the discovery of new production approaches.

1.3 Medical nuclides production techniques

The production of radionuclides, as the radioactive "core" of radiopharmaceuticals, is a very crucial step. Indeed, when evaluating the capability to produce radionuclides for nuclear medicine, not only the producible amount should be considered, but also remarkable attention should be paid to the specific activity and the radionuclidic purity. Therefore, the choice of the production technique has to deal with all these aspects.

Conventional nuclide production routines foresee the exploitation of opportune nuclear reactions, either neutron or light/heavy ions induced, in nuclear reactors and accelerator facilities, respectively.

Table 1.3: *Overview of the conventional medical nuclides production techniques* [1.4]

	Nuclear Reactors	Generators	Cyclotrons
Principle of production	Target material inserted in the neutron flux field undergoes fission or neutron activation transmuting into radionuclide of interest	Long-lived parent radionuclide decays to short-lived daughter nuclide of interest. Daughter nuclide elution follows in pre-determined cycles	Target material irradiation by charged particle beams. Inducing nuclear reactions that transmute the material into radionuclide of interest
Transmutation base	Neutrons	Decay	p, d, t, ^{3}He, α or heavy ion beams
Advantages	- Production of neutron rich radionuclides, mostly for therapeutic use - High production efficiency - Centralized production: one research reactor able to supply to large regions or in some cases globally	- Available on site, no need for logistics - Mostly long shelf life - Easy to use - Limited radioactive waste: returned to manufacturer after use	- Production of proton rich elements used as β^{+} emitters for PET scans - Decentralized production allows for back-up chains - High uptime - High specific activity in most cases - Small investment in comparison to nuclear reactor - Little long-lived radioactive waste
Disadvantages	- Extremely high investment cost - High operational costs - Considerable amounts of long-lived radioactive waste - Long out-of-service periods - Trouble to back-up in case of unforeseen downtime - Demanding logistics, often involving air transport - Public safety concerns - Non-proliferation treaty concerns	- Supplies in cycles according to possible elution frequency; in-house use must be timed accordingly - Trace contaminants of long-lived parent nuclide in eluted product	- Regional network of cyclotrons and complex logistics needed for short-lived produced radionuclides - Radionuclide production limited depending on installed beam energy

In addition to the reactor- and accelerator- based techniques, generators can be considered as a third approach for radioisotopes production, particularly used and advantageous for short-lived isotopes. Table 1.3 summarizes the main features of the three aforementioned techniques, highlighting also the related advantages and disadvantages.

As general consideration, normally accelerator based techniques are suitable for the production of diagnostic nuclides, whereas nuclear reactors are more adapt for therapeutic nuclides, however there are many exceptions. Indeed, for example, there are also diagnostic radionuclides that are normally produced in reactors, as shown in figure 1.4. In addition, as highlighted in figure 1.4, there are also nuclides that are produced with similar results with both techniques.

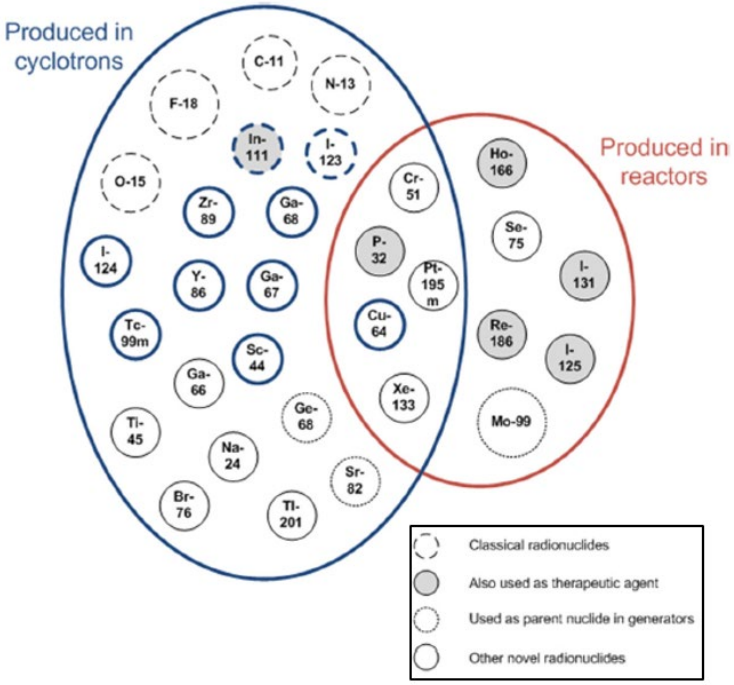

Figure 1.4: *Summary of diagnostic radionuclides grouped according to their possible production techniques* [1.4]

In the next paragraphs the three state-of-art approaches are presented in detail.

1.3.1 Nuclides production in nuclear reactors

Nuclear reactors are the main facilities where, through neutron induced reactions, a large variety of β^- emitting radionuclides are produced, primarily for Targeted Radionuclide Therapy [1.32]. At such facilities, either stable targets are inserted in neutron fluxes and neutron-rich radionuclides, close to stability valley, are generated, or fissile targets irradiated and undergo fission.

Due to the high installation costs, the number of reactors devoted to the production of medical radionuclides is globally limited, but nuclear reactors facilities are generally large, and capable anyway of supplying the demand of entire regions, since the produced amounts are generally

very high. In table 1.4 the main research reactors involved in the production of medical radionuclides are listed [1.32].

Table 1.4: *Main research reactors involved in the production of medical radionuclides* [32]

Reactor	Country	Start of operation	Expected shut-down	Power [MW]	Max thermal neutron flux [e+14 n/cm^2.s]	Operating days per year
NRU	Canada	1957	2016	135	4	300
LVR-15	Czech Rep	1957	?	10	2	200
HFR	Netherlands	1961	2018	45	3	280
BR2	Belgium	1961	2020	120	10	140
SM-3	Russia	1961	?	100	30	?
SAFARI	South Africa	1965	2020	20	3	300
HFIR	United States	1965	?	100	20	170
OSIRIS	France	1966	2015	70	2	180
MURR	United States	1966	2026	10	4	300
MARIA	Poland	1974	?	30	4	240
HANARO	Rep Korea	1995	?	30	4	220
FRM-II	Germany	2004	?	20	2	240
OPAL	Australia	2006	?	20	3	300

The achievable specific activity (S) of the produced radionuclides, if we consider a one-step transmutation reaction, can be calculated according to the equation 1.1:

$$S = \frac{N_A}{A}\,\sigma\,\varphi\,(1 - \exp\left(-\frac{\ln(2)\,t_{irr}}{T_{1/2}}\right) \tag{1.1}$$

where N_A is the Avogadro constant, A is the atomic mass, σ is the reaction cross-section, φ is the neutron flux density and t_{irr} is the irradiation time. As highlighted by equation 1.1, the achievable specific activity is directly proportional to both the neutron flux (φ) and the cross section (σ), thus high values of such parameters are fundamental, to convert a high fraction of the stable target into the desired radioisotope. Few radionuclides are produced with appreciable levels of specific activities with this reaction (^{60}Co, ^{153}Sm, ^{169}Yb, and ^{177}Lu) [1.33]. Such drawback can be mitigated by the employment of isotopically enriched targets, but such solution may be very expensive and complex, causing an increase in the production costs.

On the other hand, neutron capture reactions allow the production of carrier-free radionuclides if the desired radionuclide is the "daughter" of the reaction product. Indeed, the desired nuclide is chemically different from the target material and therefore can be selectively harvested with a chemical purification process. In addition, if the "mother" nuclide is short-lived, then a single purification step is performed because it quickly decays. In case of longer half-lives the "mother" nuclide can be exploited as generator parent nuclide.

As final consideration, as highlighted in table 1.4, most of the existing reactors devoted to the production of medical nuclides were opened more than 50 years ago, and are consequently undergoing aging. The closure of some of them is indeed foreseen both for obsolescence and for economic and political reasons, and other accelerator-based approaches are being investigated to prevent the shortage of the nuclides normally produced are such facilities [1.32].

1.3.2 Accelerator-based production

Accelerator-based production of medical nuclides foresees the irradiation of solid, liquid or gaseous targets with a beam of light ionized particles, such as protons, deuterons and alphas, or heavy ions. The most diffused accelerators used for nuclear medicine are cyclotrons, and are mainly employed for the production of imaging nuclides (PET and SPECT).

As highlighted in table 1.5, medical cyclotrons can be divided in types according to the available projectile energy. The most common are Small Medical Cyclotron (SMC) with projectile energies up to 20 MeV. Large hospitals with PET scanners may be equipped with a SMC, devoted to the production via proton induced direct reaction of short-lived standard radionuclides for PET studies, such as ^{18}F [1.4]. Cyclotrons delivering protons of an energy between 20 and 35 MeV are considered intermediate energy cyclotrons or medium cyclotrons, and are normally accelerating protons or deuterons (very few of them offer a α beam). They are normally found in major commercial plants or research institutes, and are used to produce classical SPECT or novel PET radionuclide as well as generator parent nuclides. Finally, high energy cyclotrons with beam energy above 35 MeV are found in large research institutes and can provide beam of wide variety of particles, from protons to heavy ions. Such machines can be used to produce unique novel radionuclides for both diagnosis and therapy, as well as generators parent nuclides. In particular, in case very high projectile energies are achievable, spallation reactions may be induced, thus producing radionuclides far from the stable isotopes of the target material.

Table 1.5: *Overview of the cyclotron types* [1.4]

Cyclotron type	Energy Range (MeV)	Approximate number	Typical location
Small medical cyclotron (SMC)	< 20 MeV	1050	- hospitals - universities - local commercial plants
Intermediate energy cyclotron	20–35 MeV	100	- regional commercial plants - research institutes
High energy cyclotron	> 35 MeV	50[a]	- research institutes - cancer proton therapy centers

[a]Excluding proton therapy cyclotrons

1.3.3 Generator-based production

When feasible, the use of generators as medical nuclide sources is the most efficient solution, since it combines the need of short-lived radioisotopes for imaging with the logistic issues. Indeed, hospitals and research institutes not equipped with an in-house production facility, such as SMC, can purchase generators to meet their needs.

Generator systems exploit a long-lived radionuclide, called "mother" or "parent", that decays to the daughter radionuclide, which is eluted (milked) just before the use [1.34]. The milked product is generally a carrier-free high specific activity solution, and generators can be milked various times before depletion of the parent nuclide load. A successful example is the ^{99}Mo/^{99m}Tc generator, which enabled the widespread use of ^{99m}Tc, probably the most successful SPECT radioisotope [1.35].

The drawback of generators is that the parent nuclide is often a more exotic radionuclide, whose production, performed with reactor- or accelerator-based approaches, could require more efforts. In addition, the degradation of the substrate trapping the parent nuclide could lead to the unwanted release of traces of contaminants in the milked solution.

1.4 Unconventional production techniques based on Mass Separation

The challenges for the innovation in the production of medical radionuclides concern not only the discovery of novel nuclei, never or less studied before, but also the advances on the production techniques, especially considering that shut-down of some of the existing nuclear reactors facility is planned. In this framework, research efforts are now focussed in the advance of the accelerator-based production technologies, either studying new reactions and new target concepts for the production of therapeutic nuclides [1.36], or exploring totally new techniques, with a novel approach exploiting research accelerator technologies. Among those, mass separation based methods are being studied and evaluated independently at CERN and at INFN-LNL, where the MEDICIS facility [1.37] and the ISOLPHARM project [1.38], respectively, are being developed. Both approaches foresee the performance of the extraction of the produced nuclides as an ion beam, that is lately delivered to an analysing magnet, where the different masses are deflected with different radii, according to their mass number. Thus, by intercepting only the mass number corresponding to the isotope of interest, an extremely pure collection of the desired nuclide is possible.

In the next paragraphs the two different methods are presented in detail.

1.3.1 The MEDICIS facility at CERN-ISOLDE

From its very first operation, in 1967, the ISOLDE facility at CERN has been used to produce a large assortment of radionuclides with its on-line mass separator, that were used for a broad variety of applications, from fundamental to applied physics [1.39]. As one of its applications, a small fraction of the beam time at ISOLDE was also reserved for the production of medical nuclides [1.40], but no routinely availability for distribution and use was foreseen, thus the potential use of the so-collected radionuclides was slowed down.

MEDICIS (MEDical Isotopes Collection from ISolde), a spin-off facility of ISOLDE (figure 1.5a), is specifically addressed to solve this issue. It is designed to operate parasitically exploiting the ISOLDE proton beam time. Indeed, almost 85% of the 1.4 GeV proton beam delivered onto the ISOLDE target, traverse it without any interaction and is lost in the beam dump. Thus, by placing the MEDICIS target between the beam dump and the ISOLDE target station, not only value is added to this lost beam, but also advantage is taken of the fact that a large part of its characteristics remain intact (figure 1.5b) [1.37].

The parasitic mode of operation of MEDICIS will provide greater flexibility in the production schedule and allow a wide variety of radionuclides to be available for medical applications.

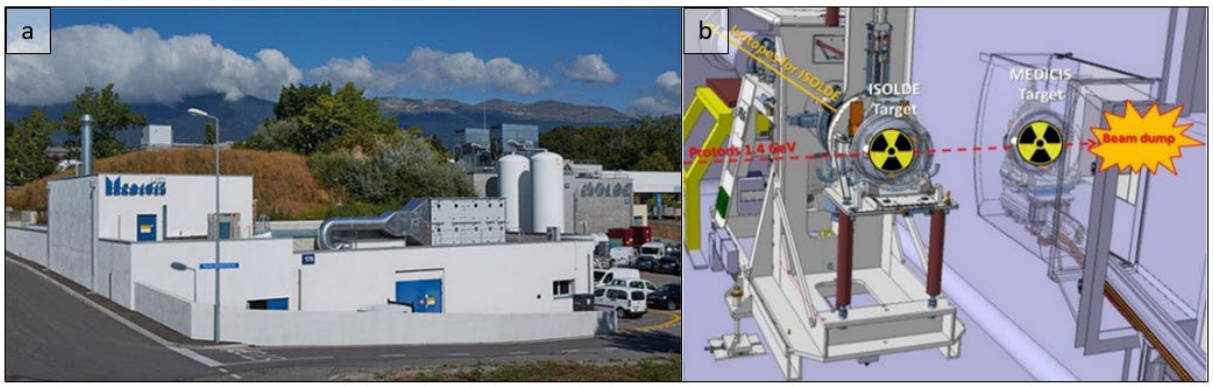

***Figure 1.5**: The CERN-MEDICIS facility, close to ISOLDE facility (a) and overview of the irradiation point (b).*

After irradiation, the MEDICIS target is automatically moved towards a newly installed off-line mass separator for extraction and purification of the radionuclides of interest. There, the target is heated up to 2300°C by Joule effect and the produced isotopes are thus released, ionized, extracted into a beam and consequently mass separated with an opportune analysing magnet. The extracted and purified beam is finally dumped on appropriate collection target, that is lately chemically treated to recover the nuclides of interest [1.41].

MEDICIS has been commissioned in November/December 2017 and has started operation in May of 2018. However, the facility was running with the standard ISOLDE target ovens which are non-ideal. To run at full capacity, the development of the large tantalum was required, that was also relevant and important for the upgrade of the current ISOLDE proton to neutron

converter [1.42]. Thus a 50 mm diameter target oven was developed, and is currently under testing phase (figure 1.6) [1.43].

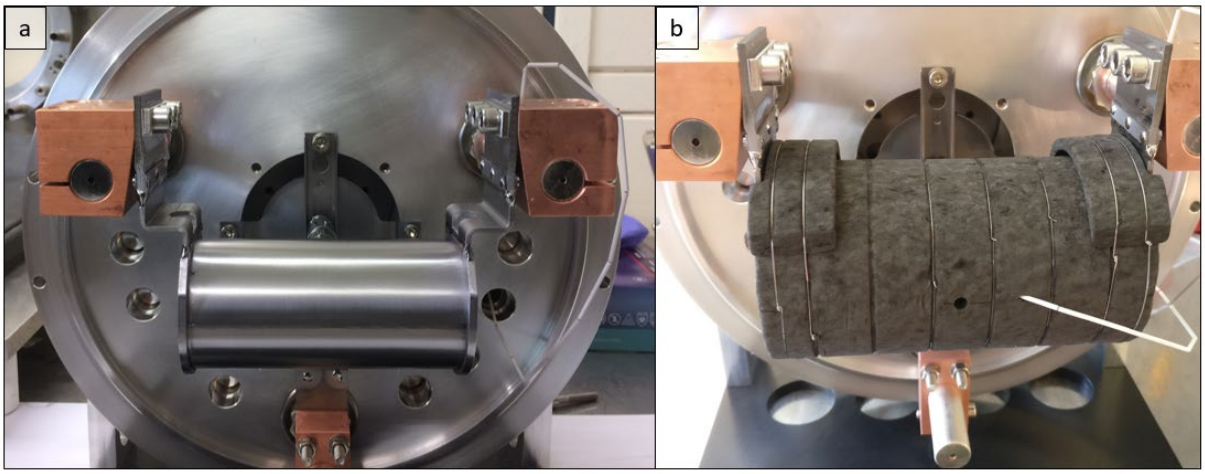

Figure 1.6: *the new MEDICIS target oven with 50 mm diameter (a). A graphite foam thermal shielding was added to increase the target temperature (b)* [43]

The aim of MEDICIS is to produce collections of innovative radionuclides that are difficult to produce by conventional techniques. In addition, the use of mass separation allows to achieve high specific activity allowing a wide variety of applications for both imaging and therapy protocols. Radionuclides will be available for hospitals and research centers and used for in vitro and in vivo studies. Table 1.6 summarizes some of the nuclides of interest at MEDICIS [1.44].

In order to support the launch of this facility, a Marie Curie innovative training network from the H2020 framework program on the European Commission has started the MEDICIS-PROMED.

Table 1.6: *Overview of some of the MEDICIS producible radionuclides* [1.43]

Element	Radionuclide	Application	Facilities needed for the production
Scandium	Sc-43	PET	12 - 30 MeV cyclotron
	Sc-44	PET / 3γ	12 - 30 MeV cyclotron
	Sc-47	Therapy	Reactor / 18 - 70 MeV cyclotron
Copper	Cu-61	PET	15 MeV cyclotron
	Cu-64	Therapy / PET	12 MeV cyclotron
	Cu-67	Therapy / SPECT	Reactor / 70 MeV cyclotron
Arsenic	As-72	PET	70 MeV cyclotron, via Se-72
	As-76	Therapy	18 MeV cyclotron
Terbium	Tb-149	Therapy / PET	High energy mass separator / 70 MeV cyclotron
	Tb-152	PET	High energy mass separator / 15 - 70 MeV cyclotron
	Tb-155	SPECT	High energy mass separator / 15 - 70 MeV cyclotron
	Tb-161	Therapy	Reactor

1.4.2 The ISOLPHARM project at INFN-LNL-SPES

At the Istituto Nazionale di Fisica Nucleare–Laboratori Nazionali di Legnaro (INFN–LNL), a new facility, SPES (Selective Production of Exotic Species) is under construction and will be able to produce radioactive ion beams of neutron-rich nuclei with high purity and a mass range of 80–160 amu. As one of its applications, the ISOLPHARM project explores the feasibility of exploiting SPES technology to produce high specific activity beta-emitting radionuclides as radiopharmaceutical precursors. This technique is expected to produce radiopharmaceuticals that are difficult to obtain in standard production facilities, with less environmental impact than reactors, and less costs. The innovation of the ISOLPHARM method was recognized and an international patent was deposed in Europe, USA and Canada (INFN) [1.38].

According to the ISOLPHARM project (figure 1.7), the radionuclides of interest are produced in a target from nuclear reactions induced by tens of MeV energy protons, coming from SPES cyclotron. The Isotope Separation On Line (ISOL) technique is adopted to extract a pure isobaric beam, that is lately collected on an adequate beam trap. Isobaric contaminants in the collection may potentially affect radiochemical and radionuclide purity, but proper methods to separate chemically different elements can be developed [1.33].

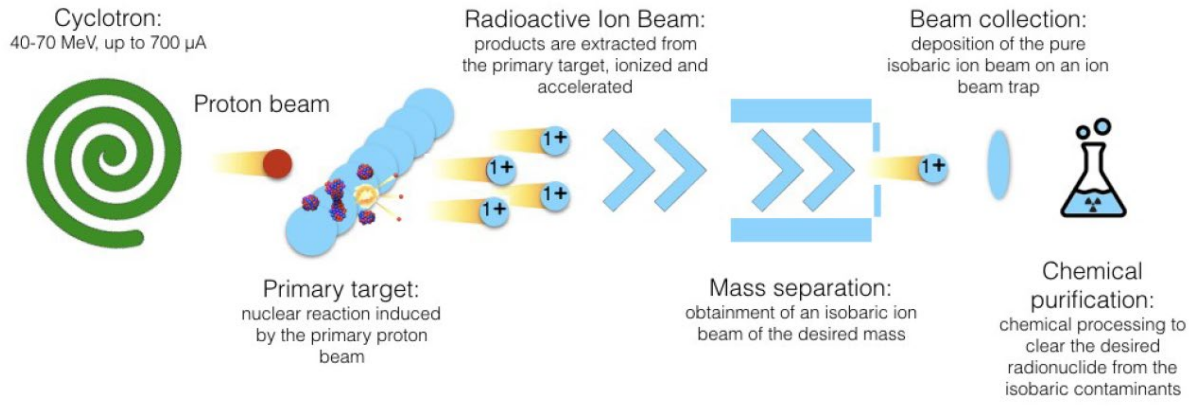

Figure 1.7: *overview of the ISOLPHARM characteristic method* [33]

In addition to INFN-LNL several Italian institutions are involved in the ISOLPHAM local collaboration network, in particular University of Padua (departments of Physics, Chemical Sciences and Pharmaceutical Sciences), INFN section of Padua, TIFPA, as well as hospitals, such as Sacro Cuore Hospital in Negrar (Verona), Acispedale S.Maria Nuova in Reggio Emilia

and S. Giacomo Apostolo Hospital in Castelfranco Veneto (Treviso). International partners are the Radioisotopes Centre POLATOM (Poland) and National Center for Scientific Research – Demokritos (Greece), but both national and international networks are currently expanding and new institutions are starting to participate in the collaboration.

A more detailed dissertation about both ISOLPARM and SPES will be presented on the next chapter, together with a deeper focus on the ISOL technique fundaments adopted for the production of Radioactive Ion Beams.

1.5 Conclusions

In this chapter the potentialities both diagnostic and therapeutic applications of radiopharmaceuticals were presented in detail, together with the state-of-art of the related production techniques of medical nuclides. Indeed, existing solution showed promising results in both imaging and cancer treatment, and promoted research in the field, in order to expand the feasibility of the use of radiopharmaceuticals in various cancer diseases.

The emerging trend of theranostics, in particular, can increase the efficacy of the treatment, since the same molecule is used for both imaging and therapy, thus its most probable bio-distribution is known prior of the administration of the therapeutic dose.

However, such new approaches require to increase the availability of nuclides suitable for the use in nuclear medicine, in terms of both producible amounts and variety. Thus the exploration of the feasibility of new nuclides in ongoing in many research institutions, keeping into account also that some of the existing nuclear reactors devoted to the production of medical radionuclides are close to the end of operation.

Thus, in addition to the conventional techniques, nuclear physics facilities, that were primarily aimed at fundamental and applied physics studies, can contribute to increase the availability of medical isotopes, by exploring unconventional production routines, as in the case of ISOLDE-MEDICIS and SPES-ISOLPHARM. Furthermore, with such novel approaches, new emerging medical nuclides might be discovered, thus boosting new research lines in the field of radiopharmaceuticals.

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Chapter 2

The SPES-ISOLPHARM Project at INFN-LNL

"Nil tam difficile est quin quaerendo investigari possit."

"Nothing is so difficult but that it may be found out by seeking."

Publius Terentius Afer (Roman playwright, 195/185 – c. 159? BC), *Heauton Timorumenos,* Act IV, scene 2.

2.1 Introduction

Soon after the discovery and understanding of the nature of radiation, the idea of a beam of elementary particles arose, laying the foundation for the development of the particle accelerators. Fed by the technological advances and the scientific curiosity, accelerators grew in size, energy and variety and variety of transported particles, and are nowadays used in many fields of science.

In particular, the scientific community showed a wide interest in the development of Radioactive Ion Beams (RIBs), that boast a remarkable variety of applications and can be produced mainly with two techniques, the In-Flight Separation technique [2.1] and the ISOL technique [2.2].

Within the applications of RIBs, especially in the case of facilities employing the latter method, a new trend is emerging, proposing that RIBs, originally investigated for the purpose of research in nuclear physics, could be employed as innovative source for medically usable radionuclides, along with the conventional and well-established techniques. This is the case of the operating ISOLDE-MEDICIS facility [2.3] and the under construction SPES project, with its planned branch ISOLPHARM [2.4].

In the following chapter, the RIB production techniques will be presented, with a particular focus on ISOL. Successively, the SPES ISOL facility at Legnaro National Laboratories of

Istituto Nazionale di Fisica Nucleare (INFN-LNL) will be described in detail, along with its branch, the innovative and patented ISOLPHARM project, aimed at the employment of SPES technologies for the production of a new generation of medical nuclides. Finally, as first test case, the ISOLPHARM_Ag project is presented, a study focussed on the production of an innovative radiopharmaceutical labelled with ^{111}Ag, producible at SPES and never studied in detail as active core of an anti-cancer drug.

2.2 The production of Radioactive Ion Beams

The broad aim of nuclear physics is to study the properties and structure of nuclei, and the mechanisms involved in their creation. The nucleus can be seen as a balanced combination of nucleons, namely protons and neutrons. All the discovered nuclides are gathered in the chart of nuclides (figure 2.1) where the stable nuclei are positioned on the "valley of stability", identified by the black squares. The other isotopes are unstable and they stochastically decay into different elements releasing a typical spectrum of radiation. Each nuclide has his own typical half-life, namely the time required to halve an initial amount of isotopes. The longer the half-life, the longer is the usual life of such isotope. The most unstable atoms are usually far from the stability valley and they can be very interesting for the research in nuclear physics.

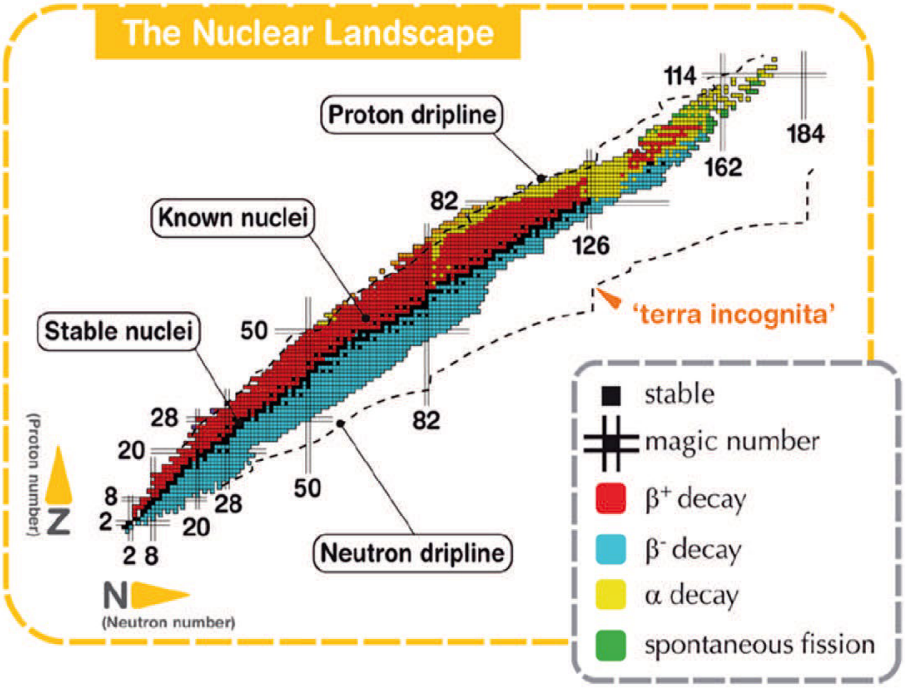


***Figure 2.1**: a representation of the chart of nuclides*

The nuclear properties of approximately 3600 radioactive nuclei, called "exotic nuclei", have been studied and they can be produced in several facilities all over the world. However theoretical calculations predict the existence of more than 6000 unstable nuclei in between the

so-called proton and neutron and driplines (dashed lines showed in Fig. 1.1). Beyond such boundaries, the instability of the nucleus leads an immediate decay emitting nucleons forthwith after its formation.

Radioactive Ion Beams (RIBs) are one of the fundamental tools used to study the properties of unstable nuclei [2.5, 2.6]: a large variety of exotic species is producible and furthermore such beams can be exploited for advances in research in many different fields of science. In the following paragraphs the main techniques for the production of RIBs are presented, with a deep focusing on the Isotope Separation On Line (ISOL) technique. Finally, the INFN-LNL SPES (Selective Production of Exotic Species) project for the production of RIBs according to the ISOL technique is presented in detail.

2.2.1 RIB production techniques

Radioactive Ion Beams have been corner stones of studies in nuclear physics research, but their production is challenging and requires special dedicated techniques: the in-flight separation technique [2.1] and the Isotope Separation On Line (ISOL) technique [2.2].

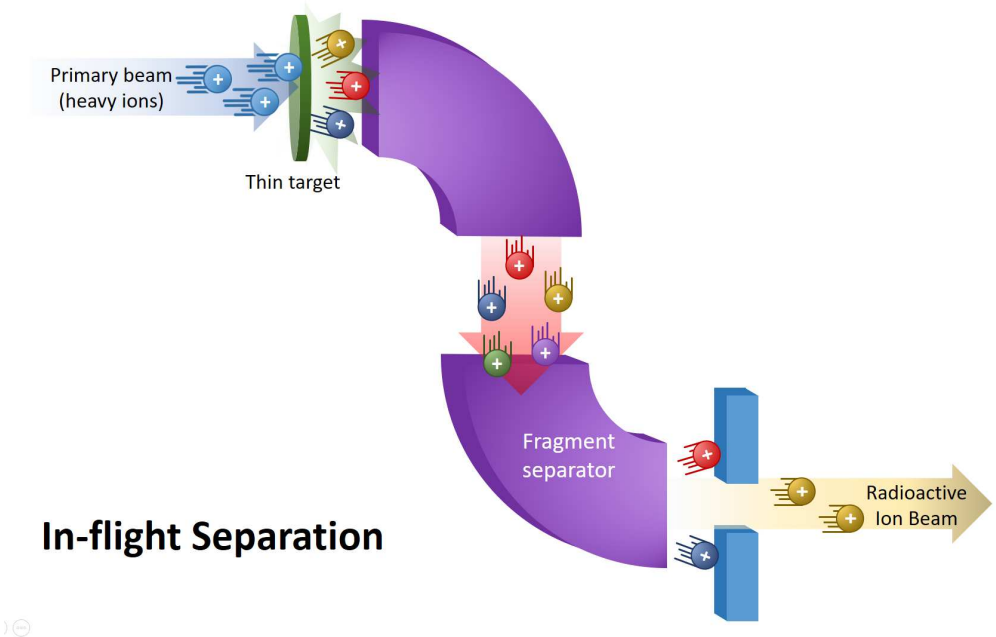


***Figure 2.2**: schematic representation of the in-flight separation technique*

The in-flight separation technique is shown in figure 2.2: a highly energetic beam of heavy ions is sent towards a thin target, where beam atoms fragment into smaller atoms. Since such fragments retain part of their kinetic energy, they can proceed towards the fragment separator, where the undesired nuclides are dumped, and the requested radioactive ion beam can be delivered to the experiments. According to such technique, the fragments are ejected without limitations due to the lifetime or the chemical processes, and intense beam can be obtained.

However, high beam intensity losses may occur due to the high dispersion in terms of fragment energy and ion angular momentum. It is indeed impossible to tune the energy of the fragments generated by the interaction with the target, thus mono-energetic beams, that can efficiently re-accelerated are not obtainable.

The fundamentals of the ISOL technique are shown in figure 2.3: a primary beam of light particles is sent to a thick target, generating nuclear reactions. The produced nuclides are then released thanks to the high working temperatures of the target and migrates to an ion source. After ionization, the obtained ions are extracted and accelerated towards a separating magnet, where the undesired isotopes are dumped, whereas the selected radioactive ion beam can be further sent to the experiments.

The RIBs obtained with such technique are generally excellent (highly pure and mono-energetic), consequently they can easily post-accelerated, however the process is generally more complicated, because the various processes involved (release from target, ionization, mass separation, beam transport) have to be:

- Efficient, to prevent excessive beam losses
- Fast, to ensure the capability to produce RIBs of the most exotic nuclei
- Selective, in order to guarantee the beam purity requested by the users
- Highly productive, to maximize the RIB intensity.

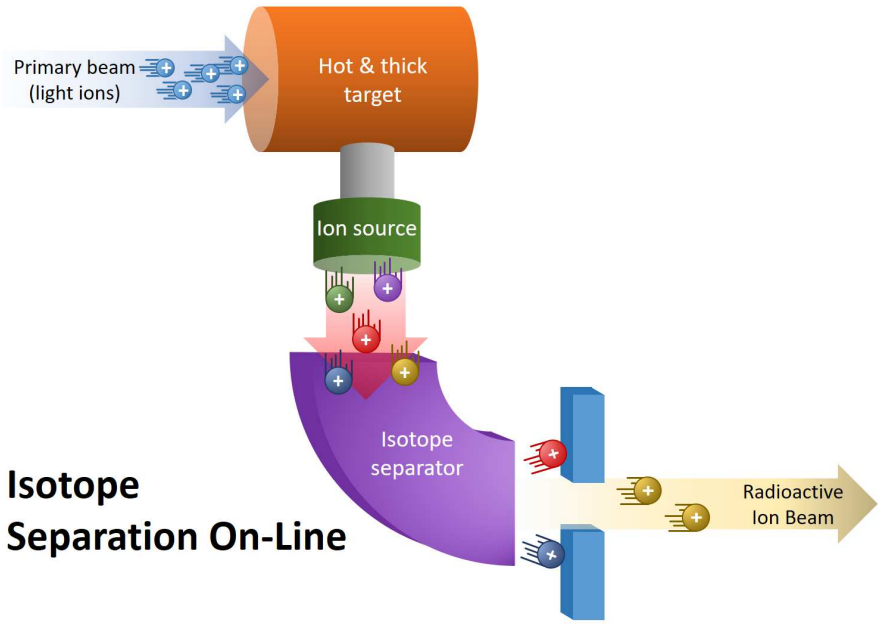


***Figure 2.3**: schematic representation of the Isotope Separation On-Line technique*

Some of the most important ISOL facilities in the world are:

- ISOLDE at CERN (Geneva) [2.7]: a high energetic proton beam (1 or 1.4 GeV) beam is delivered by the Proton Synchrotron (PS) booster, that provides protons also for the

worldwide famous LHC (Large Hadron Collider), currently the largest accelerator in the world. Several target configurations are used, including uranium carbide. When the latter is used, the estimated fissions rate is about $2.5 \cdot 10^{12}$ fissions/s for a 1 GeV 2 μA proton beam.

- ISAC at TRIUMF (Vancouver) [2.8]: a 500 MeV proton beam can be delivered by a high energy cyclotron, impinging several targets, such as U, Th, Si, Ta etc. When the uranium carbide target is used the maximum delivered beam current is about 10 μA, for a total power of 5 kW.
- ALTO at IPN Orsay (Paris) [2.9]: a 50 MeV electron beam impinges a converter which produces photons in the range of gammas. Such photons impinge a uranium carbide target for an expected rate of $1.2 \cdot 10^{11}$ fissions per second, with a 10 μA electron beam.
- HRIBF at ORNL [2.10]: recently closed facility, where a 50 MeV up to 20 μA proton beam was delivered to various targets. The uranium carbide version could provide about $4.8 \cdot 10^{11}$ fissions per second.

In the following paragraph the ISOL technique is further discussed in detail.

2.2.2 The ISOL technique

The ISOL technique was invented in Copenhagen almost 70 years ago [2.11] and lately migrated to CERN, where the ISOLDE facility was built and is currently running . The ISOL technique eventually spread to other laboratories worldwide, where it was further developed and studied resulting as one of the main techniques for on-line isotope production of high intensity and high quality radioactive ion beams.

The typical setup of an ISOL system consist of a series of different steps (figure 2.4): isotope production, thermalization of the produced nuclei, ionization and subsequently extraction, mass separation, cooling, charge-state breeding and finally acceleration. These processes are governed by physical and chemical phenomena, thus both physical (e.g., production cross-section, decay-half life, ionization potential) and chemical (e.g., molecular formation probability, volatility) properties of the nuclei of interest and of the target material have to be taken into account.

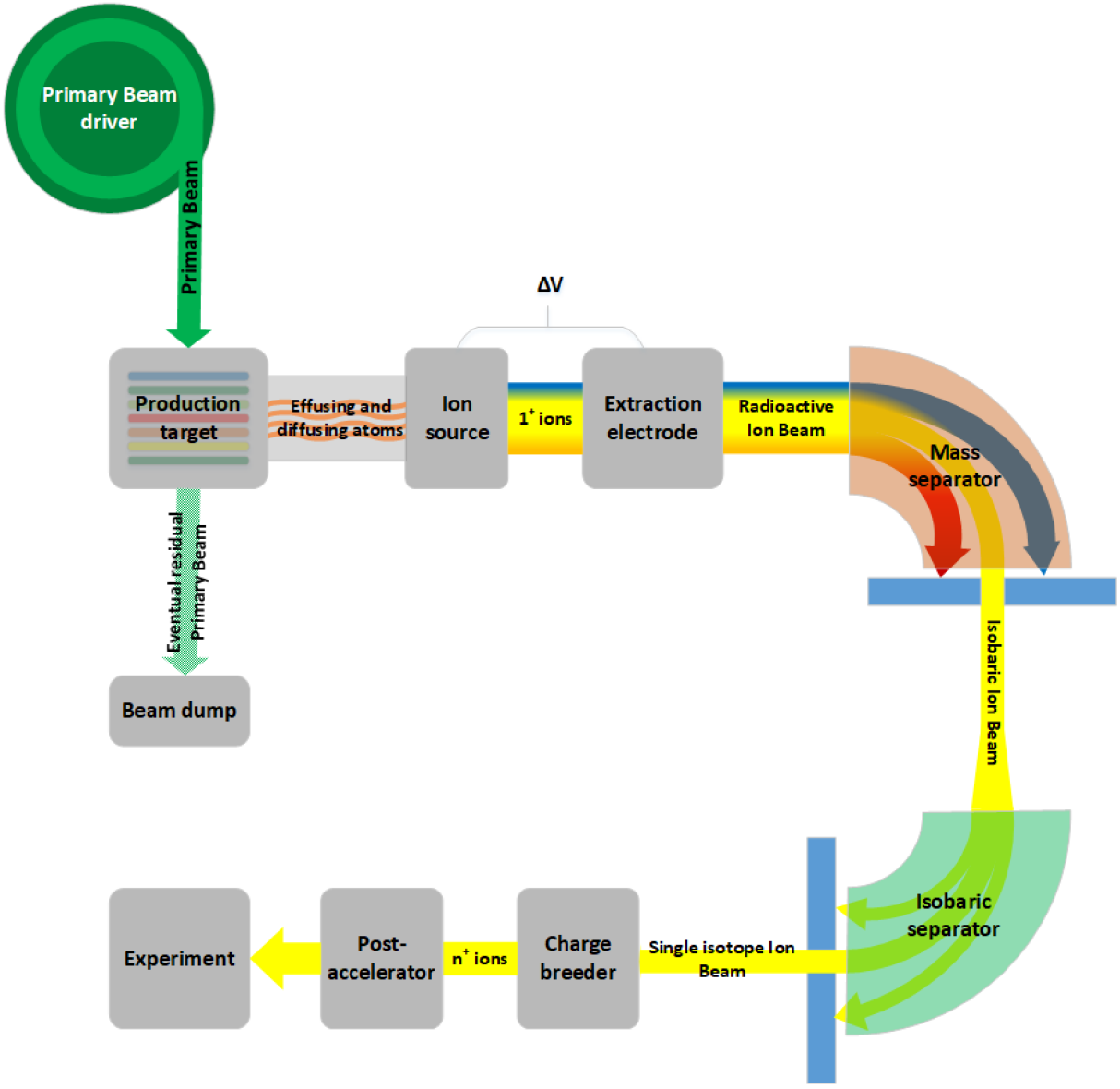


***Figure 2.4**: typical scheme of an ISOL system*

The first essential ingredient of an ISOL facility is the primary beam accelerator, namely the primary beam driver. There a primary beam is extracted and accelerated to the desired energy, and delivered to the production target. Several types of primary beams can be used:

- Low energy protons, deuterons or alphas (between 30 to 100 MeV): as example SPES at LNL (protons at 40-70 MeV) [2.12]
- High energy protons ranging from 500 MeV to 1500 MeV (as ISOLDE with 1-1.4 GeV protons or TRIUMF with 500 MeV protons)
- Heavy ions from 4 to 100 MeV/u
- Thermal neutrons
- Electron beams (as ALTO with 50 MeV electrons)

Such primary beam impinges a fixed target (usually solid fissile materials as e.g. uranium carbides, but there are also some experiments with molten or gaseous targets) inducing nuclear reactions. The types of nuclear reactions that essentially occur in the target are:

- Fission: it can occur in long lived actinides target targets such as ^{238}U or ^{232}Th. The target nucleus splits into two main fragments with similar masses, generally between 80 and 150 amu, with the emission of few neutrons.
- Spallation: it occurs when a large number of protons, neutrons deuterons and/or α particles are ejected from the target nucleus. In most cases the products are neutron-poor and have a mass number slightly lower than the target atom.
- Fragmentation: it can be named target fragmentation if a light ion beam (with energy generally above 50 MeV) impinges a heavy target and primary beam fragmentation when heavy ions collide a light nuclei target. The product variety is often wide but close to the projectile and target nucleus.
- Light- and Heavy-Ion Fusion Evaporation reactions or direct reactions: such reactions produce generally a narrower variety of nuclides if compared to the three aforementioned reactions. The Light-Ion Induced Fusion Reaction produces proton rich nuclei close to the valley of stability, whereas the Heavy-Ion Induced Fusion Reaction produces very exotic neutron deficient nuclei.

The produced nuclei are subsequently thermalized at a temperature above 2000°C. After thermalization, the isotopes will (partially) have enough energy to escape from the target through the transfer line towards the ion source thanks to diffusion and effusion processes.
The ion source normally is optimized to provide generally only the 1^+ or 1^- charge state, and several different ionization techniques are used, e. g. Surface Ionization, Electron Impact (plasma) ionization or Resonant Laser ionization [2.13].
The Surface Ionization is the simplest technique to be implemented, since a very small number of components is required [2.14, 2.15]. It is based on the solid-state physics principle of the work function, which is the is the minimum thermodynamic work (i.e. energy) needed to remove an electron from a solid to a point in the vacuum immediately outside the solid surface, and it's a typical property for each material. When neutral atoms interact with a surface, they can lose an electron turning to a positive ion if their ionization potential is smaller than 7 eV, or they can get negatively charged if their electron affinity is greater than 1.5 eV. In practice, all this translates into the use of source materials with work function higher than the ionization potential for positive ions or lower than the electron affinity for negative ions. As well as by the work function and chemical properties of the materials involved, the efficiency of such

process is deeply influenced by the temperature, consequently typical working temperatures are of the order of magnitude of 2000°C. Typical materials used for a standard Surface Ion Source are tantalum, tungsten and rhenium for positive ion beams, LaB_6 and BaO for negative ion beams.

The Electron Impact Ionization technique is mostly employed when multi-charged ions are sought or to ionize high ionization potential elements such as noble gases and halogens [2.16, 2.17]. According to such technique, the neutrals travelling within the source are bombarded by a plasma of electrons, causing the emission of one or more outer electrons from the atom. The electron plasma energy can be tuned according to the cross section for electron impact ionization of the wanted element, in order to maximize the efficiency. However, such method is very unselective and, in general, it does not offer any chemical selectivity, but, on the other hand, it is the most efficient method available to ionize some elements with the current technology.

The Resonant Laser Ionization implementation at ISOL is quite recent but nowadays the most used technique [2.18, 2.19]. In this case, the atoms travelling within the source are stepwise excited by different laser photons (usually from 1 to 4). The quantum of energy of each photon is precisely tuned to the energy levels of the electron shell of a specific element, obtaining thus the ionization of the desired atom. Consequently, such technique is very efficient and, especially, very selective. The obtained beams are extremely pure, since the only contaminants are essentially due to the unwanted surface ionization.

After ionization the beam is created by means of an extraction electrode, with extraction potential normally ranging between 40 and 60 kV.

Such low energy beam is opportunely handled and finally sent to an analyzing magnet where mass separation is performed, obtaining thus an isobaric beam. In some case extremely pure beams are requested, therefore a second step of beam purification is implemented using a high resolution mass spectrometer capable of separating different isobars.

When the desired purity is reached other devices may be used to increase the quality of the beam. In example a “cooler” device is used to literally cool down the ion beam in order to improve its ion optical properties. Cooling is intended as the reduction of the radial momentum or energy spread of the beam. After cooling the beam may be bunched, in order to increase the peak to background ratio of certain experiments like laser spectroscopy experiments or to inject the beam into a charge-state breeder, in order to have a simpler and more efficient post-acceleration. Such device transforms a singly charged ion beam into a multiple charged one. Commonly, two types of charge-state breeding ion sources are used in ISOL facilities: the Electron Beam Ion Source (EBIS) [2.20] and the Electron Cyclotron Resonance (ECR) [2.21]

ion source. Both are based on an intense bombardment of the beam ions with energetic electrons, which stepwise ionize the beam in higher charge states. The difference is that the first is a pulsed source, whereas the latter is a DC device.

The highly charged ion beam from the charge-state breeder or the beam of singly charged ions is subsequently injected into the accelerator. This process is referred to as post-acceleration. Finally, the energetic beam of radioactive ions is sent to experimental set-ups.

Currently there are some running ISOL facilities, but they generally deliver weak intensities and have modest post acceleration capabilities. However, second generation facilities are being built with the aim to increase the intensities and/or the "exoticism" of the available beams. The experience gained with the construction and operation of these facilities may lead to the design of even more challenging and innovative third generation facilities such as EURISOL [2.22] in Europe, which is expected to lead to new discoveries. SPES (Selective Production of Exotic Species) is one of the second generation ISOL facilities, currently under construction at INFN-LNL.

2.2.3 Possible applications of RIBs

As already introduced, RIBs are essential tools for the research in nuclear physics. However, several applications in other fields have been currently developed, ranging from astrophysics, solid state physics and finally nuclear medicine [2.2, 2.6, 2.23]. A summary of some possible applications of RIBs in the aforementioned fields will be provided in the following paragraphs.

2.2.3.1 Nuclear physics

The current knowledge about the possible nucleus structures is based on the measured properties of the well-known isotopes placed close to the "valley of stability" or in the proton-rich side of the nuclide chart. Indeed, they are easier to produce, and consequently to be studied. On the other side, very few information is available for the understanding of the less-known exotic nuclides properties. In such cases theoretical models have been developed, but their reliability has to be experimentally verified. In fact, such models. been extrapolated from the available data and, inevitably, errors and wrong suppositions may have been introduced. Thus, dedicated experiments with RIBs could provide more information to validate or eventually revisit and modify some basic concepts of such theories. In the following paragraphs a more detailed description of the possible contribution of RIBs in the field of nuclear physics is provided.

(I) Standard model improvement and verification

The current standard model for nuclear physics considers three of the four fundamental interactions, namely the strong nuclear interaction, electromagnetism and the weak nuclear interaction. All the properties and interactions between all known particles are included in such model, but, since it was based on some assumptions that are not yet verified, there are still some unexplained phenomena. In example, the baryon asymmetry is not fully contemplated by the standard model, as well as the full theory of gravitation as described by general relativity. In addition, it does not account the accelerating expansion of the Universe, according to dark energy theories, or any dark matter particle with all properties deduced from observational cosmology. Finally, the neutrino oscillations and their non-zero masses are not described. Measurements on very exotic RIBs could provide precise information on the decay properties of some less-known isotopes, allowing to verify or update the fundamental assumptions of the current standard model.

(II) Complex nuclei structure studies

Quarks are the subatomic particles forming protons and neutrons (nucleons), and their physical action oversteps the confinement of the nucleons in which they are contained. Indeed, it was experimentally observed that the interaction acts differently between free nucleons and between nucleons in the same atom. In fact, the characteristic nucleus neutron and proton density influences the behaviour. Currently quantum-mechanics calculations can predict the nucleons interaction only in the case of light nuclei, whereas no mathematical model was identified for heavier isotopes. The results of dedicated experiments employing RIBs can contribute significantly to overcome the difficulties in expanding the current theoretical model.

(III) Nucleus radius measurement: halo nuclei

The size of the nucleus is dependent form the number of its nucleons and can be easily estimated through the relation 2.1:

$$R = R_0 A^{\frac{1}{3}} \tag{2.1}$$

Where:

- R is the nuclear radius;
- R_0 is a constant equal to 1.2 fermi (1 *fermi* = 10^{-15} *m*)
- A is the mass number.

In some particular conditions, especially in the case of very exotic neutron-rich nuclei, the aforementioned equation is not representative. In fact, in such region the interactions occurring

between nucleons become extremely weak leading to formation of different nuclear shapes, such as neutron skins or halo nuclei. Nuclear skins are particular configurations in which the nucleons are not homogenously distributed, but the nucleus presents higher concentration of neutrons on its surface. The halo nuclei are even more exotic since they are characterized by up to two weakly bonded neutrons orbiting around the main agglomerate of the nucleus (valence neutrons). Proven examples of such nuclear shape are ^{6}He, ^{11}Li and ^{11}Be [2.24]. In the particular case of ^{11}Li, it should have an average nucleus size similar to ^{48}Ca, but the presence of two orbiting valence neutrons increases its overall dimension up to a size close to the more massive ^{208}Pb (figure 2.5).

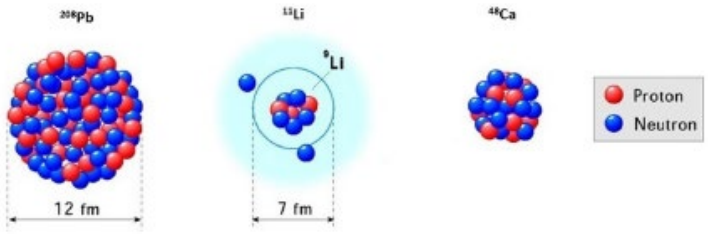


***Figure 2.5**: representative comparison of the nuclear dimensions of ^{11}Li (halo nucleus) with the heavier ^{48}Ca and ^{208}Pb nuclei. The presence of the valence neutrons increases its size up to the same as ^{208}Pb.*

Atomic spectroscopy apparatus can be used to determine the distribution of the protons, employing radioactive beams at low energy and lasers. However, to discover the overall nucleons distribution, high energy RIBs are necessary.

(IV) Superheavy elements production

About 90 elements can be found in nature: from Hydrogen to Uranium. In the last decades, nuclear fusion opened the possibility to synthetize heavier and heavier nuclei thus extending the known elements up to Z= 118. Such elements, indicated as superheavy [2.25], can be formed around the so-called "island of stability", corresponding to the area of the nuclide chart surrounding the configuration of 114 protons and 184 neutrons, which is considered particularly stable. Since the upper limit of the existence of such nuclei is yet not known, dedicated experiments have to be performed. The condition for the formation of such elements might be met when neutron-rich RIBs impinge neutron-rich (stable) targets.

2.2.3.2 Nuclear astrophysics

The aim of nuclear astrophysics is to understand the universe structure and composition as well as the processes involved in its origin and evolution. Nowadays, one of the main research topic of nuclear astrophysics is the stellar cycles description and characterization. Stars are natural nuclear reactors where both stable and unstable nuclei interact releasing amounts of energy [2.26]. Such processes can last either billions of years, moving stepwise in different phases, or

a timescale of seconds, being sudden and explosive. In the lifespan of stars, new elements are formed, both through known reactions of nucleosynthesis, thus following the valley of stability, and through more obscure processes, that are yet not fully identified. In order to define models able to describe such processes, the half-lives, the masses and the decay chains of some specific nuclei far from stability have to be studied. RIBs can contribute significantly in the characterization of such nuclides.

2.2.3.3 Solid state physics

The aim of solid state physics is to study the rigid matter, investigating its mechanical, optical electric and magnetic properties. Most of the research in such field is concerning the study of crystals and the definition of mathematical models to extrapolate their properties. In the following paragraphs it is shown how the use of radiation can contribute to identify the crystal lattice shape and study its defects.

(I) Radio Tracer Diffusion (RTD)

The Radio Tracer Diffusion (RTD)technique was born in 1920 and consists in implanting some radioactive nuclei into a solid system, and consequeltly detecting the emitted particles or radiation. Since such technique works even if very few radioactive atoms are used, it is considered one of the most common way to study atomic diffusion processes.

The “probe” radioisotopes can be implanted in the solid medium by diffusion, through nuclear reaction or ionic implanting. The information that RTD can provide concerns:

- The interactions between the probe atom and the crystal lattice;
- The electric and magnetic field in the crystal;
- The diffusion process and the interactions between the probe atoms;
- The crystal lattice defects.

(II) Doped semiconductor and emission channelling technique

The electric and optical properties of a crystal are strongly influenced by the presence of intrinsic or extrinsic defects. In the perspective of the miniaturization of electronic components, technological efforts are undertaken in order to develop smaller and smaller semiconductors, thus a precise control of the crystal defect is mandatory as well as the study of the electrical activation with different doping impurities. Since radioactive isotopes have the same chemical properties of their stable counterparts, they can be used to influence the optical and electrical behaviour of the semiconductor, depending on their positioning inside the crystal lattice. Also the size of the semiconductor may influence its properties: in small sized semiconductors significant changes can be verified in presence of a defect in a concentration of less than 10^{12}

atoms/cm^2. As a consequence, defect evaluation techniques with large chemical sensitivity and high defects concentration detection sensitivity are required.

Radioactive ion beams can be used as a powerful diagnostic tool to provide detailed information on the substrate in which they are implanted. One of the application in such field that implies the use of RIBs is represented by the Emission Channelling technique, used to study the structure and properties of impurity-defect complexes in solids, particularly in semiconductors. The technique (figure 2.6) relies on the emission and transport of charged particles through a single crystal subsequent to the decay of a radioactive isotope previously implanted into the lattice [2.27]. The particles are detected by 2-dimensional position sensitive sensors. Such method is based on angle dependence of the intensity of the emitted radiation as a function of the orientation of the host crystal (different crystal axes and planes). Indeed, the detectors reveal an anisotropic radiation intensity spectrum, thus allowing to identify with great accuracy the position occupied by the radioactive isotope in the crystal lattice.

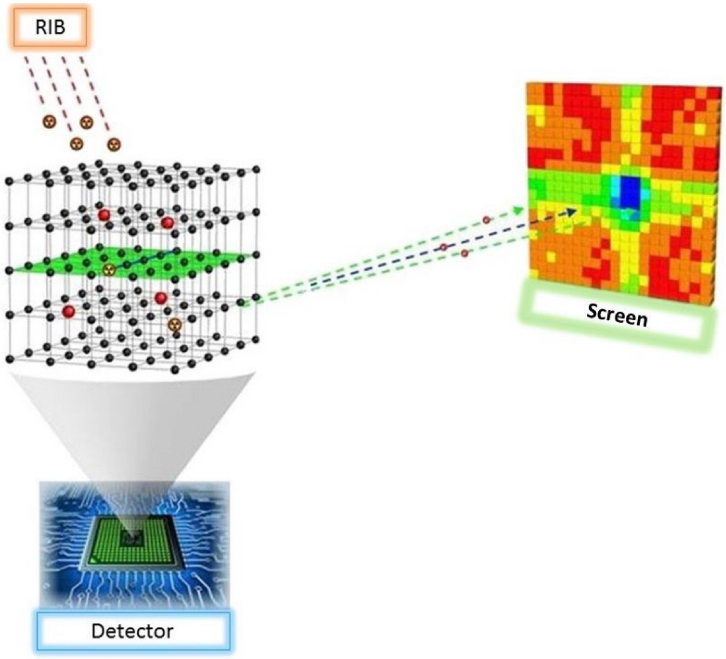


Figure 2.6: *schematic representation of the emission channelling technique.*

2.2.3.4 Nuclear medicine

The use of radiation as essential tool for the nuclear medicine practices of diagnosis and therapy of various diseases was widely discussed in chapter 1. In particular, drugs including radioisotopes, the so-called radiopharmaceuticals, are developed in order to selectively bind to a target tissue, thus delivering a radioactive dose only on it. The radionuclides used in such field are normally produced with traditional techniques, such as thermal neutron capture in reactors or direct reactions in medical accelerator facilities. The technology developed for the production of RIBs can significantly contribute also in this research field, thanks to its

capability of producing a wide range of nuclides. The exploitation of RIBs may potentially overcome the limits of the current techniques, pioneering new research lines involving innovative or difficult to produce nuclides [2.28].

2.3 The SPES project

SPES, which is the acronym for "Selective Production of Exotic Species", is a project devoted to develop and install a second generation ISOL facility at INFN –LNL (Istituto Nazionale di Fisica Nucleare –Laboratori Nazionali di Legnaro)[12]. SPES is furthermore the Latin word for "hope", indeed the project represents the future and hope of LNL. Such facility will produce mainly neutron-rich nuclei in range of mass 80-160 amu when a uranium carbide target is used, with an estimated proton induced fission rate of 10^{13} fissions/s. Neutron-deficient beams will be obtained using other target materials, such as silicon carbide, currently under development. The produced beams will be employed for studies in many branches of science, ranging from nuclear astrophysics up to material sciences and nuclear medicine.

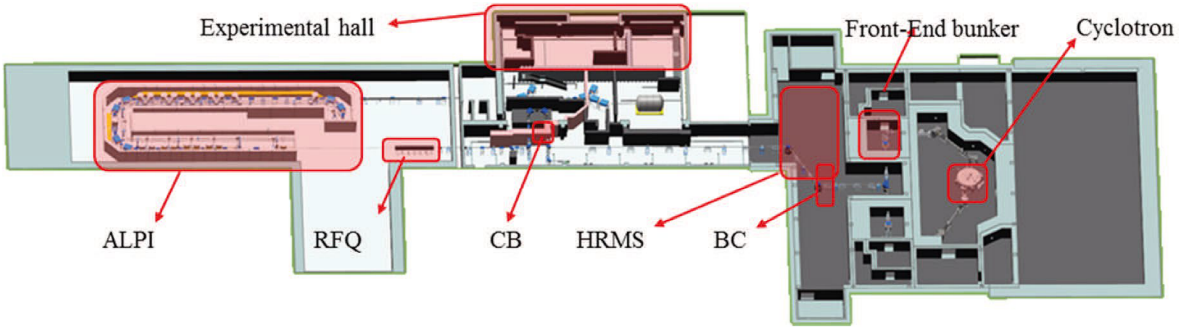


Figure 2.7: *overview of the SPES ISOL facility*

A general overview of the SPES ISOL facility can be seen in figure 2.7: a primary proton beam (generally 40 MeV – 200 μA – 8 kW) is extracted from a cyclotron and sent to the Front-End bunker, inducing nuclear reaction in the installed production target. The Front End includes all the devices necessary for the ionization, first acceleration kick, and first mass separation step (Wien Filter) of the produced isotopes. The obtained low energy isobaric beam is successively injected into a Beam Cooler (BC), a device capable of decreasing the beam longitudinal and transversal emittance, and then into High-Resolution Mass Separator (HRMS), where the second step of beam purification is performed. The obtained isotopically pure RIB can be delivered directly to users for low energy experiments or eventually be injected into a Charge Breeder (CB), a device to increase the beam charge state. Another mass/charge ratio separation step will be performed in order to select the most intense charge state and finally, the beam is post- accelerated. The post-acceleration will be performed by the combination of a Radio

Frequency Quadrupole (RFQ) and the already existing ALPI Linac. Such highly energetic isotopically pure beam can be finally sent to the experimental hall.

At SPES the chosen primary driver is the 70p commercial cyclotron [2.29] manufactured by the BEST Cyclotron Systems Inc., a member of TeamBest™ (figure 2.8). Such machine is able to deliver up to two simultaneous energetic proton beams (maximum energy 70 MeV – 49 kW) with a maximum overall intensity of 700 μA

Figure 2.8: *the BEST cyclotron used at SPES*

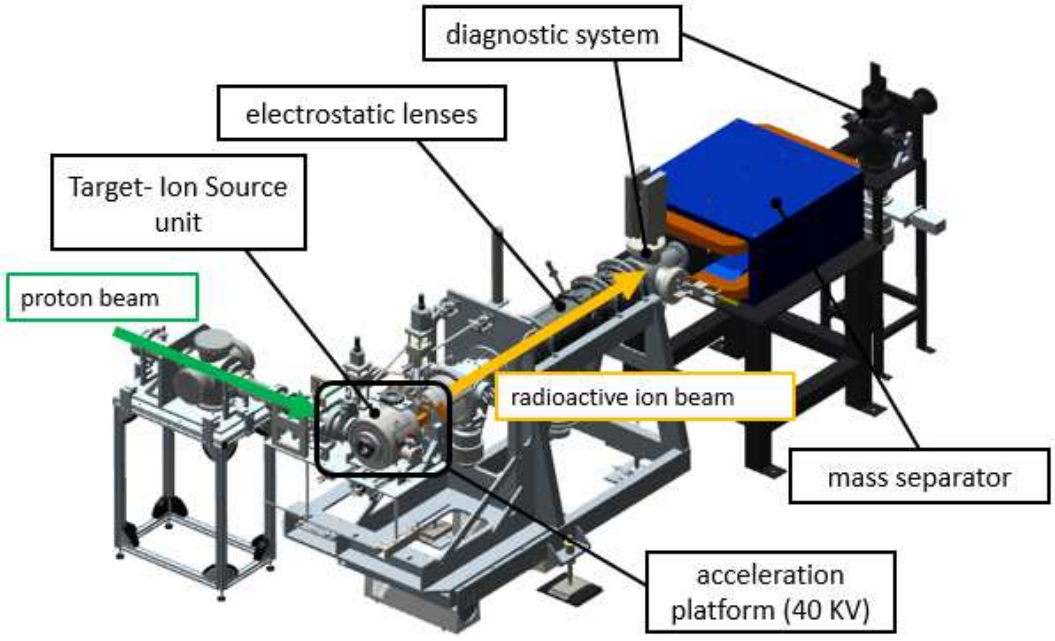


Figure 2.9*: the SPES Front-End scheme*

The SPES Target-Ion Source unit is coupled on the Front-End (figure 2.9). Such machine will be installed in a dedicated bunker and it is composed by two beam lines intersecting at the target position, called respectively the Protonic Front-End and the Radioactive Front-End. The

Protonic Front-End has the function to transport the proton beam up to the target with the desired characteristics. Indeed, it includes several diagnostics devices (such as beam profilers and Faraday cups for the monitoring of the beam current) as well as a set of collimators, in order to guarantee the appropriate beam size.

The Radioactive Front-End acts as primary accelerator for the Radioactive Ion Beam since it includes a high voltage platform (up to 40 kV), that extracts the ions generated in the TIS unit and provides them the first acceleration kick. It includes also electrostatic lenses, which are used to correct the trajectory of the beam (deflectors) or to focus (triples of quadrupoles). A Wien filter, which is a velocity separator, is used to perform the first mass separation step, in order to obtain an isobaric beam. In addition, beam diagnostic devices are installed along the Radioactive Front-End to verify the size and alignment of the RIB (beam profilers) or to measure the obtained RIB intensity (Faraday cups). Figure 2.10 shows the prototype of the Radioactive Front-End, which has been developed and tested for the SPES facility and will be soon installed in the bunker.

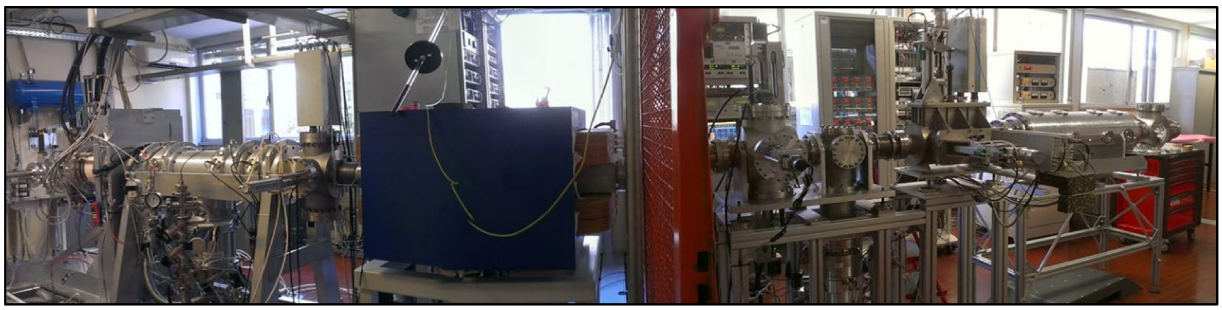


***Figure 2.10**: the SPES Front-End prototype in the offline laboratory*

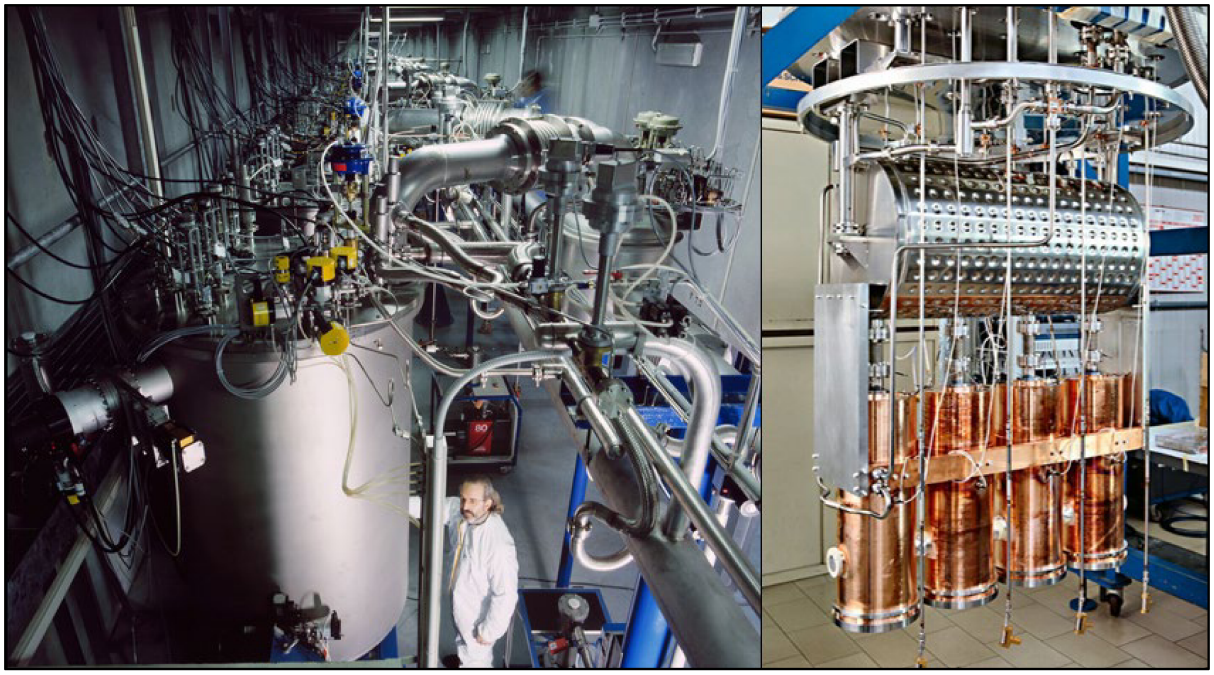


***Figure 2.11**: the ALPI linac (on the left) and a detail of its RFQ cavities (on the right)*

The post-accelerator for the SPES project is the existing ALPI Linac (figure 2.11) [2.30], which has been operating in Legnaro with stable beams. Minor upgrades of such complex are foreseen in order to improve its performances with the beams expected from SPES. The total accelerator assembly will be able to deliver ion beams at energies of 10 A MeV and, for the 130 amu mass in the neutron rich region, the expected rate available to the users will be above 108 pps.

2.3.1 The SPES Target – Ion Source unit

The Target – Ion Source (TIS) unit is core of the SPES facility, where the Primary Proton Beam (PPB) coming from the SPES cyclotron impinges a production target, inducing nuclear reactions. When uranium based targets are used, a characteristic set of neutron rich isotopes with mass ranging from 70 to 160 amu is generated as fission reactions product (figure 2.12).
SPES introduced an innovation in the design of ISOL targets developing its new concept: instead of considering the traditional thick single-piece ISOL target, the target volume is split in many thin disks. The typical SPES uranium carbide multi-foil target, designed for a 40 MeV 200 μA PPB, is made up of seven coaxial disks (40 mm diameter and 0.8 mm thickness) opportunely spaced and positioned inside a cylindrical graphite box, closed at its extremities by thin graphite disks [2.31]. The main advantages of such target design are the increased acceptable PPB intensity, since the beam power deposition is split between the seven disks, and the improved release capabilities, since the diffusion paths through the target are generally shorter.

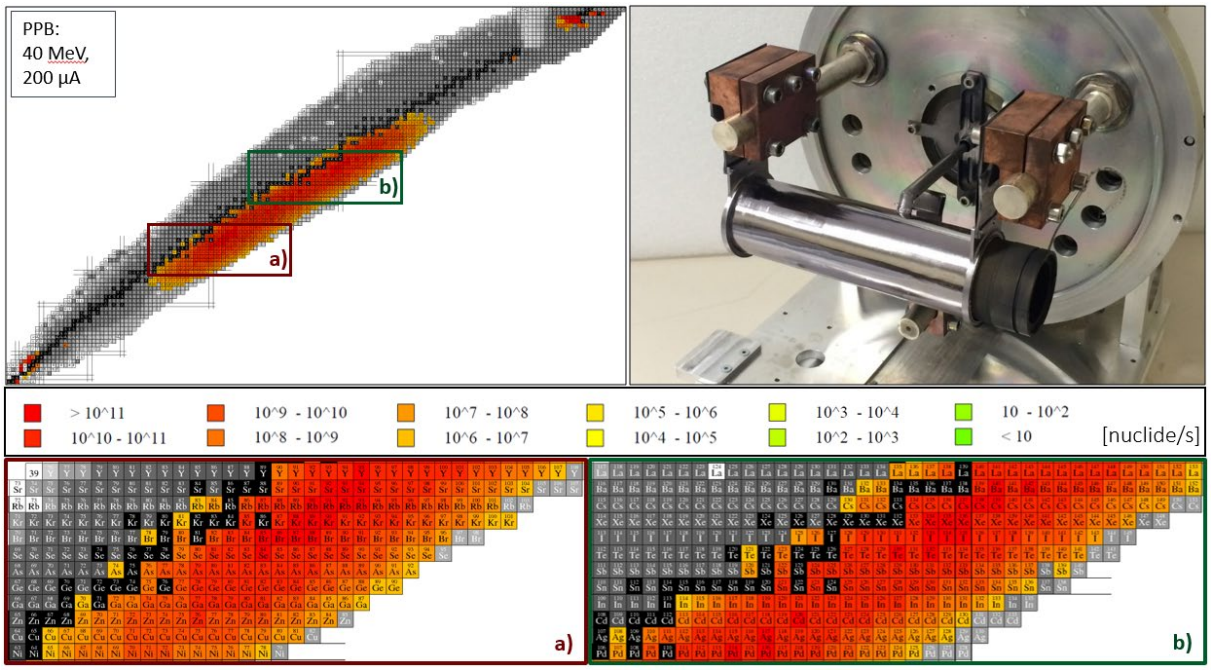


***Figure 2.12**: the expected in-target yields for the SPES Uranium Carbide target (on the top right)*

Since the maximum beam energy at SPES is 70 MeV, the production target is designed in order to dump completely the PPB. In example the 8 kW PPB (40 MeV 200 μA) is completely absorbed by the 7 disks uranium carbide target, which, thanks to the sole contribute of the deposited power, is capable of reaching a temperature level generally above 2000°C. In addition, the target disks are opportunely spaced in order to guarantee a homogeneous temperature level in the target.

The graphite target container is inserted into a tubular tantalum heater, which can provide by Joule effect the amount of power required to heat the target at high temperature during the conditioning phase (purification of the target at high temperature before the irradiation with the PPB), or in case of PPB interruption. Normally the maximum current required to reach temperatures generally above 1800 °C is 1300A, corresponding to a heating power of 10 kW.

Figure 2.13 shows the expected temperature profiles with the two different thermal loads, as calculated with a validated ANSYS® FEM model [2.32].

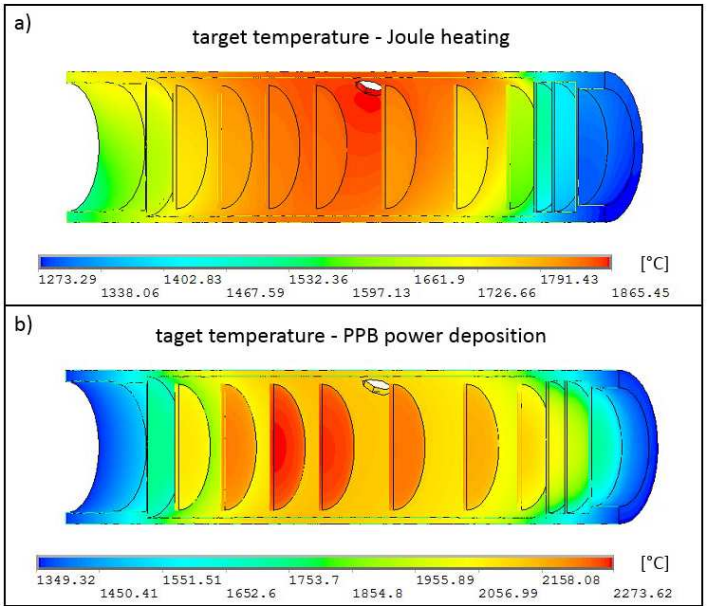


***Figure 2.13**: the expected in-target temperature distributions for the two thermal loads*

A tubular tantalum transfer line connects the production target with the ion source, where the isotopes acquire the 1^+ charge state, which is needed for their extraction. In the context of the SPES project, two types of ion sources will be used: the SPES surface ion source [2.14], and the SPES FEBIAD (Forced Electron Beam Induced Arc Discharge) [2.17] ion source. The first one will be used for both the laser and surface ionization processes, while the second one is designed for the plasma ionization process.

Figure 2.14 summarizes the planned ionization process for each of the produced elements with the SPES uranium carbide target. Some elements are currently considered not extractable, because they are not released by the target since they are refractory. Some early stage research

activities are being performed to evaluate the possibility extract them in the form of volatile molecules, thus forming molecular beams.

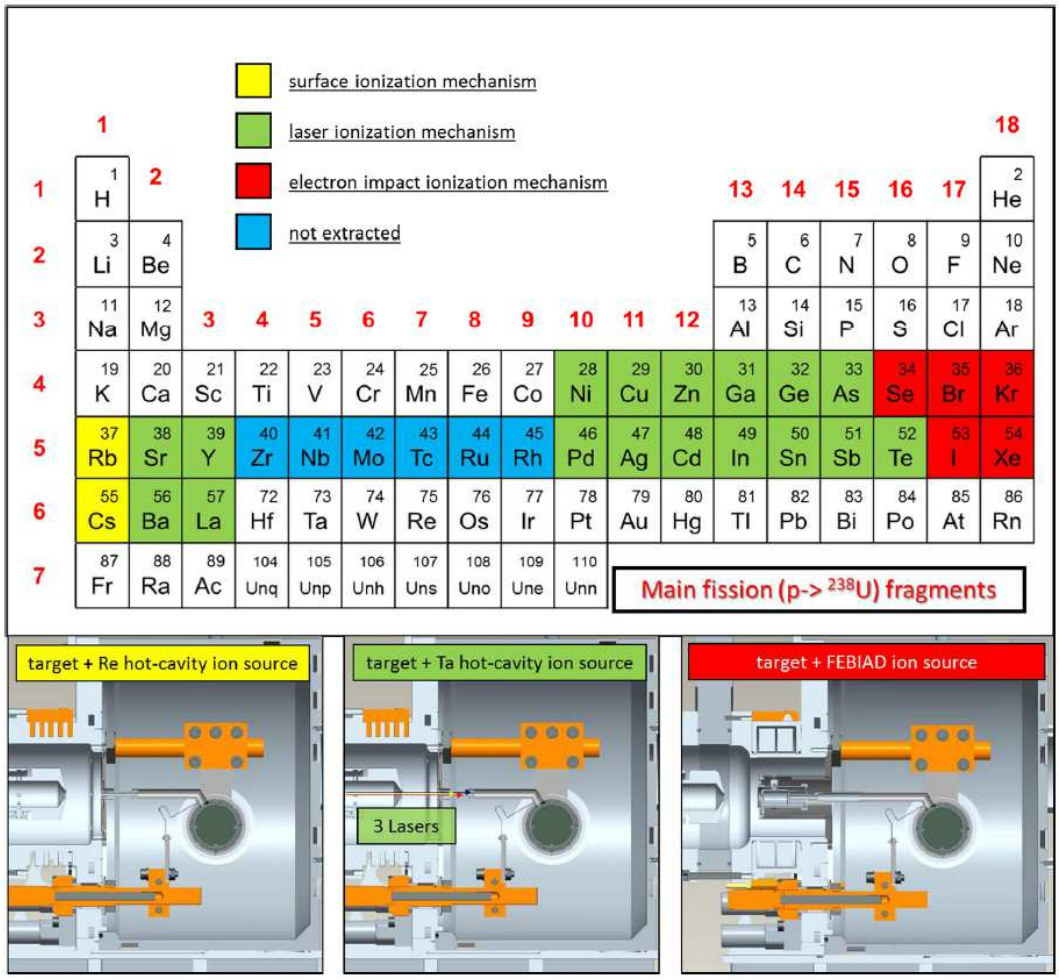


***Figure 2.14**: the SPES ion sources with an indication of the expected ionization process for the different elements produced with the SPES Uranium Carbide target*

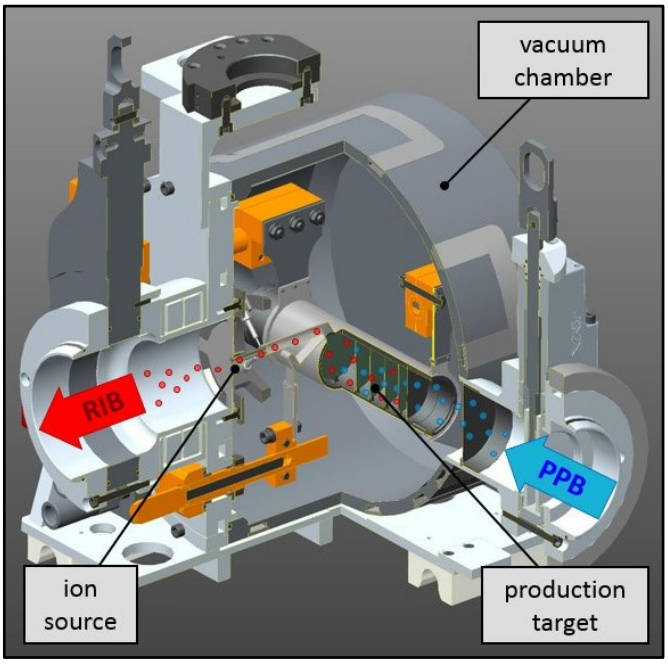


***Figure 2.15**: the SPES Target-Ion Source (TIS) unit*

The SPES TIS unit includes also a water cooled vacuum chamber, where the Target and Ion Source system is housed (figure 2.15). The entire TIS unit is generally replaced after up to 15 days of irradiation, using a remote handling system.

2.3.2 The SPES project phases

***Figure 2.16**: the four leaf clover logo of SPES identifying its main four phases*

The visionary aim of the SPES project [2.33] is to promote forefront research in nuclear structure, reaction dynamics and multidisciplinary fields like medical, biological and material sciences, exploiting the high intensity and high-quality neutron-rich produced in the INFN facility. The project has been organized in four phases, as suggested by the four leaf clover logo of SPES (figure 2.16):

- **SPES-α: at the heart of SPES: the cyclotron and ISOL target.**
  This phase, close to its completion, consists in the acquisition, installation and commissioning of a high performance cyclotron with high output current (0.7 mA) and high energy (up to 70 MeV), together with the related infrastructure for the accelerator and experimental stations. The cyclotron has the capability to deliver simultaneously beam from two exit ports, a configuration well aligned with the double mission of the laboratory: basic research and technological application developments. One of the two beams will be devoted to the ISOL facility (producing mainly neutron-rich RIBs from a Uranium Carbide target); the second will be dedicated to applied physics;
- **SPES-β: the acceleration of neutron-rich unstable nuclei.**
  The produced neutron-rich RIBs will be accelerated towards suitable targets. Thus nuclear reaction will occur forming new, extremely neutron-rich nuclei, similar to those generated in advanced stellar life stages and not found on Earth because of their short lifetime. The

investigation on such systems is a new frontier of physics, for extending the knowledge of nuclei at extreme conditions and for providing basic information in the study of stellar evolution;

- **SPES-γ: production of radionuclides for applications.**
  Such phase mostly deals with the production of radionuclides of medical interest by using the cyclotron installed at LNL-INFN as foreseen in the SPES-α phase. The goal is the production of innovative radiopharmaceutical both for ISOLPHARM (ISOL technique for radioPHARMaceuticals), which will exploit the ISOL facility technology, and LARAMED (LAboratory for the production of RAdioisotopes of MEDical interest), which is aimed to evaluate the accelerator based production of emerging radionuclides. In addition, such phase includes the study of new accelerator-based approaches for the production of conventional radionuclides;
- **SPES-δ: multidisciplinary neutron sources.**
  It aims to the study and development of an intense neutron source, impinging suitable targets with the beam from the SPES cyclotron and/or from a high intensity LINAC based on radio-frequency quadrupole (RFQ) technology. Applications of such neutron source range from nuclear astrophysics (as in example the test of electronics neutron induced damage in space), characterization of nuclear waste to experimental tumor treatments.

2.4 The ISOLPHARM project

As introduced in the previous paragraphs, the SPES project at INFN-LNL foresees applications of the installed and developed technology in various fields of research, including nuclear medicine. In this framework, ISOLPHARM is an INFN project with the visionary aim to go beyond the current state of the art of nuclear medicine by developing innovative radiopharmaceuticals prototypes exploiting RIBs producible with the ISOL technique at SPES. Its driving idea is the capability to produce high specific activity carrier-free radioisotopes thanks to the intrinsic purity of the ISOL RIBs.

Indeed, the mass separation step allows the selection of the isotopes composing the beam, leading to the generation of isobaric beams. Such beams are extremely interesting for the harvesting of medical radionuclides in the view of the fact that the specific elements of interest are provided only as the particular isotopes sought for diagnostic or therapeutic purposes.

As proof of the proposed innovation, the aforementioned method was recognized with an international INFN patent, deposited in European Union, United States of America and Canada [2.4]. Further evidence of the excellence of the project is provided by the interest of

international partners in a collaboration. In particular, the Polish research center POLATOM and the Greek institute N.C.S.R. DEMOKRITOS are interested in cooperating, for the performance of radiochemistry and radiopharmacy research using the nuclides producible in the framework of the ISOLPHARM project.

One of the project main aim is the application of the SPES technologies for the production of innovative radiopharmaceuticals of medical interest.

The key features of ISOLPHARM are (figure 2.17):

- The presence of a strong local collaboration between INFN-LNL, INFN-PD, TIFPA and UNIPD in many fields of research, ranging from the production of the RIBs to the employment of the radionuclides
- The ISOL technique, which can easily provide high specific activity radionuclides
- The INFN patent, which proves the innovation and excellence of the project
- The low environmental and social impact, since nuclear reactors are not used for the provision of the radionuclides, which traditionally may be obtained irradiating massive amount of materials, that lately become tons of nuclear wastes.

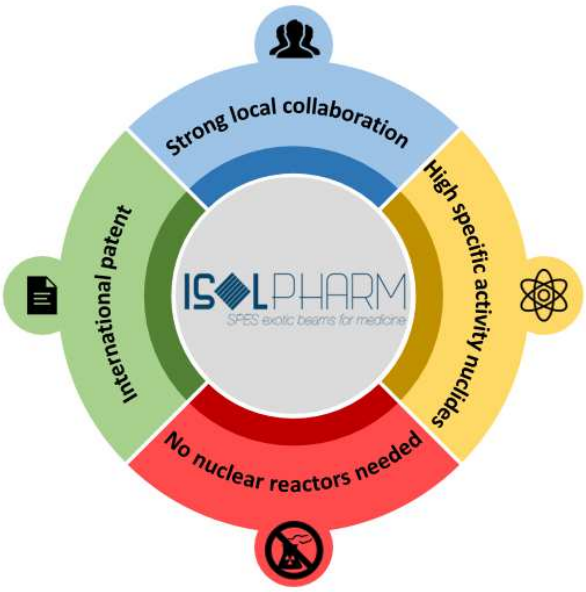


***Figure 2.17**: the ISOLPHARM project key features*

The strength points of the project are the extremely high specific activity, close to the maximum value, and the high isotope production flexibility. The first is easily achievable because the ISOL technique ensures the on-line production of high intensity and high quality radioactive ion beams. The latter refers to the fact that the same production target can be used to produce a set of isotopes of interest, simply by changing the mass separator settings and switching to a new deposition target.

ISOLPHARM will mainly deal with both fundamental aspects of the research in the field of radiopharmaceuticals:

- the isotope production, performed according to the ISOL technique,
- the new radioPHARMaceuticals labelling with the produced nuclei, after the radionuclide purification.

Radionuclides will be produced in dedicated target, called production target, by inducing nuclear reactions by means of a primary proton beam extracted from the SPES cyclotron (up to 70 MeV, 700 μA). The high working temperatures of the production target (up to 2200-2300 °C), will activate the diffusion and effusion processes, fundamental phenomena for the release and the consequent migration of the produced nuclei towards the ion source [2.6]. Afterwards, a potential difference up to 40 kV allow the extraction and acceleration of a RIB. Mass separation will provide the desired single-mass nuclide beam (Isobaric RIB) which can be sent to on an appropriate collection target, called also secondary target. Since the collected isotopes are characterized by a single mass number, a subsequent chemical separation process will provide the desired single isotope of interest. Finally, pharmaceutical processes will be performed, thus high specific activity drugs will be available for diagnosis and therapy research activities (figure 2.18).

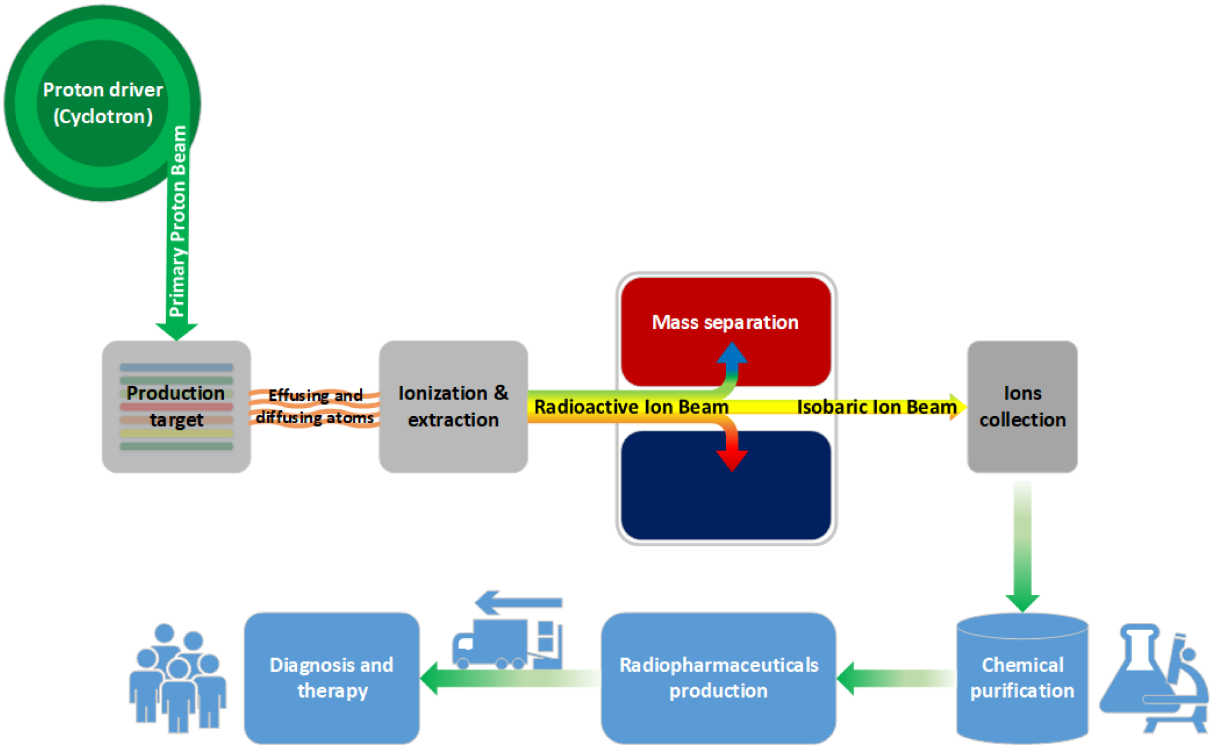


***Figure 2.18**: detailed scheme of the ISOLPHARM method*

It is easy to understand that to design and study such complex system, a wide range of multidisciplinary knowledge must be taken into account and combined, ranging from nuclear physics to engineering, material science, chemistry, technological production and

radiochemistry. In the following paragraphs the current state-of-art and achievements of the research in the framework of the ISOLPHARM project will be presented.

2.4.1 The ISOL producible isotopes of medical interest

As already introduced, in the framework of the SPES project, a multi-foil uranium carbide production target has been designed with the capability of generating approximately 10^{13} fissions when impinged by a 40 MeV 200 μA proton beam. The production yields of such target were widely studied with Monte Carlo codes, and the models were also experimentally validated with appropriate tests at ORNL (USA)[2.34].

The first idea of the ISOLPHARM project arose by noticing that some of the SPES target fission fragments are ^{89}Sr, ^{90}Y, ^{125}I, ^{131}I, ^{133}Xe, which are isotopes already known in nuclear medicine. In addition to the aforementioned nuclides, the theragnostic ^{64}Cu, whose medical application is in advanced research stage, was soon identified as other good candidate for a feasibility study for the ISOLPHARM project (figure 2.19).

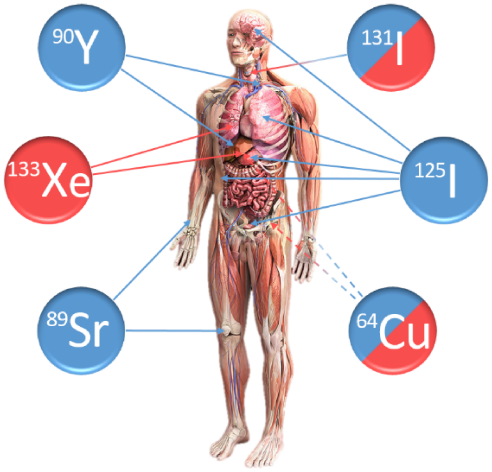


***Figure 2.19**: nuclides considered for the ISOLPHARM feasibility study*

It was soon realized that the ISOLPHARM method will have the capability of going beyond the state of art of the current radiopharmaceuticals research topics. Indeed, the ISOL technique can provide a wide range of carrier-free isotopes from many different regions of the nuclide chart, once identified a proper production target.

The availability of such isotopes may potentially open new research lines for the development of a new generation of radiopharmaceuticals, based on nuclides so far never studied, because of their production difficulties with traditional techniques. Up to now, almost 60 isotopes were found, that are suitable for their production according to the ISOL technique. They were identified because of their decay properties conform for radiolabeling drugs, in terms of half-

life and radiation emission. Figure 2.20 summarizes all the selected ISOL isotopes, identifying their possible use in diagnostic, therapeutic and theranostic radiopharmaceuticals.

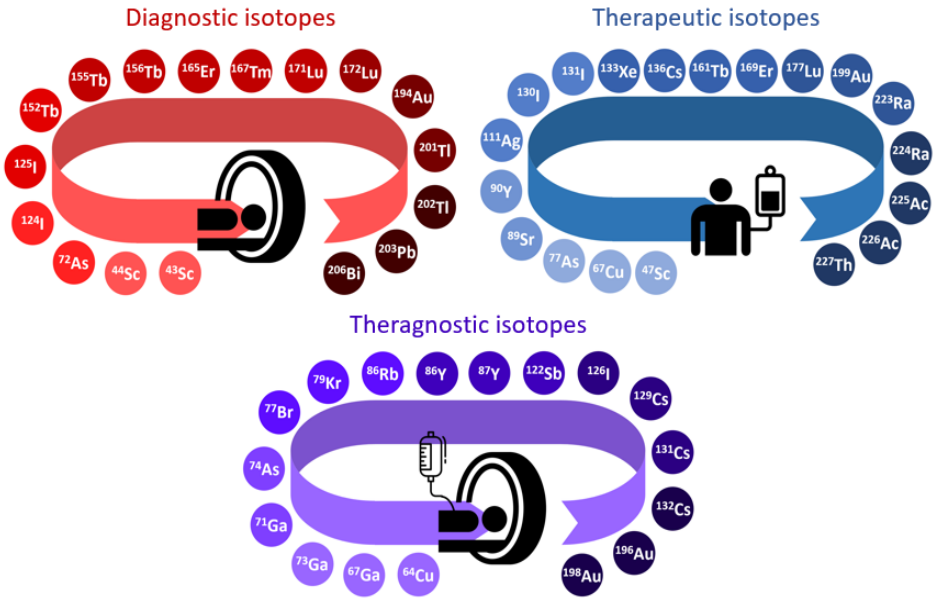


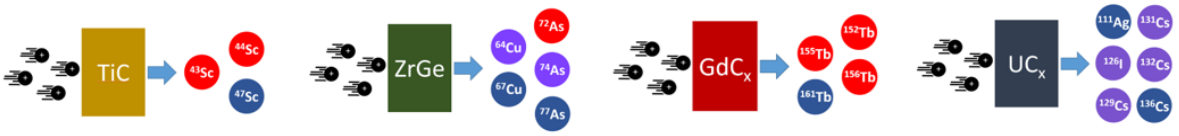
***Figure 2.20**: ISOL nuclides of possible medical interest*

2.4.2 The research of new ISOL targets

Once some isotopes of potential interest have been identified, the following step is the development of the most suitable dedicated production target. The selection of the target materials deals with many aspects, concerning both nuclear physics and material science.

Nuclear physics concerns regard the production yield for the desired nuclides: in fact, the target material should include stable isotopes that can produce the desired nuclei with a satisfactory proton induced nuclear reaction cross section. Material science aspects concern the material chemical and physical properties. Indeed, ISOL production target have to be refractory (or in general more refractory than the element whose production is sought) since they normally work at high temperature (over 2000°C in most cases) to allow and facilitate the release of the desired species. In addition, at SPES only solid targets can be handled for safety concerns.

Furthermore, material technology aspects have to be taken into account while developing a new target concept: precisely the microstructural properties influence the isotope release (e.g. porosity, pore size and size distribution, average length of the diffusion paths in crystals, tortuosity of the effusion paths through pores) and the reliability of the target (thermomechanical properties). In this way, much attention must be paid in the target manufacturing process, considering also new technologies such as additive manufacturing, that ensures more control in the final product microstructure.



TiC isotope production (100 µA 40 MeV PPB, 5 irradiation days)											
Isotope	Half-life	Decay radiations								Produced activity	
	$t_{1/2}$	β-		β+/ϵ		γ		Auger		[MBq]	[mCi]
^{43}Sc	3.891 h	/	/	100%	b+	22,50%	373 keV	8,93%	3.3 keV	3,23E+04	873,14
^{44}Sc	3.97 h	/	/	100%	b+	99,90%	1157 keV	4,14%	3.3 keV	2,39E+05	6445,95
^{47}Sc	3.3492 d	100%	0.6 MeV	/	/	68,30%	159 keV	0,22%	(4 keV)	8,14E+04	2199,08
ZrGe isotope production (100 µA 70 MeV PPB, 5 irradiation days)											
Isotope	Half-life	Decay radiations								Produced activity	
	$t_{1/2}$	β-		β+/ϵ		γ		Auger		[MBq]	[mCi]
^{64}Cu	12.701 h	38,50%	0.579 MeV	61,50%	b+	0,48%	(1345 keV)	22,51%	6.54 keV	5,52E+04	1491,30
^{67}Cu	61.83 h	100%	0.561 MeV	/	/	48,70%	184.577 keV	6,87%	7.03 keV	1,39E+03	37,58
^{72}As	26.0 h	/	/	100%	b+	81%	833.99 keV	5,56%	8.56 keV	2,22E+05	5997,30
^{74}As	17.77 d	34,20%	1.352 MeV	66,20%	b+	0,29%	(1204 keV)	14,50%	8.56 keV	1,44E+04	389,43
^{77}As	38.83 h	100%	0.683 MeV	/	/	1,59%	239 keV	0,06%	(9.67 keV)	4,26E+01	1,15
GdC$_x$/GdB$_4$ isotope production (100 µA 40 MeV PPB, 5 irradiation days)											
Isotope	Half-life	Decay radiations								Produced activity	
	$t_{1/2}$	β-		β+/ϵ		γ		Auger		[MBq]	[mCi]
^{152}Tb	17,5 h	/	/	100%	b+	3,00%	974 keV	4,80%	34,9 keV	2,02E+05	5,46E+03
^{155}Tb	5,32 d	/	/	100%	ϵ	1,48%	367,36 keV	7,90%	34,9 keV	5,77E+05	1,56E+04
^{156}Tb	5,35 d	/	/	100%	ϵ	12,20%	1422 keV	8,10%	34,9 keV	2,66E+05	7182,70
^{161}Tb	6,89 d	100%	0,593 MeV	/	/	10,20%	75 keV	1,46%	37,2 keV	1,67E+03	45,26
SPES UC$_x$ isotope production (200 µA 40 MeV PPB, 5 irradiation days)											
Isotope	Half-life	Decay radiations								Produced activity	
	$t_{1/2}$	β-		β+/ϵ		γ		Auger		[MBq]	[mCi]
^{111}Ag	7.45 d	100%	1.036 MeV	/	/	6,70%	342 keV	0,04%	(19.3 keV)	8,29E+04	2241,85
^{126}I	12.93 d	47,30%	1.258 MeV	52,70%	b+	32,90%	666.33 keV	5,53%	22.7 keV	3,65E+01	0,99
^{129}Cs	32.06 h	/	/	100,00%	b+	30,60%	371.92 keV	13,10%	24.6 keV	4,62E+00	0,12
^{131}Cs	9.689 d	/	/	100,00%	ϵ	/	/	9,30%	24.6 keV	3,68E+01	0,99
^{132}Cs	6.480 d	2%	1.279 MeV	98,13%	b+	1,58%	464 keV	9,40%	24.6 keV	2,14E+02	5,79
^{136}Cs	13.04 d	100%	2.548 MeV	/	/	80,00%	1048 keV	1,24%	26.4 keV	1,16E+04	313,75

***Figure 2.21**: list of ISOLPHARM nuclides and a preliminary indication of the producible activities*

In the framework of ISOLPHARM, the first research efforts in target development will be focused on a selected group of isotopes that are particularly promising.

In example, new diagnostic and therapeutic radiopharmaceuticals can be obtained using Scandium isotopes (^{43}Sc, ^{44}Sc, ^{47}Sc), in particular matching ^{43}Sc and ^{47}Sc. Such isotopes may be producible at SPES using titanium based targets, such as Titanium Carbide (TiC). This topic which will be presented in Chapter 5.

^{64}Cu is a radionuclide perfectly suitable for PET (diagnosis), whereas ^{67}Cu has very good decay properties for therapy, but is extremely difficult to produce with the current techniques. For such nuclides a dedicated Zirconium Germanide (ZrGe) target is under development, with the capability to produce also promising Arsenic isotopes: the diagnostic ^{72}As the theragnostic ^{74}As and therapeutic ^{77}As. Chapter 4 will be dedicated to such developments.

Terbium has some interesting isotopes for both diagnosis (^{152}Tb, ^{155}Tb and ^{156}Tb) and therapy (^{161}Tb). In such case Gadolinium based targets are being considered (Chapter 6)

Finally, the SPES UC_x target has the capability of providing other interesting nuclei such as ^{111}Ag, ^{126}I and Cesium isotopes (^{129}Cs, ^{131}Cs, ^{132}Cs, ^{136}Cs), as widely discussed in Chapter 3. Figure 2.21 summarizes the aforementioned isotopes, highlighting their decay properties along with preliminary Monte Carlo results for the expected in-target produced activity within 5 days.

2.4.3 The development of beams of medical interest

Once the proper production target has been identified, the capability to ionize, extract and transport a beam of the desired element at SPES has to be verified. Currently this research activity is led in the offline Front-End laboratory at SPES, with stable isotope beams of the same chemical element of the nuclides of interest, using the SPES Surface Ion Source and the SPES FEBIAD ion source (Laser ionization is not implemented in the off-line laboratory). Indeed, since the ionization and transport processes involve only the chemical properties, the results can be reasonably extended to the corresponding radioactive isotopes, that show the same chemical behavior.

With a view to evaluate the overall efficiency of the ionization, transport and mass separation processes and to test the feasibility of the ISOLPHARM project, preliminary tests with strontium, yttrium and iodine stable beams were performed. Such tests were executed according to the Mass Marker technique [2.35, 2.36], which will be explained in detail in the next chapters. Essentially, such method consists in connecting the ion source with a small oven containing a well calibrated amount of the desired element, usually tens of μg (Figure 2.22).

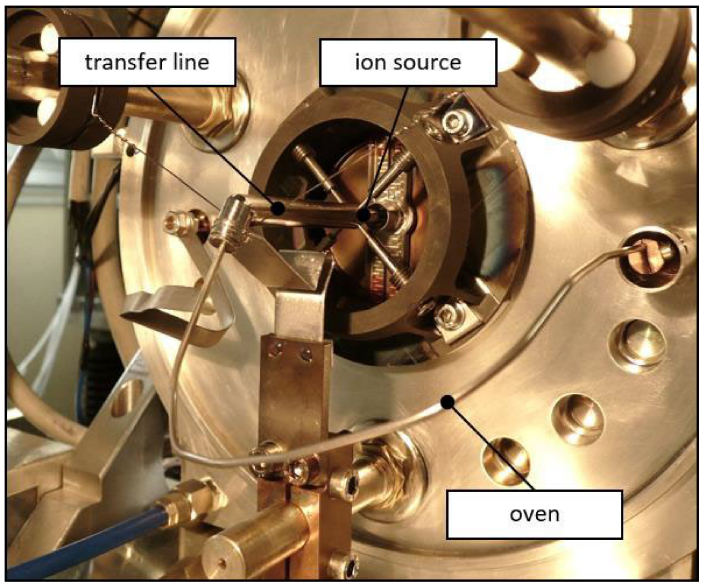


Figure 2.22: *the apparatus used for the ionization tests with the Mass-Marker technique*

The oven temperature is stepwise increased up by Joule effect heating, allowing that the loaded atoms gradually escape towards the ion source. By integrating in time the beam current for the element of interest it is possible to discover the total amount of atoms that were ionized,

extracted, transported and selected through mass separation. The ratio of such amount to the known number of loaded atoms is the efficiency of the beam formation process, hence the expected in-target production yields have to be corrected with such factor in order to estimate the total available isotope amounts at the end of the ISOL process.

In addition, silver, copper, scandium and terbium beams are being developed and will be presented in detail in the following chapters. Such tests represent a proof of principle of the validity of the separation and collection methodologies that will be used in ISOLPHARM.

2.4.4 The development of the collection targets

A subsequent important topic is the development of appropriate collection targets, where the extracted nuclei forming the beam are stopped and implanted. For the development of the beam the technology already studied in the framework of the SPES project is in most cases sufficient, but, since such secondary targets are unique to ISOLPHARM, new devices have to be designed. The selected design for such collection targets consists in a thin solid substrate that have to be capable of trapping the highest quantity of the impinging radioactive ions and to release them with appropriate chemical dissolution processes. Such substrates are generally produced by pressing in a dye very pure powders of the selected material.

Preliminary tests were performed collecting beams of stable isotope of strontium, yttrium and iodine in order to validate the chosen secondary target and evaluate its isotope harvesting efficiency [2.37]. For strontium and yttrium, pure sodium chloride substrates were used, whereas iodine was deposited on activated carbon targets (figure 2.23).

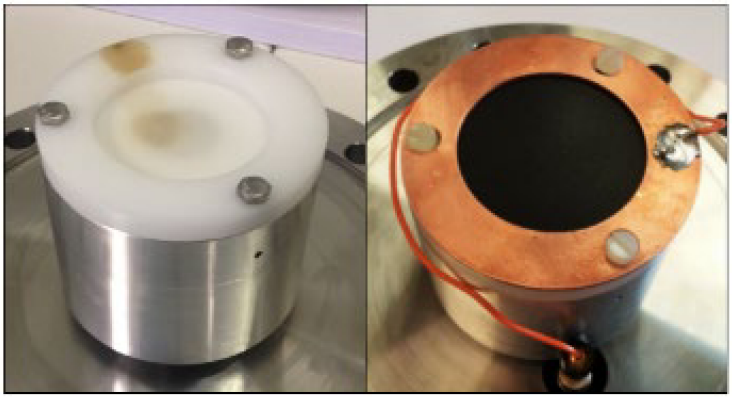


***Figure 2.23**: the secondary targets used for the deposition tests, a NaCl disc (on the left) and an activated carbon disc (on the right)*

In addition to the development of the substrates, a new secondary target station has to be designed, where such disks can be held and irradiated. A new target module is under study taking into account that:

- the overall activity in the collection target includes only the desired isotopes and eventually low amounts of isobaric contaminants,
- the device has to be easily uncoupled from the beam line and taken to the radiochemistry laboratories,
- the size of the device has to be easy to open to access the collection target.

According to such requirements a first prototype of secondary target module was developed, as shown in figure 2.24 [2.38].

***Figure 2.24**: the prototypical secondary target unit* [38].

It is a small and lightweight device in order to fulfill the requirements of easy handling, and can be easily opened by removing some accessible screws. Since the overall activity in the secondary target is generally due only to the desired isotopes, an internal tungsten shielding should be sufficient to prevent the exposure to excessive radiation doses to operators while manually removing the target module from the beam line. Such device will be described in detail in the dedicated appendix B.

2.4.5 Radiochemistry studies

As previously discussed, mass separation, as one of the fundamental steps of the ISOL technique, provides isobaric RIBs that can be collected using appropriate secondary targets. However, the product obtained by the dissolution of such targets may not be enough pure for the subsequent radiopharmaceutical processes. Indeed, also isobaric and pseudo-isobaric contaminants can affect the purity of the final radiopharmaceutical precursors, especially when long-lived radioisotopes or stable nuclei of the same mass are produced in the primary target along with the desired ones. If the vapor pressure of such unwanted species is low enough, they may escape form the production target, be ionized and finally collected on the deposition

substrate together with the radionuclides of interest [2.28]. As a consequence, after secondary target recovery and dissolution, an additional step of chemical purification may be required in order to harvest only the desired nuclei.

Radiochemistry studies include also the eventual development of a bi-functional chelator, a molecule that can both stably trap the isotope and its daughter nuclides and allow the binding with the targeting agent.

Regarding such radiochemical aspects, the preliminary case studies of ^{89}Sr e ^{90}Y were considered as proof of concept in the early stages of the ISOLPHARM project.

^{89}Sr (half-life: 50.563 days) is a radionuclide normally used as a chloride ($SrCl_2$) for palliating painful bone metastases secondary to prostate cancer [2.39] and can be produced with the SPES UC_x target [2.31]. Since 89-mass Uranium-fission products are short-lived neutron-rich radionuclides which rapidly decay to ^{89}Sr, after a very short decay time only ^{89}Sr and its stable daughter ^{89}Y can be found in the collection target.

^{90}Y (half-life: 64 hours) can also be produced according to the ISOL technique, using the SPES UC_x target [2.31]. In such case the main isobaric contaminant is its long lived parent ^{90}Sr (half-life: 28.79 years), whereas the eventually produced stable ^{90}Zr is not extracted from the target, being a refractory element. Thus, a method for the chemical separation of strontium form yttrium was developed. An ion exchanger inorganic material, Sodium nonatitanate (Na4Ti9O20·xH2O), abbreviated as NaTi, was chosen for its very high selectivity and affinity for strontium [28]. since the affinity for strontium of NaTi is PH-dependent, the trapped strontium can be lately recovered through the elution of the resin with an acid solution. Furthermore, in the case of ^{90}Y, NaTi could be potentially used to develop a ^{90}Sr/^{90}Y generator loading the side-produced ^{90}Sr, since the ^{90}Y produced by its decay is unbound to the resin and can be milked from the resin through the elution of demineralized water.

In addition to the proof-of-concept investigations on the ^{89}Sr and ^{90}Y case studies, ongoing radiochemistry research is being performed for other medically relevant radionuclides which can be produced with the ISOL technique. Among such species, ^{111}Ag is one of the most promising because of its decay properties (half-life of 7.45 days, beta- emission with 1037 keV end-point energy, low associated gammas), and the possibility to produce it with the SPES Uranium Carbide target. Such studies include:

- the development of purification methods to eliminate ^{111}Cd, the main isobaric contaminant;
- the study of Ag^+ complexation chemistry to develop a suitable bifunctional chelator, the investigation of the complex formation and disruption kinetics, and the in vitro study of their toxicity.

2.4.6 Radiopharmaceuticals development studies

As stated in the previous paragraph, the ISOLPHARM radiochemistry research activities are aimed to finally provide the nuclide of interest in a very pure form trapped into a bifunctional chelator. The next step to finalize the development of prototypical drug is to study and synthetize appropriate targeting agents and molecules capable of linking the latter with the aforementioned bifunctional chelator. As clarified in Chapter 1, targeting agents are organic compounds that selectively bind with specific biological targets that are normally overexpressed in some particular cancer cells types.

In the framework of ISOLPHARM, a prototypical therapeutic radiopharmaceutical radiolabeled with ^{111}Ag is being developed. Currently, two possible biological targets are being considered:

- Calreticulin (CRT), an endoplasmic chaperon molecule that can translocate from the cytosol to the cell surface, particularly during ER stress induced by *e.g.*, drugs, UV irradiation and microbial stimuli [2.40];
- Cholecystokinin receptor 2 (CCK2R), a biological target overexpressed in different tumor types like pancreatic, medullary thyroid, lung, breast, ovarian, gastrointestinal tract and colon [2.41].

Once the prototypical radiopharmaceutical has been developed, firstly *in-vitro,* secondly *in-vivo* tests will be performed to evaluate the efficacy of the new drug and its stability in a biological environment. Such tests will be performed in collaboration with ISOLPHARM partners.

2.5 The ISOLPHARM_Ag CSNV project: a case study

As already stated, in the framework of ISOLPHARM, the potential medical application of a wide set of nuclides can be evaluated and, if promising, studied into detail. Each of the latter nuclei can consequently represent a case study, and every step of the radiopharmaceutical research and development chain has to be considered, from the ISOL target material choice to the selection and synthesis of an adequate targeting agent.

One of such promising nuclei is ^{111}Ag, very suitable for internal radiotherapy for its decay properties. Indeed, it is a β^- emitter with medium half-life (7.45 d), convenient β^- energy and medium tissue penetration (average β energy 360 keV and average tissue penetration 1.8 μm) and low percentage of associated γ-emission [2.42]. The production of ^{111}Ag in carrier-free form, that enhances the efficiency of biomolecule radiolabeling, is not possible via classical

neutron irradiation methods, unless an enriched ^{110}Pd target is used. The ISOL method could be suitable to produce ^{111}Ag at high purity with high production rate (see table 2.1). The purity is indeed achieved thanks to the already explained on-line mass separation, which allows the elimination of all the isotopic contaminants, except for only the isobar ^{111}Cd. Indeed, the other radionuclides of the mass 111 isobaric chain, decay quickly to ^{111}Pd, a refractory parent nuclide of ^{111}Ag, that for this reason cannot escape from the target, and eventually some ^{111}Ag may generate its stable daughter ^{111}Cd, that may be collected on the secondary target. Radioactive silver nuclides were already successfully produced using a SPES UC_x target prototype and delivered to experimental areas in dedicated experiments.

***Table 2.1**: in target estimated production for ^{111}Ag with the ISOL method at SPES.*

^{111}Ag production (SPES UC_X target, 40 MeV, 200 μA)		
Time	Produced activity	
[days]	[GBq]	[Ci]
0,5	9,46	0,26
1	19,17	0,52
1,5	28,48	0,77
2	37,39	1,01
3	54,01	1,46
4	69,15	1,87
5	82,95	2,24

In the framework of the ISOLPHARM, a two-year experiment collaboration project named ISOLPHARM_Ag was submitted and accepted by INFN CSNV (Commissione Scientifica Nazionale V). Such project has the aim of studying and demonstrating as a proof of principle the production and use of the promising ^{111}Ag, investigating both its ISOL production and its possible application as a radiopharmaceutical precursor, with both computational and experimental investigations. Computational studies will focus on the development of Monte Carlo codes able to estimate the production and release of ^{111}Ag from the primary target. Such codes are expected to be computing intensive, thus they will be executed thanks to the support of a cloud infrastructure in the CloudVeneto. The experimental studies will involve the ionization and transport of silver, that will be tested at the SPES Front End, the chemistry studies to develop and characterize silver complexes and biological studies on such molecules, to evaluate the radionuclide carrying to different cellular targets. The ISOLPHARM_Ag experiment includes the participation of 3 INFN sections/laboratories, namely Legnaro National Laboratories (INFN-LNL), Padova division (INFN-PD) and the Trento Institute for Fundamental Physics and Applications (INFN-TIFPA). In particular:

- LNL participates to both computational and experimental studies in physics, chemistry and biology, thanks to the competences of its personnel (which includes researchers from

Padova University, Departments of Chemical Sciences and Pharmaceutical Sciences) in development of Monte Carlo codes, beam transport, chemistry and pharmaceutical development.

- PD is involved in computational studies, due to the competences of the involved personnel in setup and maintenance of cloud infrastructures (CloudVeneto) and in software engineering for the creation of dedicated workflows for parallel execution of MC codes and development of web based user portals.
- TIFPA takes part to experimental activities regarding chemistry (characterization of properties of the developed complexes) and biology (development of cell cultures, targeting studies) due to the interdisciplinary competences of the involved personnel and the presence of the Biotech Lab.

2.5.1 Project organization

As already introduced, the ISOLPHARM_Ag project has three main goals, based on the application of the ISOLPHARM method to the production of ^{111}Ag radionuclides as radiopharmaceuticals precursors:

- Investigation of the production and release capabilities of ^{111}Ag from the SPES fission target, exploiting production, diffusion and effusion complex Monte Carlo codes on a dedicated grid computing infrastructure
- Study of the Ag chemistry in order both to develop suitable purification techniques from contaminants and to synthesize new chelators for Ag^{+} with controlled thermodynamic, kinetic and toxicity properties
- Development of targeting agents to transport ^{111}Ag to defined tumor cells

According to such three main objectives, the project was organized in three tasks, as shown in figure 2.25, in which each of the participant Institutions will have different contributions. The general supervision of the project is managed by INFN-LNL.

***Figure 2.25**: contribution of the different participants to the project tasks.*

2.5.1.1 Task 1 - Computing

The computing task involves INFN-PD and INFN-LNL and is aimed to the development of both the cloud infrastructure and the Monte Carlo codes for two different simulation studies. Such two case studies are:

- **Simulation of radionuclides production in the ISOLPHARM target**

The Monte Carlo software FLUKA [2.43] was used to perform preliminary evaluations of the amounts of nuclides of medical interest that can be produced in the ISOLPHARM targets. With the aim of improving the reliability of such data, dedicated simulations using different cross section libraries and models in Geant4 [2.44] could be run in parallel, in order to have a consistent amount of production data to be compared, for different configurations (target composition, geometry, etc.).

- **Simulation of radionuclides release from the ISOLPHARM target**

A complex Geant4 Monte Carlo model of target release (diffusion and effusion) is currently under development. Due to its complexity, such model requires a high computing power to produce plausible results in a reasonable time. Thus, the use of cloud computing resources could ensure the performance of the needed amount of simulations to obtain enough statistically significant data, and consequently the release of the medically relevant radionuclides could be studied considering different target configurations (materials, geometry, temperature, etc.).
For both these case studies the use of cloud computing resources is beneficial, in terms of both amount of producible data and required computing time. In the framework of this task, in addition to the development of the different codes, the creation of dedicated processing workflows was necessary to optimize the performance of parallel computing. Moreover, the development of a web-based user portal is foreseen, where user can both launch simulation and consult the produced results. A more detailed description of both the codes and the cloud infrastructure is presented in chapter 7.

2.5.1.2 Task 2 – Cold chemistry

The activities in task 2 involve both TIFPA and LNL, and are aimed to study:

- the ionization and acceleration of Ag using the SPES Front End in off-line modality, the production of the secondary targets for Ag^+ deposition and the deposition studies as well;
- the development of purification methods to eliminate the isobaric contaminants due to the method;

- the study of Ag^{+} complexation chemistry to develop a suitable bifunctional chelator, the investigation of the complex formation and disruption kinetics, and the in vitro study of their toxicity.

In the framework of this task, the synthesis and characterization activities will be performed using non-radioactive (cold) silver, because its chemistry is basically the same as that of ^{111}Ag. A more detailed overview of the activities related to ionization and acceleration tests of silver isotopes is presented in chapter 3.

2.5.1.3 Task 3 – Molecular biology

Also the activities in task 3 involve both TIFPA and LNL, and are aimed to study specific biological targets, that are overexpressed by cancer cells in specific conditions and to develop suitable targeting agents. Two possible biological targets were identified: Calreticulin (CRT), that is overexposed on the cell membrane if the cell is exposed to ionizing radiation, and 2.3.2. Cholecystokinin receptor 2 (CCK2R), a molecule is overexpressed in different tumor types like pancreatic, medullary thyroid, lung, breast, ovarian, GI tract and colon.

The in-vitro studies for the development of the targeting agents foresee also the preliminary radiolabeling with ^{68}Ga of the synthetized molecules.

2.6 Conclusions

In this chapter a detailed overview of the SPES facility was presented, together with its applications, with a deep focus on ISOLPHARM. Both SPES and ISOLPHARM are widely multidisciplinary projects, and require a large variety of competences, ranging from nuclear physics to engineering, from electronics to chemistry and material sciences, and, in the case of ISOLPHARM, from pharmaceutical sciences to biology.

From a general point of view, ISOLPHARM and SPES share most of the developments and studies, in particular for the targets and ion sources. Indeed, even if on the one hand ISOLPHARM fully inherited the Uranium Carbide targets, the ion sources technologies and will exploit part of the SPES accelerator system, on the other ISOPHARM will require to develop new targets, or to further develop and investigate the existing ion sources, thus populating the SPES available beams scenario with new nuclides.

In the following chapters, together with the Uranium carbide target, several additional targets are presented, that were developed to produce isotopes of specific elements of potential medical interest.

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Chapter 3

The SPES UC_x production target: from early studies to innovative medical isotopes

"Omnes scientiae sunt connexae et fovent auxiliis sicut partes ejusdem totius, quarum quaelibet opus suum peragit non propter se sed pro aliis."

"All sciences are connected; they lend each other material aid as parts of one great whole, each doing its own work, not for itself alone, but for the other parts; as the eye guides the body and the foot sustains it and leads it from place to place."

Roger Bacon (English philosopher and Franciscan friar, c. 1219/20 – c. 1292), *Opus Tertium,* chapter 4.

3.1 Introduction

When a 40 MeV proton beam with an intensity up to 200 μA will impinge the SPES Uranium Carbide target, up to 10^{13} fissions/s will be induced, thus generating a wide variety of neutron-rich nuclei, with mass ranging from 70 to 160 amu [3.1]. The first idea of the ISOLPHARM project came upon noticing that, among the available exotic species at SPES, significant amounts of state-of-art medical radionuclides could be produced, extracted as RIBs, and eventually properly collected, if a suitable apparatus would have been installed at the SPES facility [3.2]. In particular, the medically used species that could be produced by fission are ^{89}Sr [3.3], ^{90}Y [3.4], ^{125}I [3.5, 3.6] and ^{131}I [3.7]. As a consequence, in the early stages of the ISOLPHARM project, a feasibility study was performed considering as main case studies the Strontium, Yttrium and Iodine isotopes. Such feasibility studies involved the evaluation of the

produced yields with suitable Monte Carlo models, and the test of the capability to extract, transport and collect an isobaric beam using stable isotopes of the aforementioned elements.
Considering the promising results obtained with such preliminary feasibility tests, new case studies were subsequently explored, focussing on more innovative nuclides, thus expressing the true potential of the ISOLPHARM method, that is the capability to expand the variety of available medical radionuclides. For example, the SPES Uranium Carbide target could be used to produce amounts ^{111}Ag, a neutron rich nucleus with suitable properties for therapeutic applications.
The particular case study of ^{111}Ag was indeed chosen for ISOLPHARM_Ag, a CNSV project supported by INFN, with the aim to prove the feasibility of ^{111}Ag-based radiopharmaceutical using the methods and the technologies under developments for SPES-ISOLPHARM.
In the following chapter the SPES Uranium Carbide target will be presented in detail, as well as the preliminary feasibility tests with Strontium, Yttrium and Iodine. Finally, this chapter includes the calculation and tests performed for the evaluation of the ISOL producible amounts of ^{111}Ag, as foreseen in the framework of ISOLPHARM_Ag.

3.2 The SPES Uranium Carbide target

As already introduced, the SPES Uranium Carbide target design was studied with the aim to ensure its capability of generating approximately 10^{13} fissions when impinged by a 40 MeV 200 μA proton beam and of working at an extremely high temperature level, above 2000°C [3.8].

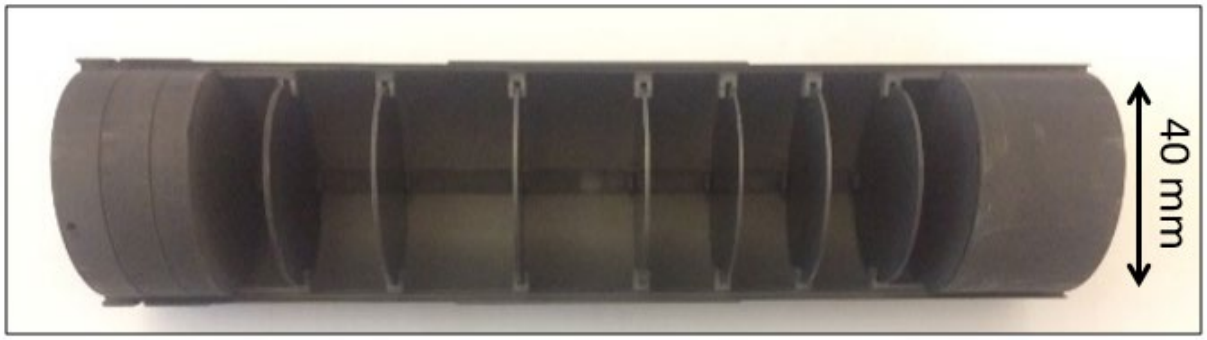

***Figure 3.1**: a SPES target multi-foil prototype*

The characteristic target architecture (figure 3.1) that was developed at SPES consists in seven Uranium Carbide disks, characterized by a diameter and a thickness of 40 and 0.8mm respectively, inserted and opportunely spaced in a tubular graphite box. Such multi-foil design has the intrinsic advantage of splitting the proton beam power deposition between the seven disks, thus increasing the surface to volume ratio respect to bulk targets. That implies that a target with such architecture can accept a more intense primary beam current, since the eventual

heating power generated by the interaction of the beam particles with the target matrix is dissipated with more efficiency, being thermal radiation the predominant heat exchange process in vacuum. In fact, boosting the primary beam intensity means increasing the producible yields of the nuclides of interest.

In addition, the disk spacing was studied in order to homogenize the target temperature, since the seven disks will absorb a different amount of power, being the last ones closer to Bragg peak.

One of the extremities of the target assembly is closed with a thin graphite windows (0.2 mm thickness), which hinders the migration of the produced nuclei outside from the target, but is alongside transparent to the proton beam. At the other side three dumping disks with a thickness of respectively 0.8, 0.8 ,1 mm are capable to dump all the residual proton beam.

The design of such a target was developed making use of massive amount of Monte Carlo simulations [3.1, 3.9], used for the estimation of both the production yields in the desired energy range and the proton beam power deposition, alongside with calculations for radioprotection purposes.

Thermal simulations of the target behavior were per-formed using the Finite Element Method software ANSYS® [3.10], considering as input the proton beam power deposition calculated with the aforementioned Monte Carlo codes [3.9].

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 power coming from the proton beam.

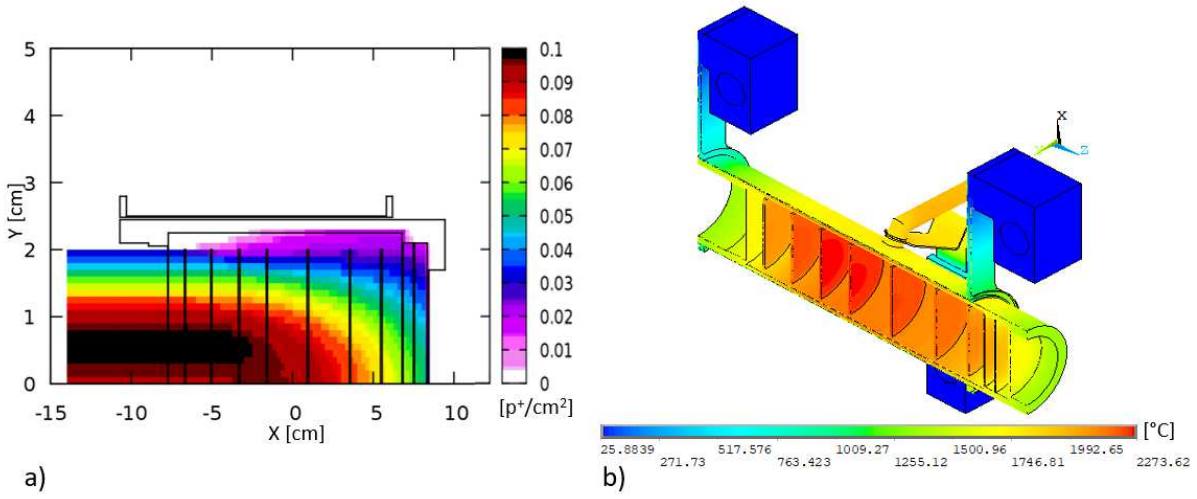

***Figure 3.2**: on the left (a) the plot of a FLUKA simulation, showing the dumping of the proton beam within the target; on the right (b) the temperature distribution as calculated with ANSYS® when the target is impinged by the proton beam.*

The performances of SPES-type Uranium Carbide target prototypes have been successfully evaluated during two low power irradiation tests at HRIBF facility of the Oak Ridge National

Laboratory (ORNL), where it was possible to measure both the isotopes production and the thermal stability [3.11, 3.12].

3.2.1 The SPES target material

Uranium Carbide is one of the most common target material, used and tested in ISOL facilities. The most common type of Uranium Carbide is commonly indicated as UC_x, highlighting that it is composed of different phases: Uranium dicarbide (UC_2), graphite (C), and a minor amount of Uranium monocarbide (UC) [3.13, 3.14]

Usually the synthesis of Uranium Carbide is performed exploiting the reaction:

$$UO_2 + 6C \rightarrow UC_2 + 2C + 2CO_2 \tag{3.1}$$

Such process is generally carried out at temperatures up to 1800 °C in high vacuum furnaces.

At SPES the UC_x target are manufactured directly in the form of disks, and their production routine consists of the following steps:

- Mixing of the precursors powders by means either of a planetary ball mill or of an agate mortar. The addition of a small quantity of a phenolic resin binder, usually 2% wt., is foreseen in order to prevent the damaging or the loss of powder of the green pellets during handling.
- Uniaxial cold pressing of the mixed powders into pellets, using a hydraulic press with a specifically designed die
- After extraction of the pressed pellet from the die, its thermal treatment is carried out in a high vacuum furnace developed to reach very high temperatures (~ 2000°C).

For the sake of simplicity, the so produced material is often referred to as UC_4, considering it as a composite with UC_2+2C stoichiometry. The obtained material is a porous medium with an average density of 4 g/cm^3 [3.15].

The development of the SPES target material was carried out taken with the aim to maximize the efficiency of the nuclides production and release processes. In particular, the latter consists of two stages:

- The diffusion of the nuclides, mostly generated in the material grains, towards the crystal surface. It is governed by Fick's laws.
- The effusion, either through the material pores or along the free spaces surrounding the target discs, towards the ion source. It consists of random motion and collisions with the enclosures, and takes place in high vacuum.

The release of the produced nuclides is boosted if the target material presents several peculiar properties, such as:

- High limiting temperature, to be able to work for a sufficient amount of time at high temperatures (more than 2000 ◦C) in high vacuum.
- High thermal emissivity and conductivity, to profitably improve the dissipation of the power deposited by the primary beam without undergoing structural damage.
- High permeability to the isotopes during their path towards the ion source. This behavior is strictly related to the presence of open interconnected porosity [3.16].

The presence of porosity and the grain size of carbides are expected to have a direct effect on the release efficiency. Indeed, recent research studies confirmed that grain size has an impact on diffusion (the diffusion constant is inversely proportional to grain size), while porosity and its interconnectivity degree affects effusion efficiency [3.17].

Recent studies at SPES promoted the use of graphene both as carbon source for UO_2 carbothermal reduction to produce UC_x targets, and additionally as functional properties booster. UC_x samples were synthesized using both graphite and graphene as the source of carbon (figure 3.3) and the target properties in terms of composition, grain size, porosity, thermal diffusivity and thermal conductivity were studied. A remarkable enhancement of the thermal conductivity was proved in the case of graphene-based targets [3.18].

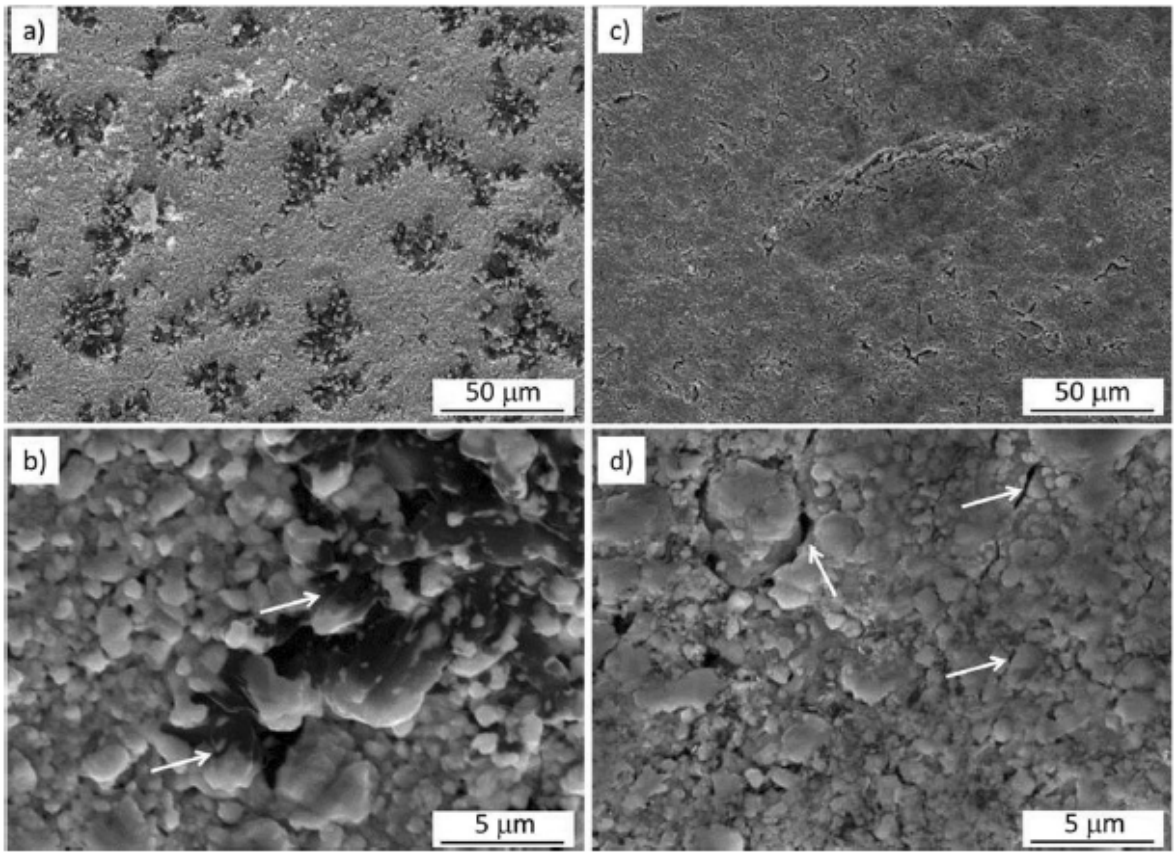

Figure 3.3: *SEM images of UCx-graphite (a,b) and UC_x-graphene (c,d). Arrows indicate residual carbon in (b) and micro-cracks in (d)* [3.18].

3.2.2 The SPES target expected yields

During the design phase of the target, an extensive campaign of simulations and tests was performed to estimate the yields achievable at SPES facility, with its characteristic target architecture. Tests on a scaled prototype of the SPES UC_x were performed at Oak Ridge National Laboratory (ORNL) [3.11], whereas simulations were mostly performed by means of the Monte Carlo codes MCNPX 2.7e [3.19] and FLUKA v2011-2b [3.20 – 3.22]. Since for both codes the accuracy for the production of individual isotope is not high in the considered energy range, the calculated results with the different models were compared [3.1].

Both MCNPX and FLUKA are fully integrated Monte Carlo packages dedicated to the simulation of the transport and interaction of particles and nuclei with matter. In both codes, since common cross-section libraries do not include all target materials, energies and reactions combinations, the ion-induced nuclear interactions are simulated through dedicated event generators. Taking into account the desired energy range, the Boltzmann master equations computational theory is implemented in the case of FLUKA [3.23], and is used for the prediction of the average multiplicities of particles emitted during the thermalization of an excited nucleus by nucleon-nucleon interaction cascades

Regarding MCNPX, the Bertini [3.24] and Isabel [3.25] intra-nuclear cascades were implemented, whereas three models, ABLA [3.26], ORNL (Oak Ridge National Laboratory) [3.27] and RAL (Rutherford Appleton Laboratory) [3.28], have been considered for the evaporation-fission action.

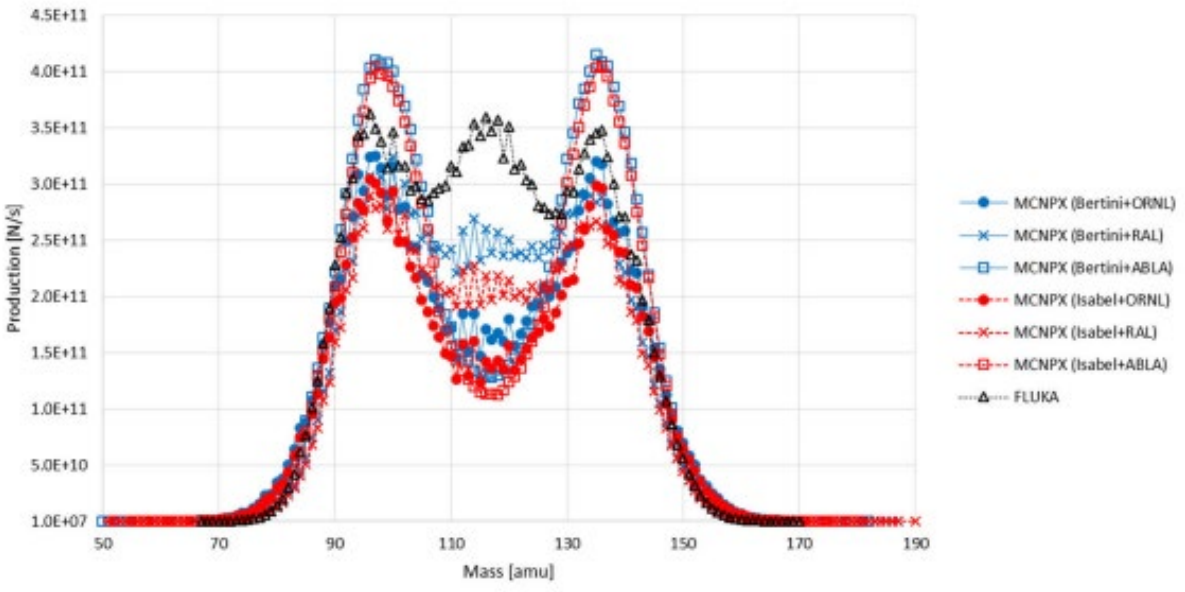

Figure3.4: *^{238}U fission yields by mass number according to different codes and nuclear models (40 MeV, 200 μA)*

As showed in figure 3.4, the MCNPX calculated yields are, as expected, varying according to the different fission models used, while the Bertini and Isabel models provide more comparable

trends. On the other hand, FLUKA results are generally coherent with the aforementioned calculations, but present an additional third peak at about 120 amu. Nevertheless, the FLUKA results were chosen for further evaluations, since even the most reliable MCNPX model in the considered energy range (Bertini+ORNL) does not foresee the expected production of most exotic neutron-rich nuclei, such as for example ^{133}Sn and ^{134}Sn [3.29].

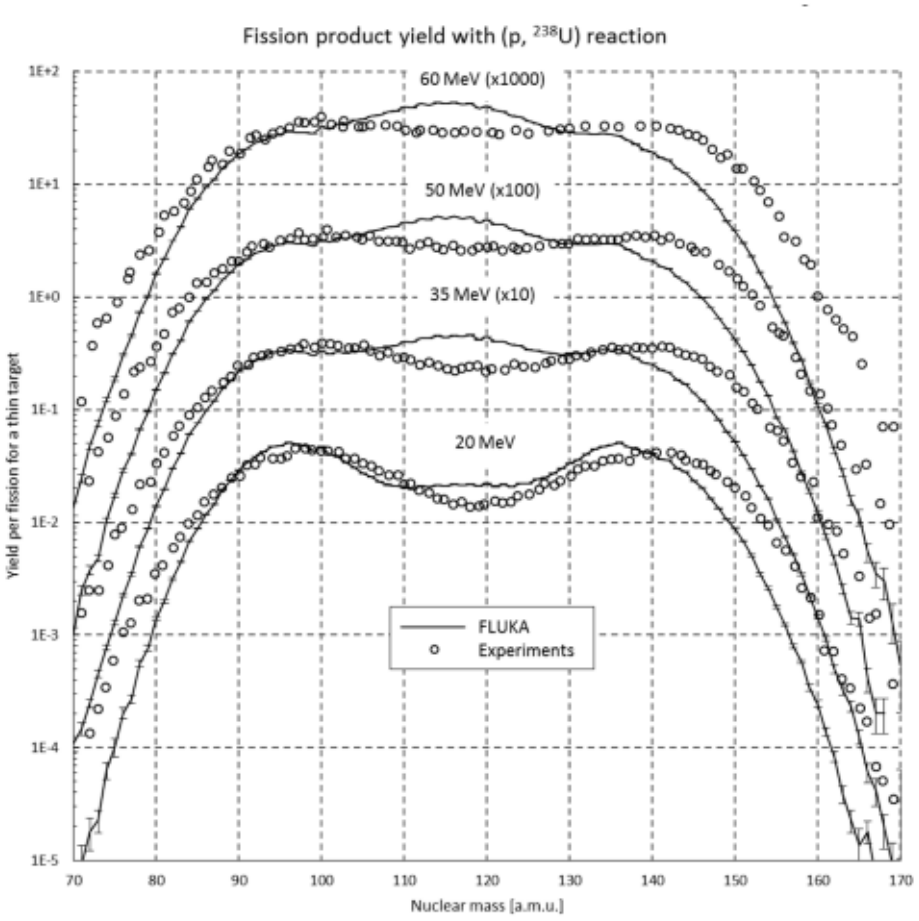

***Figure3.5**: Comparison of ^{238}U proton-induced fission yields between FLUKA simulations and experimental data* [30]*. FLUKA Monte Carlo errors are below 2% (except for the external points)*

An additional study was performed in order to validate the FLUKA results for the simulation of proton induced fissions on ^{238}U in the considered energy range. Indeed, with the aim to compare FLUKA numerical results with experimental data available in literature [3.30], fission yield spectra calculations at 20–60MeV were performed [3.1]. The simulations foresaw the modelling of a thin target with a thickness of 10 μm, in order to prevent the energy degradation of of the proton beam through the target (in the case of a 20MeV proton beam the energy degradation was only 0.2MeV), consistently with the experimental apparatus used for extracting the aforementioned data [3.30]. Figure 3.5 shows the comparison between FLUKA results and the experimental data: generally, FLUKA fission models show a good agreement, even if they lose accuracy at the extremities, for lighter and heavier masses. In addition, FLUKA data present the third central peak shape, especially for energies higher than 50 MeV, not

expected from the experimental data. Since the SPES project focuses on energies lower than 40MeV and on nuclei with 80 < A < 160, FLUKA calculations were considered as acceptable [3.1], and were used to evaluate the expected yields.

Figures 3.6, 3.7, 3.8, and 3.9 summarize the calculated in-target production for the SPES UCx target, when impinged by a 40 MeV 200 µA proton beam.

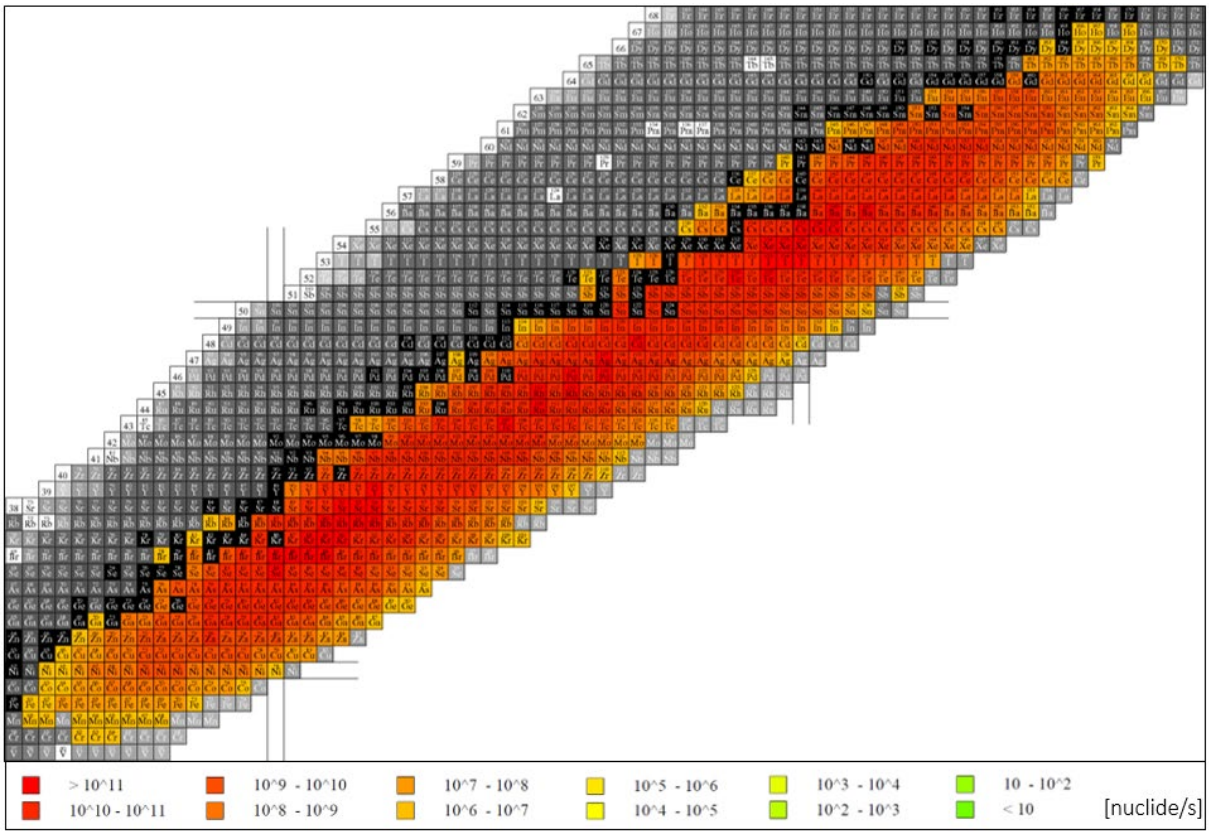

***Figure3.6**: Overview of the FLUKA calculated in-target fission products for a 40 MeV 200 µA proton beam on the SPES UC_x target.*

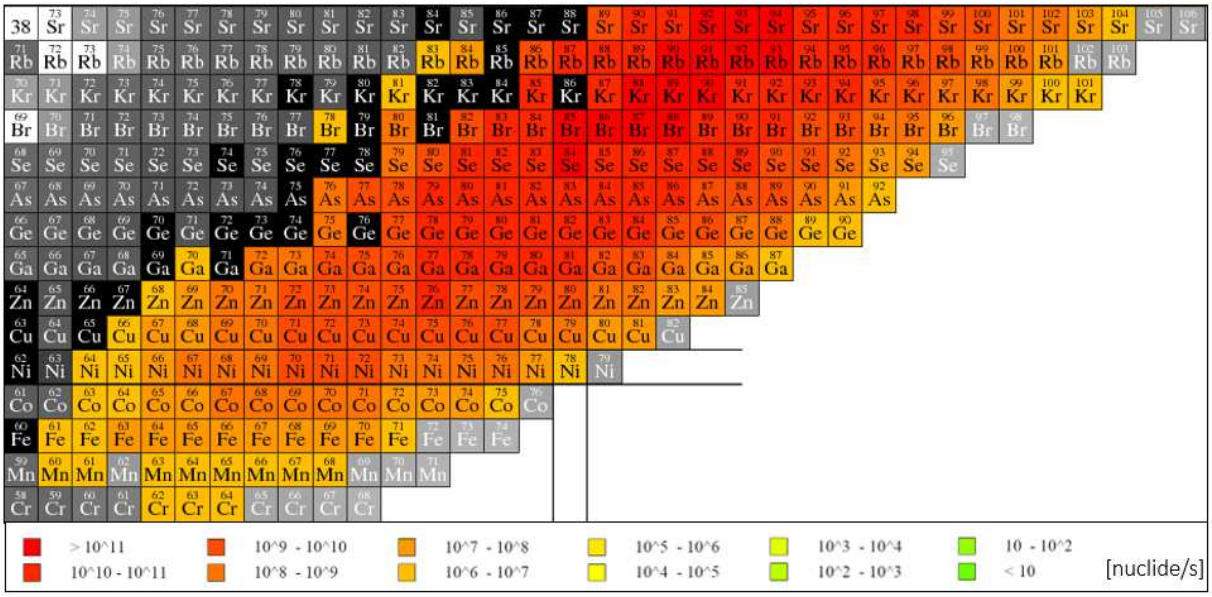

***Figure3.7**: FLUKA calculated in-target fission products of light mass for a 40 MeV 200 µA proton beam on the SPES UC_x target.*

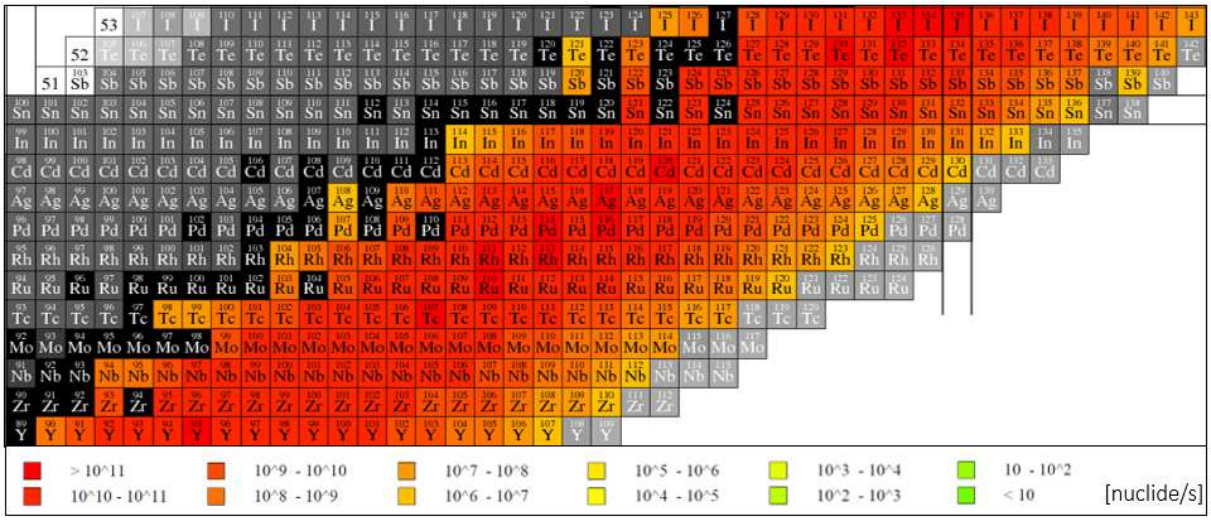

***Figure3.7**: FLUKA calculated in-target fission products of medium mass for a 40 MeV 200 µA proton beam on the SPES UC$_x$ target.*

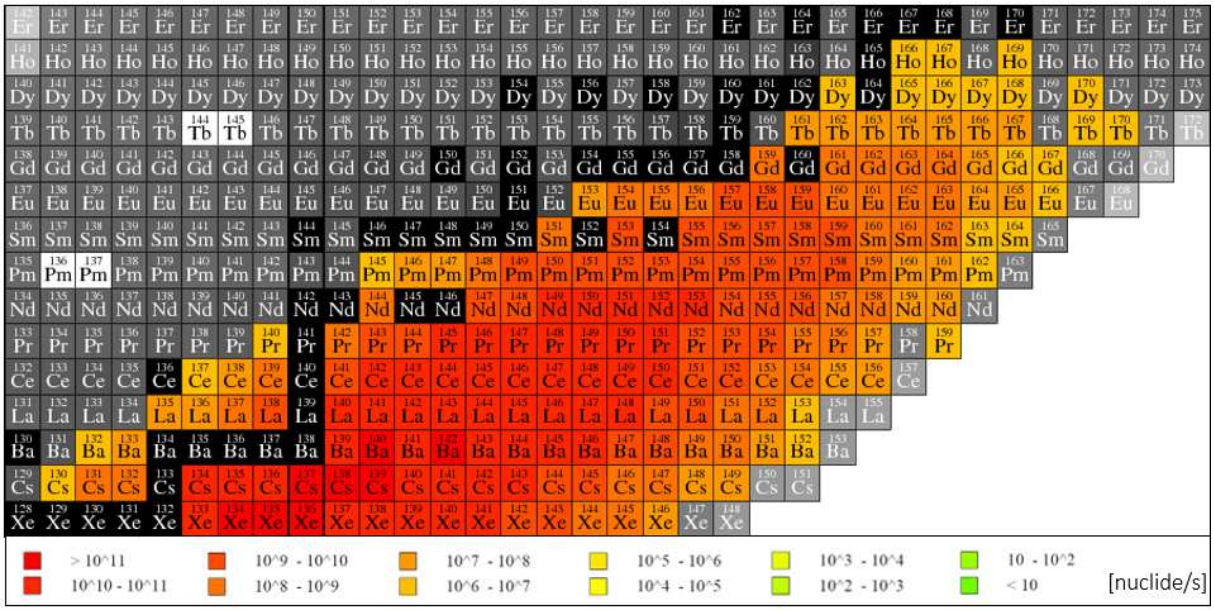

***Figure3.7**: FLUKA calculated in-target fission products of heavy mass for a 40 MeV 200 µA proton beam on the SPES UC$_x$ target.*

3.3 Medical nuclides from the SPES UC$_x$ target

As already introduced, the first idea of ISOLPHARM arose upon noticing that several radionuclides of medical interest are included in the expected fission spectrum of the SPES UC$_x$ target, with relevant production rates. Additionally, the capability to produce intrinsically carrier free nuclides with the ISOL technique promoted the idea to perform a preliminary feasibility study for the ISOLPHARM project considering state-of-art medical radioisotopes, aiming to evaluate their possible alternative production without the use of nuclear reactors.

Among the UCx fission products, the relevant radionuclides already used in nuclear medicine are:

- ^{89}Sr, a radionuclide used for treatment of painful bone metastases secondary to prostate cancer [3.3],
- ^{90}Y, successfully used in radioimmunotherapy [3.4],
- ^{125}I and ^{131}I, the first used in brachytherapy in several cancer types, e.g. the localized prostatic cancer [3.5, 3.6] , the second used for thyroid diseases [3.7] and in Non-Hodgkin lymphomas [3.4].

Production routines of commercially available ^{89}Sr foresee the irradiation of natural Yttrium targets in fast neutron reactors, inducing the ^{89}Y(n,p)^{98}Sr reaction [3.31], whereas pure ^{90}Y is generally milked from a ^{90}Sr/^{90}Y generator [3.32], prepared exploiting the ^{90}Sr extracted from fission wastes [3.33]. ^{125}I production is performed by neutron irradiation of natural Xenon with thermal neutron fluxes [3.34], whereas ^{131}I can be extracted either from neutron activated dedicated Tellurium-based targets [3.35] or as by-product from Uranium fission [3.36].

Generally, the aforementioned production routines are capable of providing in a short time commercially relevant amounts of nuclides, but they are all based on the exploitation of nuclear reactors.

Table 3.1 summarizes the in-target expected activities for the aforementioned radionuclides, that can be produced with the SPES UC_x target, when impinged by a 40 MeV 200 µA proton beam. Such results were calculated with FLUKA, activating the radioactive decays and setting various irradiation timepoints, coherently with the maximum irradiation time for a SPES target (15 days).

Table 3.1: *FLUKA calculation for the produced activities of ^{89}Sr, ^{90}Y, ^{125}I and ^{131}I at different timepoints*

SPES UC_x target production, 40 MeV 200 µA PPB								
	^{89}Sr		^{90}Y		^{125}I		^{131}I	
Time	Produced activity		Produced activity		Produced activity		Produced activity	
[days]	[Bq]	[Ci]	[Bq]	[mCi]	[Bq]	[mCi]	[Bq]	[mCi]
0.5	9.17E+08	0.02	2.34E+07	0.63	1.74E+05	4.71E-03	6.59E+09	0.18
1	1.83E+09	0.05	4.91E+07	1.33	3.48E+05	9.39E-03	1.36E+10	0.37
1.5	2.73E+09	0.07	7.26E+07	1.96	5.20E+05	1.40E-02	2.05E+10	0.56
2	3.63E+09	0.10	9.40E+07	2.54	6.91E+05	1.87E-02	2.75E+10	0.74
3	5.41E+09	0.15	1.31E+08	3.54	1.03E+06	2.79E-02	4.09E+10	1.11
4	7.16E+09	0.19	1.62E+08	4.37	1.37E+06	3.69E-02	5.37E+10	1.45
5	8.89E+09	0.24	1.88E+08	5.08	1.70E+06	4.59E-02	6.57E+10	1.77

As a general consideration, the achievable production according to the ISOLPHARM method, is not yet quantitatively comparable to the producible activities with commercialized traditional techniques. In addition, the production routines for ^{89}Sr, ^{90}Y, ^{125}I and ^{131}I provide sufficiently pure products, thus it is the ISOLPHARM method true potential cannot be expressed if state-of-art radionuclides are considered. Indeed, the ISOL technique could be used to expand the

variety of available medical nuclides by extracting radioactive species that are otherwise difficult to produce, or that were never studied, for the lack of a suitable production technique. Taking into consideration the SPES UC$_x$ target, other nuclei of potential medical interest can be found in its production spectrum, for example ^{111}Ag, ^{129}Cs, ^{131}Cs, ^{132}Cs and ^{136}Cs (figure 3.8).

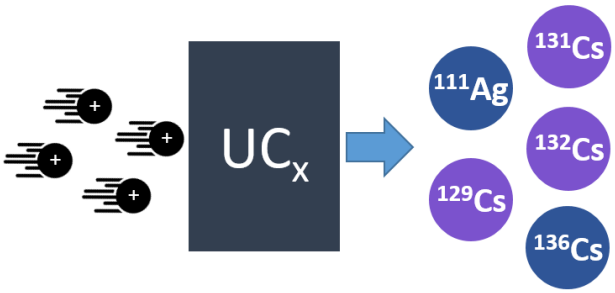

***Figure 3.8**: other possible medical radionuclides from the SPES UC$_x$ target.*

^{111}Ag could be very promising candidate for internal radiotherapy, thanks to its decay properties. Being a β- emitter with medium half-life (7.45 days), it has a convenient β- energy and medium tissue penetration (average β energy 360 keV and average tissue penetration 1.8 μm) and low percentage of associated γ-emission [3.37]. The production of acceptably carrier-free ^{111}Ag, as required for the efficient radiolabeling of biomolecules, is not possible via classical neutron irradiation methods, unless enriched ^{110}Pd (11.7% in natural palladium) targets are used [3.38]. On the contrary, ISOL technique can easily provide amounts of ^{111}Ag not only at very high purity, but also with decent production rates. Indeed, all the isotopic contaminants with different mass number will be removed thanks to the on-line mass separation, whereas most nuclei of the 111-mass isobaric chain are short-lived decay quickly either to ^{111}Ag or to ^{111}Pd. Since Palladium is refractory element, and consequently will not be released from the production target, only ^{111}Ag and low amounts of its stable daughter ^{111}Cd, mostly produced by the decay of silver, are collected on the secondary target. Radioactive silver nuclides were already successfully produced using a SPES UCx target prototype and delivered to experimental areas in dedicated experiments [3.11]. In particular, ^{111}Ag was selected as candidate for a detailed study of its production as innovative medical nuclide in the framework of ISOLPHARM. As already introduced, such detailed study is referred as the ISOLPHARM_Ag project.

In addition to ^{111}Ag, the SPES UC$_x$ target could provide amounts of isotopes of other elements as Cesium, in particular ^{129}Cs, ^{131}Cs, ^{132}Cs, ^{136}Cs. For most of them, early investigations were performed at the 70s since they show suitable properties for nuclear medicine [3.39], but such

research was lately abandoned, for the lack of both a proper production technique and technologies to detect accurately the emitted low energy radiations.

^{129}Cs decays either emitting β+ particles, or through electron capture with associated photon emission at 411 keV (22.3%) or 372 keV (30.6%) with a half-life of 32.3 hours, thus being suitable for diagnostic applications. Additionally, the associated emission of Auger electrons in the energy range of 2.5 – 5.4 keV make ^{129}Cs a possible candidate for Auger-Electron Radionuclide Therapy [3.40]. Early evaluations for the possible application of ^{129}Cs as medical diagnostic radionuclide in nuclear cardiology were already performed [3.41], but were lately discontinued for its lower availability in comparison to other nuclides [3.42].

^{131}Cs decays through electron capture, and emits X-rays and Auger electrons, mostly in the energy range of 2.5 – 5.4 keV with a half-life of 9.69 days. It was early used as a diagnostic nuclide for thyroid scanning as alternative to ^{99m}Tc and ^{131}I [3.43], and lately in permanent prostate brachytherapy implants [3.44].

^{132}Cs is mostly an electron-capture or β+ decaying isotope with the associated emission of Auger electrons, but also might emit β- particles (1.51%) with average energy of 269.9 keV. Recent studies suggest its use as analogue for the study of the biodistribution of its therapeutic counterpart ^{221}Fr [3.45] and its cyclotron based production was essayed.

Finally, ^{136}Cs is a β- emitter with average energy of 98.78 keV (70.3%) or 219 keV (13%) and half-life of 13.16 days, being thus suitable for therapeutic applications. If opportunely combined with one of the aforementioned diagnostic Cesium isotopes, a new theranostic pair based radiopharmaceutical could potentially be developed.

Table 3.2 summarizes the FLUKA calculated in-target expected activities for the aforementioned radionuclides, that can be produced with the SPES UC_x target, when impinged by a 40 MeV 200 μA proton beam.

Table 3.2: *FLUKA calculation for the produced activities of ^{111}Ag, ^{129}Cs, ^{131}Cs, ^{132}Cs and ^{136}Cs at different timepoints*

SPES UC_x target production, 40 MeV 200 μA PPB										
	^{111}Ag		^{129}Cs		^{131}Cs		^{132}Cs		^{136}Cs	
Time	Produced activity		Produced activity		Produced activity		Produced activity		Produced activity	
[days]	[Bq]	[Ci]	[Bq]	[mCi]	[Bq]	[mCi]	[Bq]	[mCi]	[Bq]	[mCi]
0.5	9.46E+09	0.26	1.14E+06	0.03	4.30E+06	0.12	2.69E+07	0.73	1.30E+09	35.22
1	1.92E+10	0.52	2.02E+06	0.05	8.45E+06	0.23	5.24E+07	1.42	2.57E+09	69.52
1.5	2.85E+10	0.77	2.70E+06	0.07	1.24E+07	0.34	7.66E+07	2.07	3.81E+09	102.94
2	3.74E+10	1.01	3.22E+06	0.09	1.63E+07	0.44	9.96E+07	2.69	5.01E+09	135.49
3	5.40E+10	1.46	3.94E+06	0.11	2.36E+07	0.64	1.42E+08	3.83	7.33E+09	198.07
4	6.92E+10	1.87	4.37E+06	0.12	3.04E+07	0.82	1.80E+08	4.86	9.53E+09	257.44
5	8.29E+10	2.24	4.62E+06	0.12	3.68E+07	0.99	2.14E+08	5.79	1.16E+10	313.75

3.4 Proof-of-concept offline tests with stable Sr, Y and I beams

The fundamental as well as peculiar steps of ISOL are the release, ionization, extraction into a beam and mass-separation of the desired nuclear species. In addition, in the case of ISOLPHARM the additional deposition step on a suitable target is foreseen. As a consequence, the numerical evaluation of the expected in-target production is not sufficient to prove the feasibility of the production of medical carrier-free radionuclides according to the ISOLPHARM method, but also additional studies should be carried out to complete the proof-of-concept assessment. Such studies include both the experimental evaluation of the capability of SPES technologies to ionize and isolate isotopes of the desired chemical element, and the development and test of suitable deposition targets [3.2]. Additionally, the evaluation of the ionization and deposition efficiencies are necessary to precisely evaluate the final available amounts for the subsequent radiochemistry and radiopharmacy studies. Again, for the preliminary proof-of-concept studies, Sr, Y and I were selected. Indeed, since their radiochemistry behavior is known, and radiopharmaceuticals based on those elements already exist, only the ISOL production step needs to be accurately evaluated.

For such studies, being SPES in the construction phase, no radioactive species are currently producible for ISOLPHARM. Consequently, stable isotopes of the elements of interest can be used in place of their radioactive counterparts, because the release and ionization processes are dependent on only the chemical properties, that thus all isotopes of a chosen element share.

Such tests were performed using the experimental apparatus present in the SPES offline Front End laboratory, that is described in detail in the following paragraph.

3.4.1 The SPES offline Front End for ionization test.

The experimental apparatus developed for the SPES project, namely the SPES Front End (FE). is now hosted in an offline laboratory and is used as test bench for the production of stable ion beams, with the aim to further develop the ion sources, the mass separators and the diagnostic devices that will be installed at the SPES facility. An updated replica of such apparatus will be soon installed in one of the SPES bunker, with a view to complete the construction of the facility and start operation. The offline SPES FE used for beam developments and tests does not include the protonic beam line, since the laboratory where it is hosted is not equipped for the activation of the target. As shown in figure 3.9, it is composed by six subassemblies: (A) the Target and Ion Source unit, (B) the first triplets and steers unit and Diagnostic Box 1, (C) the Wien Filter, namely the mass separator, (D) the Diagnostic Box 2 and the slits, (E) the second triplet system and finally the (F) secondary target station.

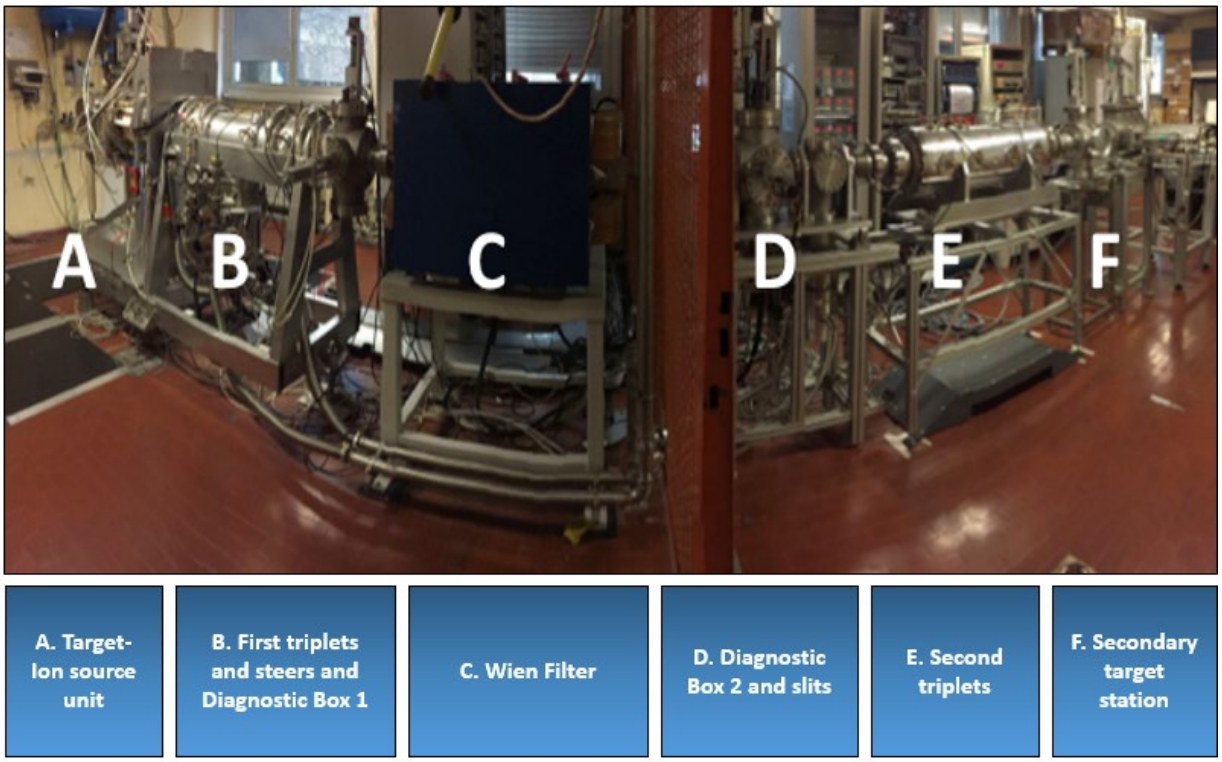

Figure 3.9: *the SPES offline Front End and its subassemblies*

The Target – Ion Source unit is normally composed by a production target connected to an ion source through a tubular transfer line, both assembled into a water cooled vacuum chamber, where pressure levels of the order of magnitude of 10^{-5} - 10^{-6} mbar are reached [3.9]. However, for the offline beam extraction tests the production target is normally not installed, since no production of exotic species is foreseen. Consequently, other different methodologies have been developed to mimic the release form the target, thus injecting the stable counterparts of the nuclides of interest into the ion source.

Gaseous elements are introduced through a controlled gas flow and injected into the ion source by means of a calibrated leak; the efficiency of the ionization process is then calculated as the ratio between the extracted beam intensity and the gas flow rate. [3.46]

In the case the element of interest is solid, it is usually chosen in the form of a soluble salt, dissolved in acidic media whit a precise concentration (usually around 1 g/L). Using a micropipette, it is possible to quantitatively depose drops of the solution on a small Tantalum foil (1x1 cm^2 usually), called Mass Marker (MM) and the solvent is lately evaporated under mild heating in a hood, obtaining thus a surface deposition of the chosen salt on the foil. The MM is then carefully folded [3.47] and inserted into tantalum tube with inner diameter of 1 mm, called oven, and one of its extremity is then sealed, whereas the other is left open and connected to the transfer line in place of the production target. During the tests, the oven can be stepwise heated by Joule effect, thus allowing the break-up of the salt and the element

atomization. Thus, the atomized neutrals effuse through the oven and migrates towards the ion source (figure 3.10).

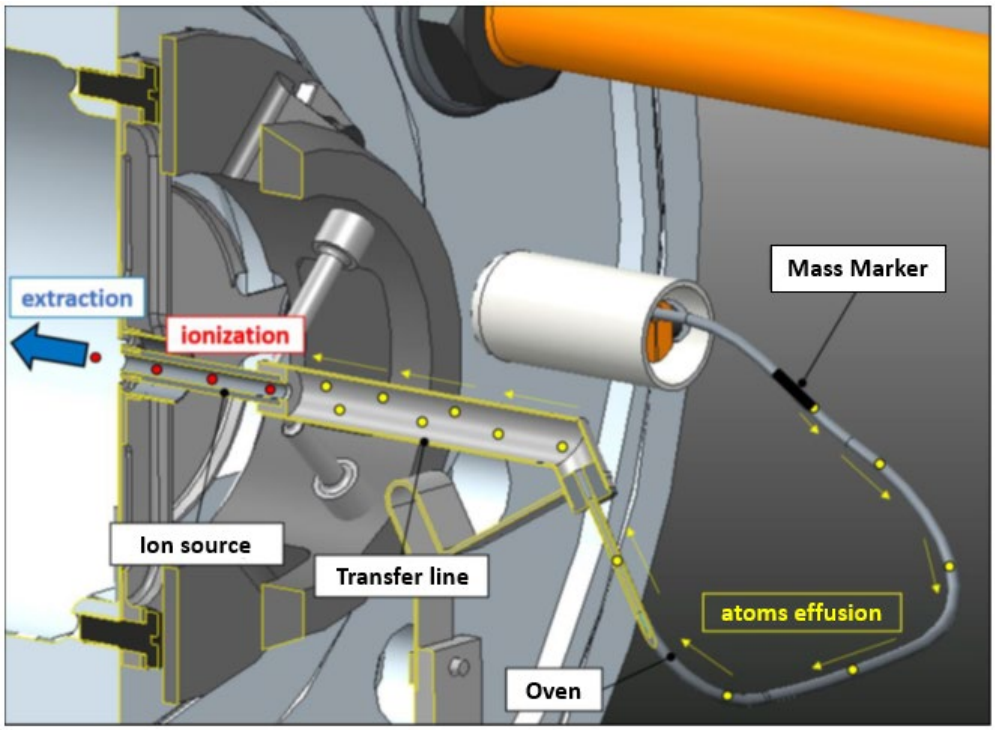

Figure 3.10: *Schematic representation of the functioning of the MM and oven system. The ion source represented is the SPES Surface Ion Source.*

The offline FE can be equipped with both kinds of ion sources developed for the SPES project. The selection of the ionization technology depends on the first ionization potential of the desired chemical element to be tested. For elements of the 1st and 2nd group, the Surface Ion Source (SIS) is adopted [3.48, 3.49]; for those with higher electronegativity, the Plasma Ion Source (PIS) is required [3.46, 3.50]. Normally the SIS could be used also for the performance of resonant laser ionization, the most efficient technique for transition metals [3.51], but the current offline FE laboratory is not equipped with a laser apparatus.

The SPES SIS [3.48, 3.49] main component is a tubular ionizing cavity with internal diameter of 4.1 mm and 34 mm length, and can be heated uniformly up to 2000-2200°C by Joule heating. It is made of high work function refractory materials, in order to efficiently produce positive ion beams for elements with ionization potential lower than 7 eV. Indeed, according to the surface ionization mechanism an atom that interacts with a heated surface can lose or gain an electron, becoming a positive or negative singly charged ion.

The other ion source used in the offline tests is the SPES PIS [3.46, 3.50], which is a Forced Electron Beam Induced Arc Discharge (FEBIAD) ion source. It is a non-selective device capable of ionizing a large spectrum of elements, including noble gasses. It is mainly composed of a tantalum cathode a molybdenum anode and a cylindrical discharge chamber. The former reaches under operation a temperature level of 2200 °C by Joule effect heating, generating thus

an intense thermionic emission of electrons (free electrons) on the cathode surface facing the anode. A potential difference of 150 V is set between the cathode and the anode, consequently the latter attracts the emitted electrons, that are injected into the cylindrical discharge chamber. A solenoid is placed around the discharge chamber, and generates a magnetic field around, oriented along its axis, thus forcing the emitted electrons to travel along spiral trajectories. An electron plasma is consequently generated in the discharge chamber, and the ionization occurs by its interaction with the neutral travelling through the ion source.

Figure 3.11 shows the experimental set-ups used for the offline tests with both ion sources [3.52].

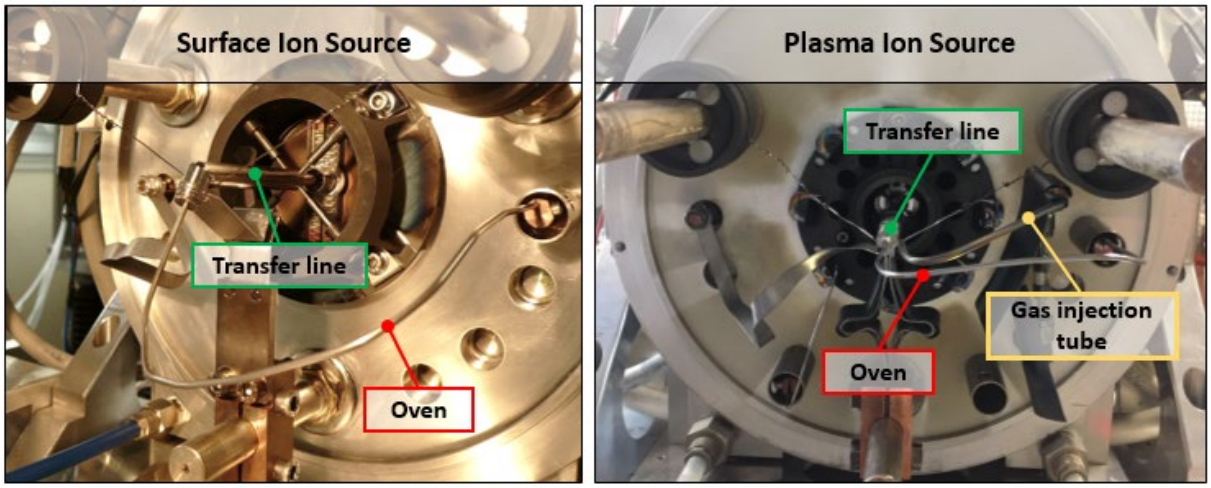

***Figure3.11**: the two ion sources as assembled for the offline tests in the FE laboratory.*

The whole TIS unit is placed on a high voltage platform, whereas the extraction electrode is set at ground potential. For the offline tests the high voltage was limited at 25 kV for safety issues, however it can potentially be increased up to 40 kV.

The first beam optics subsystem is made of a set of four electrostatic steers (S1, S2, S3 and S4) to adjust the alignment of the beam respect to the beam line a quadrupole triplet (Q1, Q2 and Q3) which allow to focus the beam properly.

The Diagnostic Box 1 contains a Faraday Cup (FC1), aimed to monitor the beam intensity monitoring and a grid-based Beam Profile (BP1) detector.

The beam mass selection is performed by a Wien Filter (WF), a device which is able to select specifically ions with a given mass/charge ratio due to mutually perpendicular electric and magnetic fields orthogonal to the ion velocity. Particles with speed equal to the ratio between electric and magnetic field proceed undeflected, whereas all other ions are deviated. Since the various masses are singly charged and accelerated at approximately the same energy (25 keV), this device can work as a mass selector.

The Wien Filter used in the SPES offline FE is composed by a vacuum chamber where the desired constant electric field is generated by two couples of electrodes, named respectively

pre-electrodes (V_{pe}) and electrodes (V_e), whereas a two coils magnet supplies the magnetic field when fed with a certain current intensity (I_{WF})

After the WF, a second diagnostic box is installed, constituted by a second Faraday Cup (FC2), and a grid-based Beam Profile detector (BP2). Such diagnostic box includes additionally the so-called slits, motorized devices that can be inserted in the beam line to reduce its aperture. They are used to stop the particles deflected by the WF, thus ensuring the isobaric purity of the beam.

After the Diagnostic Box 2 a second quadrupole triplet assembly (QT1, QT2 and QT3) is installed to refocus the beam after mass purification. Finally, the last component installed in the offline FE is the secondary target station, a modified version of a diagnostic box in order to host the secondary targets. Such targets are soluble thin disks with a diameter of 13 or 40 mm, designed in order to ensure the collection of the ions transported by the beam and to allow to easily harvest the isotopes of the element of interest after their dissolution. They are assembled in a modified version of a Faraday Cup, thus enabling the detection of the incident beam current if the chosen secondary target is a conductive material

The secondary target station includes also a third Beam Profile (BP3) monitor, in order to check the positioning and focusing of the beam in correspondence of the secondary target.

With such apparatus two types of tests can be performed: ionization tests and deposition tests.

Ionization tests are aimed to evaluate the ionization efficiency for the chosen chemical element – ion source combination, and the extracted beam is normally stopped in correspondence of the FC2, thus continuously monitoring the beam current. Consequently, during ionization tests, the second triplet assembly is normally off, since the part of the FE after the FC2 is not used. The precise count on the FC2 of the extracted particles enables the calculation of the ionization efficiency. Usually, if the MM technique is used, amounts of the desired salt of the order of magnitude of tens of μg are loaded in the oven, in order to limit the test duration to typically around 4-5 hours.

Deposition tests are performed after the evaluation of the ionization efficiency, because, once the ionisable fraction of the loaded nuclei is known, the MM load has to be adjusted with the aim to ensure an expected reasonable collection of ions on the secondary target. Indeed, the irradiated collection targets are subsequently dissolved and used for the performance of quantitative analyses of the isotope harvesting efficiency. Deposition tests foresee to additionally turn on the second triplet subassembly, since the extracted beam has to be transported up to the secondary target station. The FC2, normally out of the beam line, is generally inserted at regular intervals (circa 20 min) for few seconds, in order to monitor the deposed beam intensity.

3.4.2 Ionization tests of Sr, Y and I

Stable Sr, Y and I were used to measure the ionization efficiency in place of their radioactive counterparts ^{89}Sr, ^{90}Y, ^{125}I and ^{131}I. For all the selected elements the MM technique was chosen. In the case of Strontium, whose first ionization potential is 5.7 eV [3.53] and thus suitable for the surface ionization, the SPES SIS was employed. The MM was loaded with 40 µL of Strontium standard solution for AAS ($Sr(NO_3)_2$ 1 g/L, Fluka Analytics) and the WF was set in order to select mass 88, being the most abundant mass of natural Strontium (^{84}Sr – 0.56%; ^{86}Sr – 9.86%; ^{87}Sr – 7.1%, ^{88}Sr – 82.58%).

Yttrium, whose first ionization potential is 6.2 eV [3.53], was ionized with the SPES PIS, since the surface ionization process was expected to be less efficient. Yttrium beam production was affected by difficult atom evaporation, because of its very high boiling temperature. Indeed, in high vacuum conditions ($5 \cdot 10^{-6}$ mbar), the vapour pressure is expected to be reached above 1600 °C [54]. Preliminary tests, performed with the MM loaded with 40 µL of Yttrium standard solution for AAS ($Y(NO_3)_3$ 1 g/L, Fluka Analytics) and placed in the oven, were unsuccessful. Indeed, the loaded $Y(NO_3)_3$ degraded to the refractory Y_2O_3, thus hindering yttrium atomization. Thus other possibilities were investigated, and Yttrium beams were finally produced by either choosing the most volatile yttrium salt (YCl) and positioning of the MM directly in the hottest region of the ion source without folding. The WF settings were studied to isolate only mass 89, being ^{89}Y the only stable isotope of such element.

Table 3.3: *summary of the FE settings for the Sr, Y and I ionization tests*

Offline ionization tests - settings				
Element		**Strontium**	**Yttrium**	**Iodine**
Starting chemical form		$Sr(NO_3)_2$ (1 g/L)	YCl (1 g/L)	KI (1 g/L)
MM load		40 µL	40 µL	40 µL
MM positioning		Oven	Transfer Line	Oven
Ion source		SIS	PIS	PIS
Ion source current		350 A	420 A	400 A
Oven current range		30 - 80 A	-	10 -70 A
High voltage platform potential		25 kV	25 kV	25 kV
Steers settings	**S1**	40 V	1792 V	0 V
	S2	0 V	0 V	0 V
	S3	1 V	974 V	0 V
	S4	2 V	0 V	0 V
First triplet settings	**Q1**	1250 V	1368 V	1893 V
	Q2	735 V	703 V	891 V
	Q3	1250 V	1276 V	2010 V
WF settings	**V_{pe}**	-	-	590 V
	V_e	1000 V	1500 V	2579 V
	I_{WF}	59.34 A	89.8 A	160.2 A
	Mass	88	89	127
Slits aperture		open	open	open

Iodine (with first ionization potential of 10.5 eV [3.53]) was ionized by means of the SPES PIS. Being iodine extremely volatile, in such case, the MM was loaded with 40 µL of a solution of KI (1g/L), the iodine salt with highest boiling temperature, in order to ensure the controlled evaporation by Joule heating of the oven. The WF was set to transport only mass 127, being ^{127}I the only stable iodine isotope.

All settings used for the aforementioned ionization tests are summarized in Table 3.3, whereas figure 3.12 shows the mass scans performed to prove the ionization of the desired elements [3.52].

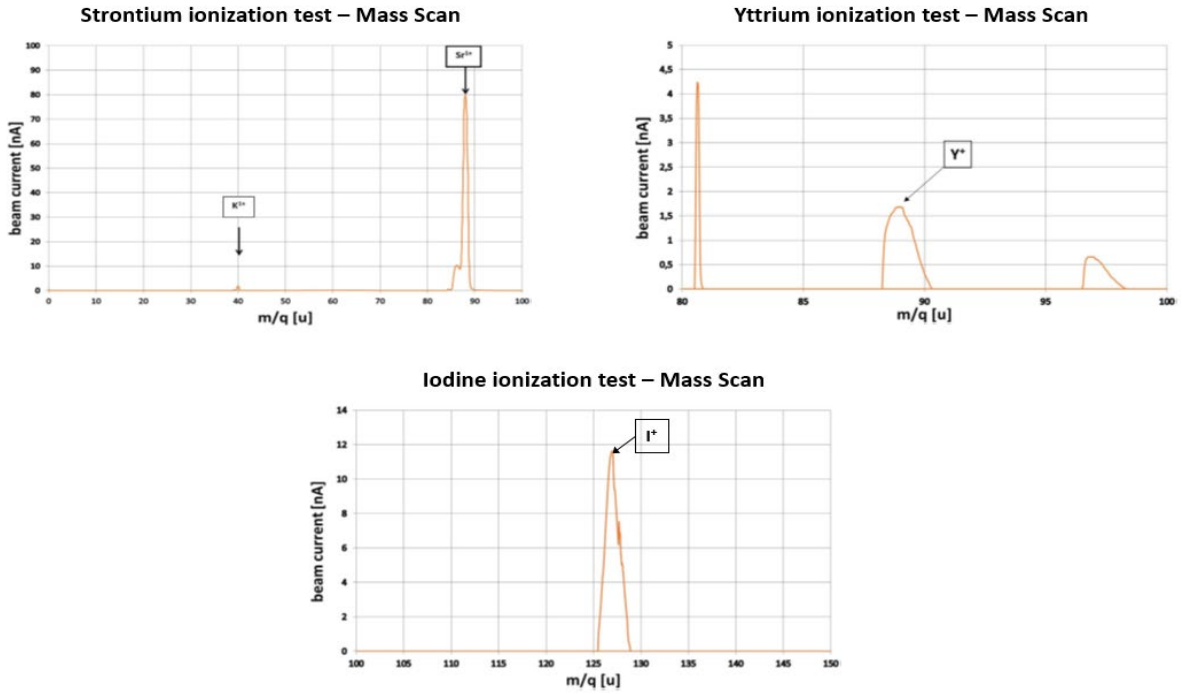

Figure 3.12: *the mass scan performed during the ionization tests of Sr, Y and I. In the case of Sr, it is possible to notice two peaks, corresponding respectively to ^{86}Sr and ^{88}Sr, the most abundant isotopes in natural Sr (the ^{87}Sr peak is not visible because hidden by the tail of the ^{88}Sr peak)*

Table 3.4 summarizes the values of the ionization efficiency measured during the aforementioned ionization tests [3.2]. In the case of Y, it was not possible to estimate accurately the ionization efficiency because the heating of the MM was not decoupled from the heating of the ion source, being the first placed into the latter. Since the SPES PIS operates efficiently only above 2000°C, some of the Y load might have been released before the source was capable to ionize it.

Table 3.4: *ionization efficiency results for Sr, Y and I*

Offline ionization tests - efficency	
Extracted element	**Ionization efficiency**
Strontium	18,5%
Yttrium	Very low
Iodine	19.34%

3.4.3 Deposition tests of Sr, Y and I

Deposition tests of Sr, Y and I nuclei were performed with the aim of both testing the capability of the dedicated secondary targets to trap the accelerated ions and of evaluating the recovering efficiency for the desired chemical element. Such preliminary tests were performed before the implementation of the second triplet subassembly and the secondary target station, consequently the collection target was placed on the flange closing the beamline, just after the Diagnostic Box 2 (figure 3.13).

In the case of Sr and Y deposition tests a Sodium Chloride (NaCl) disk with 40 mm of diameter produced by the compression of fine NaCl powder was used as collection taerget. Indeed, such material was selected because it is completely biocompatible with human administration (it can be injected or even orally taken). It has also good solubility properties, allowing its possible dissolution in biocompatible media after beam trapping.

NaCl was not used for iodine beam deposition, since it includes iodine impurities, that could be recovered together with the transported I ions, thus affecting the reliability of the recovering efficiency results. In such case, solid and resistant activated carbon disks with 50% (w/w) of PVA were developed and produced by hot pressing.

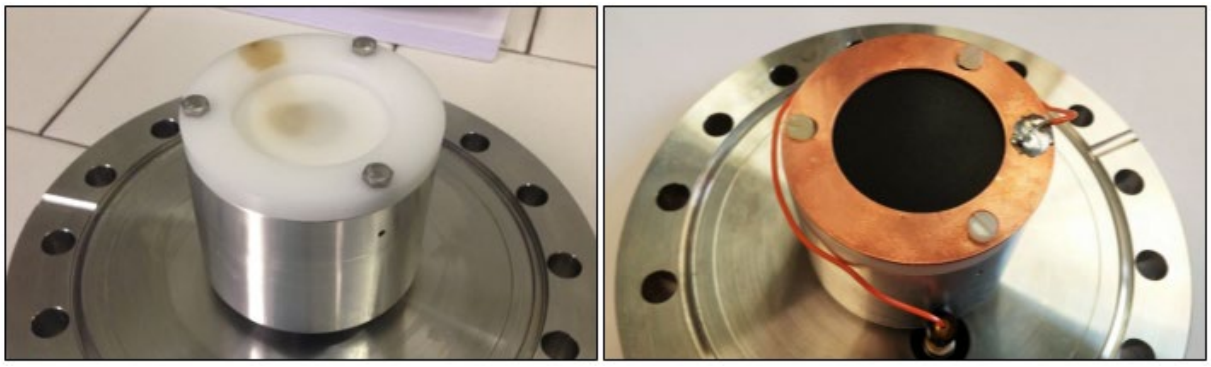

Figure 3.13: *the collection targets used for the Sr, Y and I deposition tests, that were assembled directly to the closing flange of the FE beam line. On the left the NaCl disk used for the Sr and Y tests, whereas on the right the activated carbon disk used for I.*

In the case of Strontium, the Mass Marker was loaded with 140 µL of $Sr(NO_3)_2$ water solution (1 g/L). The deposition test lasted typically 15 h, up to no more Strontium beam current was detected (current below <15 nA, considered the background threshold). The interpolating function of the punctual FC2 beam current measurements was integrated in time, thus calculating the overall collected charge impinging the NaCl substrate. At the end of the deposition, the collection target was disassembled and the NaCl substrate was dissolved in HNO_3 0.3 M for quantitative analysis via Graphite Furnace Atomic Absorption Spectroscopy (GF-AAS). The recovered strontium was 41.1% of the integrated charge [3.2].

For the Yttrium deposition experiments, the MM was charged with 900 µL of YCl_3 water solution (1 g/L) and introduced directly into the transfer line. As in the case of Strontium, the FC2 punctual measurements were used to define a beam current trend function that was lately integrated in time, thus quantifying the amount of yttrium ions collected on the NaCl target.

After irradiation, the target substrate was dissolved in 10 mL of HNO_3 0.1 M to verify Yttrium deposition by means of Inductively Coupled Plasma – Optical Emission Spectrometry (ICP-OES). It was possible to verify that 100% of the expected yttrium nuclei were recovered [2].

Finally, Iodine deposition tests were performed by loading 150 µL of KI water solution (1 g/L) on the Mass Marker. In such case the selected activated carbon substrate is a conductive material, consequently it was used as Faraday Cup to measure directly the impinging beam current. Such current was then integrated in time, allowing the calculation of the collected charge on the deposition target. Following the extraction of the activated carbon substrate from the beamline, iodine was titrated and finally quantified. The recovering efficiency was evaluated 63.70% [3.2].

Each of the aforementioned deposition tests was performed three times, in order to evaluate the repeatability of the results.

Table 3.5 summarizes the settings used for the deposition tests as well as the analytical technique used to quantify the collected amounts of Sr, Y and I. Table 3.6 summarizes the recovering efficiencies evaluated with the aforementioned analytical techniques [3.52].

Table 3.5: *summary of the settings for the Sr, Y and I deposition tests*

Offline deposition tests - settings			
Element	**Strontium**	**Yttrium**	**Iodine**
Starting chemical form	$Sr(NO_3)_2$ (1 g/L)	YCl (1 g/L)	KI (1 g/L)
MM load	140 µL	900 µL	150 µL
MM positioning	Oven	Transfer Line	Oven
Ion source	SIS	PIS	PIS
Secondary target	NaCl disk (3.6 g)	NaCl disk (1.8 g)	Activated carbon 50% (w/w) PVA 50% (w/w) 1.3 g
Analytical technique	GF-AAS (λ=460.70 nm)	ICP-OES (λ=371.03 nm)	Titration

Table 3.6: *summary of the recovering efficiencies for the Sr, Y and I deposition tests*

Offline deposition tests - recovering efficency	
Extracted element	**Recovering efficiency**
Strontium	41.10%
Yttrium	100%
Iodine	63.70%

3.5 Offline tests in the framework of ISOLPHARM_Ag

As already introduced, the ISOLPHARM_Ag collaboration project is aimed to evaluate the feasibility of the production of a ^{111}Ag-based radiopharmaceutical according to the ISOLHARM method. In the previous paragraphs the calculated in-target yields and produced activities for such nuclide were presented in detail. In order to complete the feasibility study foreseen in ISOLPHARM_Ag, a subsequent crucial step is the investigation of the ionization processes using SPES ion sources, and the design and test of an appropriate substrate to be used as collection target. Indeed, since only a fraction of the in-target produced Silver isotopes will be ionized, extracted and collected, it is important to quantify the amount of the desired nuclide that will be available for radiolabeling. Consequently, ionization tests with stable Silver beams were performed with the SPES Front End prototype, in order to evaluate the efficiency of the ionization process. Furthermore, after the design and fabrication of a proper secondary target for the collection of Silver ions, deposition tests were performed. The irradiated targets were lately used to evaluate the recovering efficiency, related to the fraction of silver nuclides harvested from the substrate.

3.5.1 Ionization tests of stable Ag

As in the case of the tests with Sr and I, a precise amount of stable Silver was introduced inside the TIS unit by means of the Mass Marker (MM) technique [3.47]. Since the first ionization potential of silver is 7.58 eV [3.53], the SPES Surface Ion Source (SIS) is not adapt to ionize such element, whereas laser ionization and plasma ionization processes can be both potentially employed for silver. However, being the SPES offline FE not yet equipped with ionizing lasers, the only available technology for the Silver ionization tests was the SPES Plasma Ions Source (PIS) [3.55]. The deposition of the silver load onto the MM was performed by dropping 40 µL of silver nitrate ($AgNO_3$) standard solution (1 g/L, Fluka Analytics) on the tantalum foil, and the aqueous solvent was subsequently evaporated. The MM, after being accurately folded, was inserted into the oven at approximately 60 - 80 mm distance from the opening. One extremity of the oven was then sealed, and the other open side was connected to the transfer line.
The following parameters were used for the performance of the ionization tests:

- The ion source and transfer line were heated by Joule effect with a current intensity of 415 A, thus reaching a temperature level generally above 2000°C.
- The ionizing electron plasma in the PIS was created by setting a potential drop of 150V between the source anode and cathode, and by providing a 5 A current to the coil around the source. Indeed, the potential drop is required to accelerate the electrons emitted by the hot

cathode by thermionic effect, whereas the coil is used to generate a magnetic field that modify the electrons trajectory to spiral, thus increasing their probability to interact with the neutrals effusing through the ion source. With such settings, a plasma current with intensity of approximately 150 mA was generated.

- The oven maximum current was set to 80 A.
- A potential drop of 25 kV was applied between the TIS unit and the extraction electrode, that was positioned at 50% of its maximum stroke.
- Regarding the first beam optics subassembly, the deflectors D01, D02, D03 and D04, were set respectively 50 V, 320 V, 10 V and 100 V, whereas the three quadrupoles of the first triplet Q1, Q2 and Q3 were set respectively at 875, 695 and 1398 V.
- The Wien Filter settings were studied in order to selectively transport ^{107}Ag and ^{109}Ag, the stable isotopes of silver (natural abundances respectively 51.84% and 48.16%), either individually or together. In the case of selection and transport of a single silver isotope, a constant electric field of 103.16 kV/m was set into the WF by means of two couple of electrodes, respectively at 590 V (pre-electrodes) and 2579 V (electrodes). The magnetic field was adjusted by means of the WF coil current, set at 148 A, for the selection of mass 107 atoms, or at 150 A for the particles with mass 109 amu. In the case of simultaneous transport of both masses 107 and 109, the WF resolution has to be decreased. Consequently, the electric field within the WF was adjusted to 74.96 kV/m, by setting 1874 V and 343 V to respectively the WF electrodes and pre-electrodes. The WF coil was fed with a current of 105.5 A. with such WF settings, the injected beam profile had to be optimised, consequently the setting of the first triplet subassembly Q1, Q2 and Q3 were updated at 914 V, 759 V and 1521 V respectively.
- In the case of single mass beams the slits were positioned leaving an aperture with 8 mm width, in order that all diverted particles are dumped. In the case both masses 107 and 109 were transported, the slits were left open.
- The second Faraday Cup (FC2) was left into the beam line, in order to measure constantly the beam current.
- The subsequent triplets were left off, since the beam was dumped onto the second FC2.

At the beginning of the tests all aforementioned parameters were set, except for the oven current, that was stepwise increased from 0A. It was possible to verify that ^{nat}Ag atomization and ionization occurred after heating the oven with a 25 A current, corresponding approximately to a 1100°C at the MM position. Subsequently the oven current was increased with 5 A steps, up to 80A, thus operating working in a temperature range of 1100-2000°C. By increasing by steps the heating current, it was possible to gradually release the loaded Silver

nuclei towards the ion source, avoiding to saturate it. Indeed, the copper current measured ranged between the 200 and 600 nA.

The effective ionization and transport of Silver was proved by means of the analysis of the ion masses transported along the beam line. As shown in the typical mass scan, reported in figure 3.14, silver was identified with the two peaks at mass 107 and 109 amu with ratio 51.35/48.65, compatible with the natural abundances ratio of ^{nat}Ag (51.84/48.16).

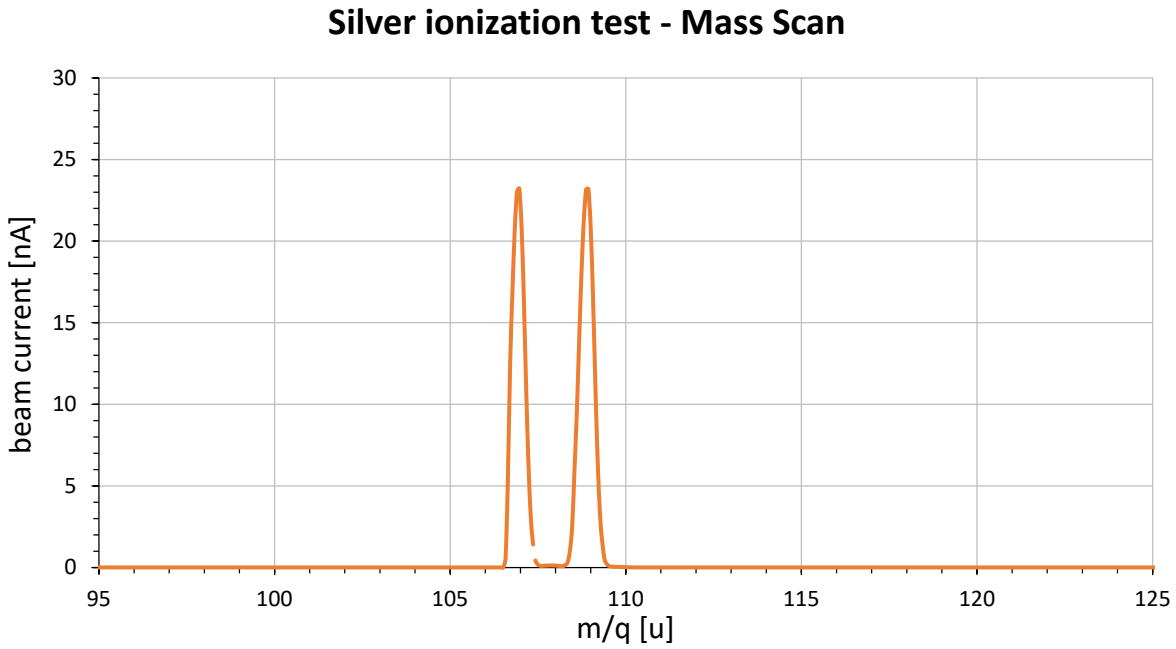

Figure 3.14: *mass scan performed during the Silver ionization tests. Mass 107 and 109 correspond to the stable isotopes of silver ^{107}Ag and ^{109}Ag*

Several ionization tests were performed and the results are discussed in the next paragraph.

3.5.1.1 Ionization efficiency measurements

Ionization tests were aimed to evaluate the ionization efficiency as the ratio between the number of charges measured with the FC2 and the amount of Ag nuclei loaded on the Mass Marker. In total 10 ionization efficiency measurement were performed, as presented in table 3.7. According to the presented results an average ionization efficiency of 11.24% with a standard deviation of 4.07% was evaluated, with a maximum value of 15.63% and a minimum measurement of 4.18%. Such high dispersion of the efficiency measurements was not expected, since the tests were repeated both in the same working conditions and using the same ion source. In order to better understand the cause of such high variability of the results, the eventual differences between the various tests were investigated in detail. As highlighted in table 3.7, the date of preparation of the Mass Marker was often not coincident with the test day, but sometimes the MM were prepared in bunches of 2/3 and employed for experiments after from few days up to almost two weeks.

Table 3.7: *summary of the performed Ag ionization efficiency measurements. In particular, the date of test performance and the date of MM preparation are highlighted.*

Silver ionization tests - efficency				
Test number	**MM preparation date**	**MM testing date**	**ΔMM dates (testing - preparation)**	**Measured ionization efficency**
[#]			[days]	[%]
1	4-Apr-18	11-Apr-18	7	10.54
2	4-Apr-18	13-Apr-18	9	8.91
3	13-Apr-18	18-Apr-18	5	16.17
4	13-Apr-18	19-Apr-18	6	11.88
5	4-May-18	9-May-18	5	8.80
6	4-May-18	14-May-18	10	4.18
7	4-May-18	14-May-18	10	6.85
8	15-May-18	15-May-18	0	15.63
9	16-May-18	16-May-18	0	14.83
10	17-May-18	17-May-18	0	14.62

In particular, the measurements performed with MM prepared with an advance of ten days showed the lowest efficiency estimations. Such phenomenon was deeper investigated by plotting the trend of the measured ionization efficiency in function of the delay between the MM preparation and its experimental employment (figure 3.15). Indeed, such trend highlighted that the longer was the aforementioned delay, the lower was the measured efficiency, thus suggesting that the unused MM are affected by an "aging" phenomenon. Such occurrence might be caused by chemical reactions arising spontaneously at room temperature between the deposed $AgNO_3$ layer and the underlying Ta substrate, that might lead to the formation of refractory compounds, such as Silver Tantalate ($AgTaO_3$) [3.56].

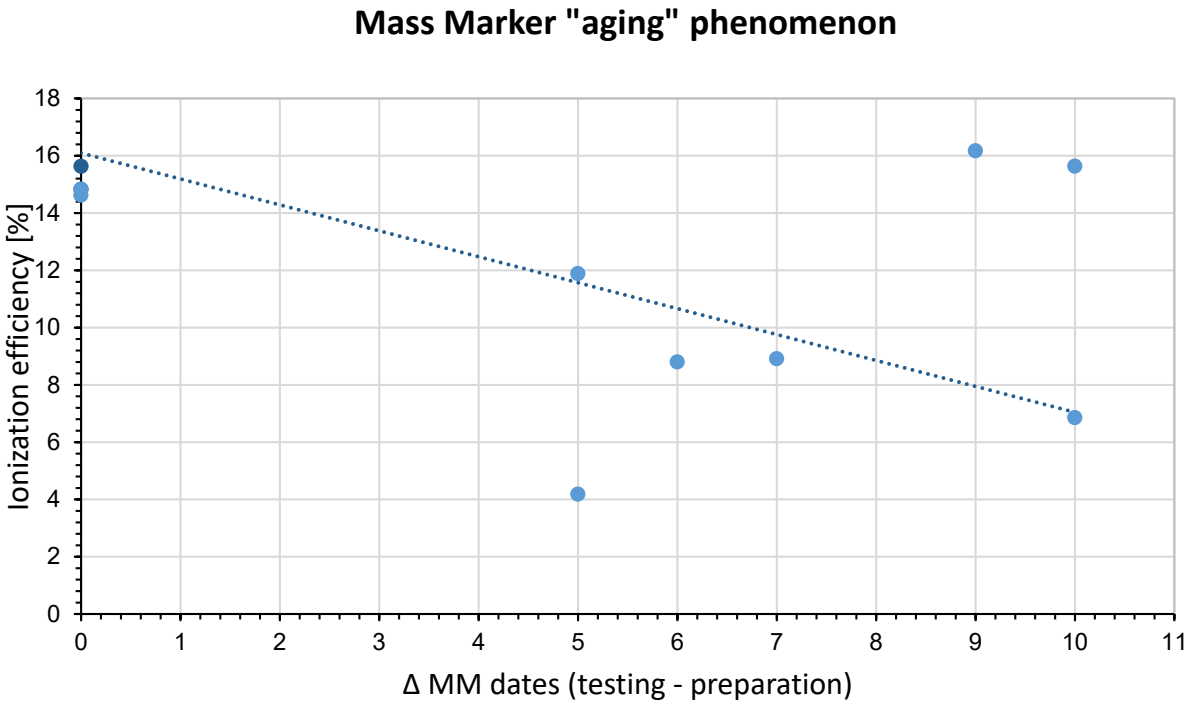

Figure 3.15: *trend of the measured ionization efficiency in function of the delay between the MM preparation and its experimental employment. It is possible to highlight that the longer the delay, the lower the measured efficiency.*

The slow formation of the aforementioned compounds might gradually subtract the available Silver atoms, that are consequently not atomized, when the oven is heated by Joule effect, thus explaining the decreasing trend showed in figure 3.15.

In order to avoid the MM "aging" phenomenon, only the measurements performed within the day of MM preparation where considered effective, whereas all the other results were discarded. Indeed, this is more consistent with the online procedures, that don't foresee to previously load amounts of the desired nuclides in the ion source, but to simultaneously produce ^{111}Ag by fission of the UC_x target and to release and extract the chosen Silver isotopes.

Table 3.8 summarizes the results of the relevant ionization tests, where the MM was prepared and directly employed in tests. According to such experiments the ionization efficiency for Silver is 15.03±0.53%.

Table 3.8: *summary of the relevant Ag ionization efficiency measurements.*

Silver ionization tests - efficency	
Test number	**Measured ionization efficency**
[#]	[%]
8	15.63
9	14.83
10	14.62
Average	**15.03**

3.5.2 Deposition tests of stable Ag

After the completion of the previously presented tests, aimed to prove the capability to ionize Silver beams and to measure the efficiency of such process, the following step was to evaluate the feasibility of the collection of the ionized Silver nuclides by means of an appropriate secondary target. Indeed, the substrate has to be successively removed and dissolved, allowing the subsequent recovery of the collected Ag from the so-obtained solution.

In the case of Silver, the choice of a proper substrate is a crucial step, because it has high chemical affinity with a wide variety of elements and it tends to form mostly sparingly water-soluble salts. The already developed NaCl secondary target is indeed not suitable, since the collected Ag^+ ions might react with the Cl atoms forming the deposition substrate, thus leading to the formation of the insoluble salt AgCl [3.57]. Since the subsequent radiochemical procedures require Ag solutions to be performed, the final product of the ISOL process has to be preferably easily soluble. Consequently, several other materials were considered, and finally Sodium Nitrate ($NaNO_3$) was selected for the deposition substrate. Indeed, even in case of

eventual reaction of the deposed Silver with the substrate, the formed $AgNO_3$ is soluble, and thus the efficient harvesting of the nuclide of interest will be possible.

$NaNO_3$ showed in addition good mechanical properties, since it was possible to manufacture 40 mm deposition targets by cold pressing in a cylindrical dye using 1.8g of ultrafine powder (figure 3.16) [3.58].

Figure 3.16: *$NaNO_3$ disk with 40 mm diameter, usable as secondary target for the Ag deposition tests.*

For the performance of the Ag deposition tests, the same settings of the previous ionization tests were employed, with the exception of the MM load, that was increased up to 200 µL of $AgNO_3$ solution (1 g/L), in order to ensure the collection of a reasonable amount of Ag^+ ions for the subsequent quantitative analyses.

In addition, the quadrupoles QT1, QT2 and QT3 of the second triplet subassembly were turned on, to ensure the best beam focalization in correspondence of the secondary target holder. The latter consists in a modified Faraday Cup, capable of hosting the collection target (figure 3.17), that was positioned in correspondence of the beam axis. Any other beam intercepting device was generally removed for the duration of the deposition test.

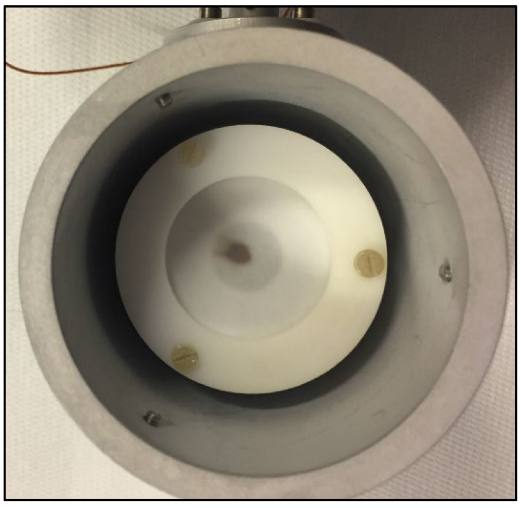

Figure 3.17: *the modified Faraday Cup used as secondary target holder*

3.5.2.1 Simultaneous deposition of ^{107}Ag and ^{109}Ag on 40 mm collection targets

The developed 40 mm $NaNO_3$ disks were used for the performance of the first deposition tests with stable Ag beams. For such experiment, the used WF settings ensured the transport of the overall $^{nat}Ag^+$ beam, meaning that both ^{107}Ag and ^{109}Ag were collected simultaneously on the same substrate.

In order to ensure the best focalization in correspondence of the secondary target with such dual mass ion beam, the quadrupoles QT1, QT2 and QT3 of the second triplet subassembly were set respectively at 1750 V, 825 V and 1975 V. The tests typically lasted approximately 4 hours.

After irradiation the secondary targets were removed, showing clearly two deposition spots, identifiable with the two masses ^{107}Ag and ^{109}Ag, as shown in figure 3.18.

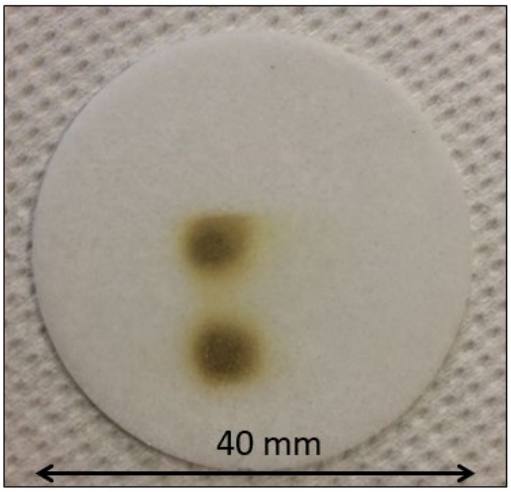

***Figure 3.18**: The $NaNO_3$ substrate after irradiation. The two spots correspond to ^{107}Ag and ^{109}Ag*

The recovered targets were subsequently dissolved and the collected amount of Ag was quantified via the GF-AAS method (Graphite Furnace-Atomic Absorption Spectroscopy), thus allowing the calculation of the deposition efficiency as the ratio between the recovered Ag amounts and the expected collected quantities according to efficiency of the ionization process. Such deposition tests were repeated three times, showing an average deposition efficiency of 76.63±6.19%.

Table 3.9 summarizes the results obtained for the aforementioned tests.

***Table 3.9:** summary of the Ag deposition tests with both ^{nat}Ag masses*

Silver deposition tests with both ^{107}Ag and ^{109}Ag - efficency			
Test number	**Expected deposed Ag**	**Recovered Ag**	**Measured recovery efficency**
[#]	[µg]	[µg]	[%]
1	4.61	3.41	74.05
2	5.66	4.08	72.15
3	3.41	2.85	83.70
Average			**76.63**

3.5.2.2 Deposition on 13 mm collection targets

With the previously presented deposition tests, 40 mm $NaNO_3$ disks were used as secondary targets. However, because of the quantity of solvent required to completely dissolve such secondary targets, the achievable concentration of Ag in the solution might be too low for the performance of the subsequent radiochemical studies, and an additional process may be necessary to decrease the solution volume. Since the beam deposition spots showed in figure 3.18 are small in size (approximately 5 mm of diameter), smaller collection targets were produced exploiting a 13 mm dye. Consequently, it was possible to produce solid 13 mm diameter $NaNO_3$ disks with smaller mass (up to 0.4 g), that could be dissolved with less solvent. The produced deposition substrates were subsequently employed for tests, where only ^{107}Ag, the most abundant Ag natural isotope, was collected. Indeed, the size of the disks does not allow to depose simultaneously both ^{107}Ag and ^{109}Ag.

For the performance of such tests, the FE settings already defined for the previous ionization tests were used, with the exception of the optical devices after the WF. Indeed, in order to ensure the best beam focusing at the secondary target, the quadrupoles QT1, QT2 and QT3 of the second triplet subassembly were set respectively at 1690 V, 830 V and 1690 V. In addition, for such tests, the FE was upgraded and equipped with a couple of deflectors between the Diagnostic Box 2 and the Second triplets, in order to correct the beam alignment. This was necessary since less tolerance on the beam position was acceptable because of the smaller size of the collection target. Such deflectors D1 and D2 adjust the horizontal and vertical alignment of the beam and were set at 150 V and 65 V respectively.

After approximately 4 hours of irradiation, the secondary targets were removed, and, according to the deposition spot position and size, the beam optics setting adopted were acceptable. Figure 3.19. shows a typical 13 mm $NaNO_3$ disk, after irradiation with a $^{107}Ag^+$ beam.

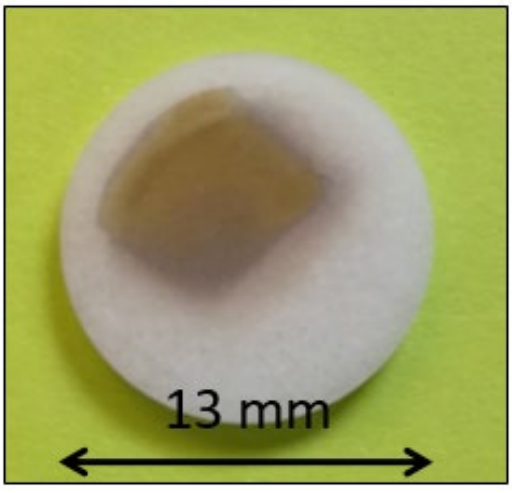

***Figure 3.18**: The $NaNO_3$ 13 mm substrate after irradiation with $^{107}Ag^+$ beam*

The recovered targets were subsequently dissolved and the collected Ag was quantified as in the case of deposition tests on 40 mm targets, in order to calculate the recovery efficiency. Similarly, even such tests were repeated three times, showing an average deposition efficiency of 68.84±0.70%.

Table 3.10 summarizes the results obtained for the aforementioned tests.

Table 3.10: *summary of the Ag deposition tests with 13 mm $NaNO_3$ disks*

Silver deposition tests (^{107}Ag on a 13 mm disk) - efficency			
Test number	**Expected deposed Ag**	**Recovered Ag**	**Measured recovery efficency**
[#]	[µg]	[µg]	[%]
1	9.50	6.53	68.73
2	10.22	7.05	68.95
3	19.09	12.91	67.64
Average			**68.44**

3.5.3 Preliminary effusion tests of stable Ag

Once the ionization and deposition efficiencies were evaluated, one open question was to understand if Silver could be released from the Uranium Carbide target. Indeed, as highlighted with the MM "aging" phenomenon, Silver tends to easily react with many chemical elements, and thus the eventual formation of Ag complexes with the target material can decrease the amount of recoverable Silver isotopes of interest. Such eventual Silver compounds either might be extracted as molecules, and thus are eliminated with the mass separation since they have a different mass number, or, if refractory, they might not be released.

Regarding such aspect, Silver is known to form complexes with Carbon at room temperature, such as Silver Acetylide (Ag_2C_2) [3.59], that is however unstable above 120°C. Anyway, the high temperature chemistry of many elements is yet not known, consequently the eventual formation of other Ag - C complexes, that might be stable at high temperature and influence the release from the production target, was further investigated.

Therefore, for the performance of such tests, a graphite substrate was used to mimic the Uranium Carbide target material. In such case the MM technique was not applicable, since it was impossible either to fold a graphite substrate without breaking it or to quantitatively depose $AgNO_3$ drops on a graphite piece small enough to fit the 1 mm diameter hole of the Ta oven. Consequently, for such tests, a 5x5 mm^2 graphite foil (thickness 0.2 mm) was loaded with 40 µL of AgN O_3 solution (1g/L), and inserted directly in the transfer line of the ion source, as shown in figure 3.19. With such solution, however, since the heating of the sample is not decoupled to the heating of the ion source, that operates efficiently only at high temperatures

(2000°C), quantitative evaluations of the released amounts of Silver are not possible, anyway useful information regarding the extracted masses can be retrieved.

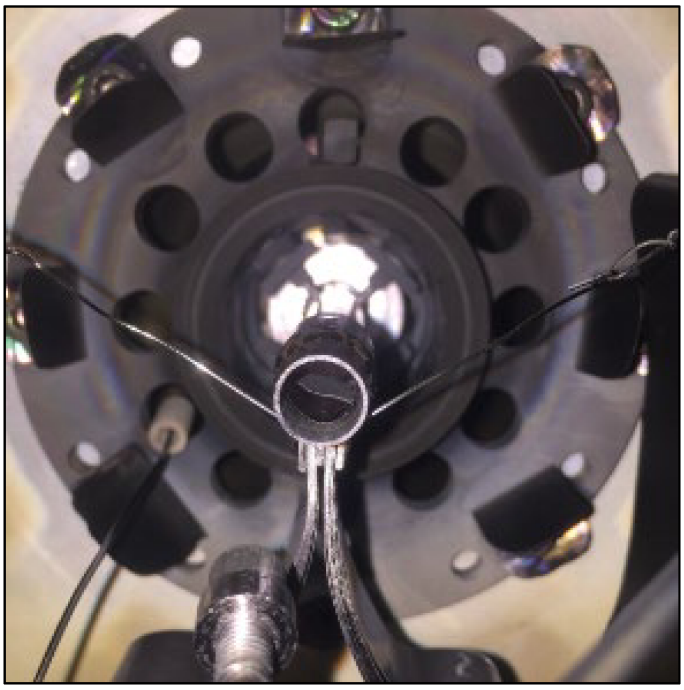

Figure 3.19: *the graphite substrate with the Ag load, inserted directly in the ion source transfer line*

Figure 3.20 shows a mass scan performed during the tests, when the ion source heating current was 340 A, corresponding to approximately 1800°C at the ion source and 1400°C at the graphite sample. It was possible to easily identify the two peaks corresponding to ^{107}Ag and ^{109}Ag, whereas no other unexpected peaks were found, thus excluding the formation of volatile Ag complexes.

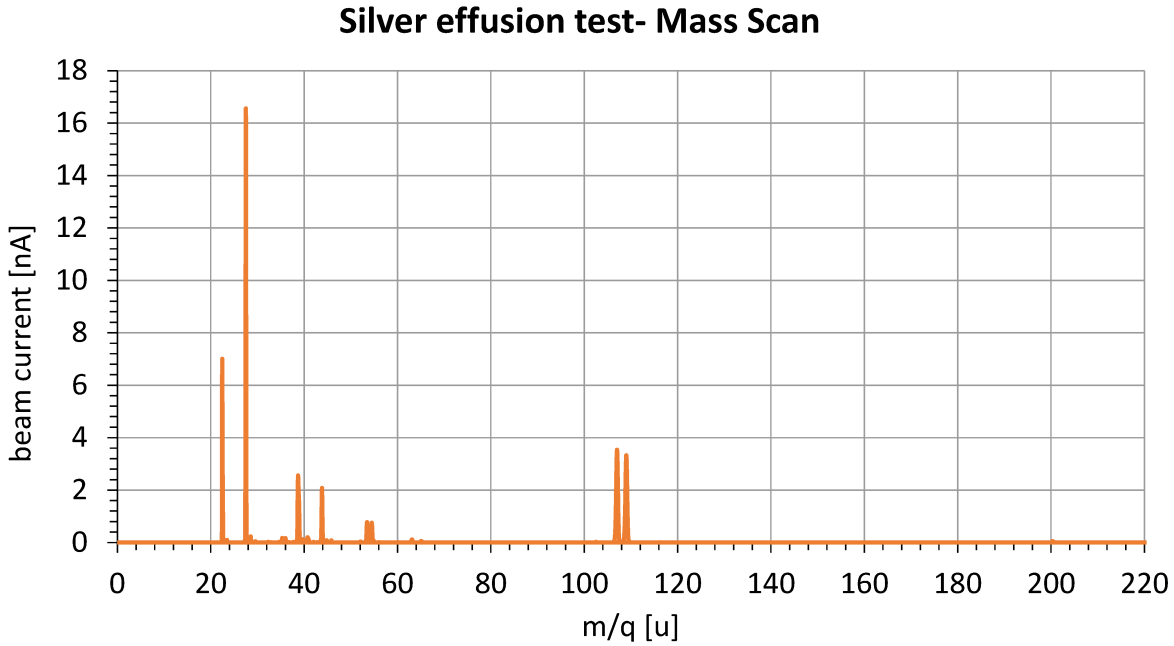

Figure 3.20: *mass scan performed during the Silver effusion tests. Mass 107 and 109 correspond to the stable isotopes of silver ^{107}Ag and ^{109}Ag. No unexpected Ag complexes were found.*

The mass scan was repeated also at higher temperature levels, showing similar plots. In addition, after tests the samples were analysed through X-ray Powder Diffraction (XRD) and no Ag traces were found, thus confirming that also no refractory Silver compounds were generated.

3.6 Caesium ionization tests

As already introduced, many Caesium isotopes of potential medical interest can be produced with the SPES UC_x target, consequently the capability to ionize Cs (with first ionization potential of 3.89 eV [3.53]) has to be evaluated. However, since such element was chosen as reference for the development of the SPES Surface ion Source (SIS) [3.48, 3.60], the performance of dedicated tests for the evaluation of the ionization efficiency was not necessary in this work. Indeed, according to literature results on the SPES SIS, the ionization efficiency of Caesium is 45.8±2.8% [3.48].

Mass scans performed during such tests with stable Caesium, as shown in figure 3.21, confirmed the presence of such element within the extracted beam, since a peak was identified at mass 133, being ^{133}Cs the only stable Caesium isotope [3.60].

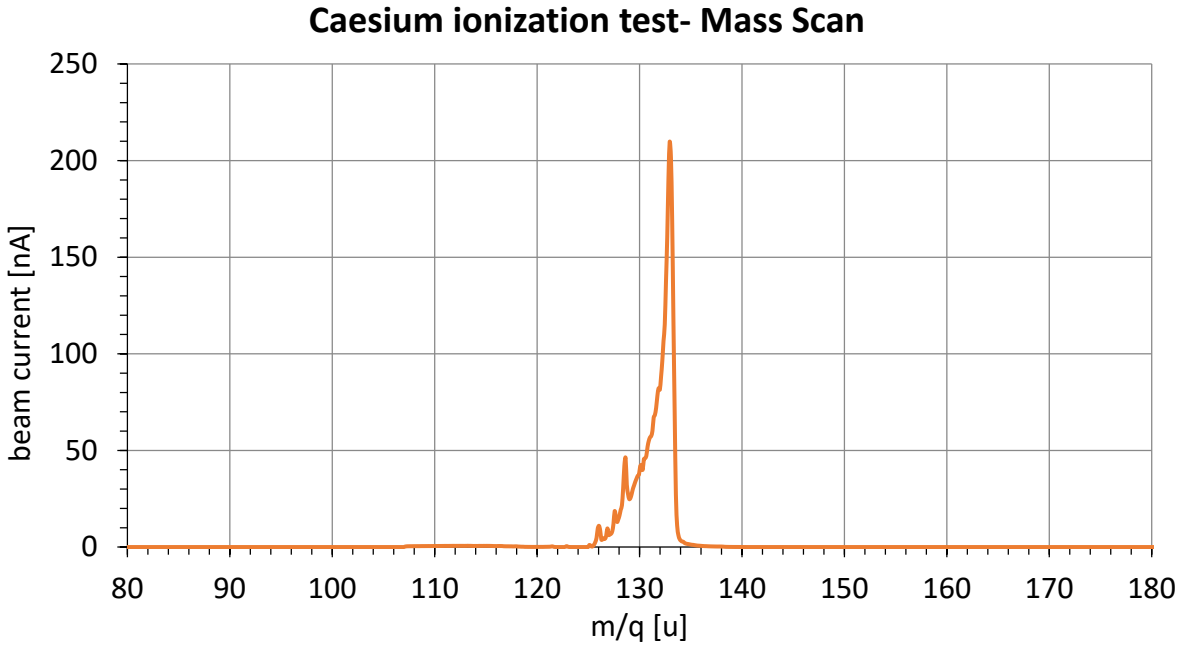

Figure 3.21: *mass scan performed during the Cesium ionization tests. Mass 133 corresponds to the stable isotopes of Cesium ^{133}Cs.*

Deposition tests with Caesium were not yet performed, and an appropriate substrate for its collection was not yet selected.

3.7 Discussion and conclusions

The primary aim of the studies presented in this chapter was to perform the proof of principle study for the possibility of producing the innovative isotope ^{111}Ag as radiopharmaceutical precursor according to the ISOLPHARM method, exploiting the technologies and developments that will be available at SPES. In addition, early consideration on the feasibility of the ISOL production of promising Caesium isotopes with possible medical application were undertaken.

The possible production yields of the aforementioned isotopes were calculated by means of Monte Carlo codes, in particular FLUKA and MCNPX, that were also experimentally validated. The presented in-target production estimations for ^{111}Ag showed promising results, however, the final nuclide amounts, that will be effectively available as radiopharmaceutical precursors, will be lower, since the ISOL technique involves several steps and each of them introduces an additional efficiency factor.

In particular, to have a better estimation of the ^{111}Ag effective final collection, offline ionization and deposition tests were performed, using in both cases the SPES PIS and stable Silver isotopes. According to such tests an ionization efficiency factor of ~15% was measured, thus suggesting that the finally harvested amounts of silver nuclides are one order of magnitude lower than the effective in-target production.

Since only the plasma ionization technique was testes, such presented result could be potentially increased by switching to the resonant laser ionization technique [3.61], that normally ensures a more selective ionization, since the laser is tuned to the typical wavelengths of the desired element [3.62]. Dedicated tests with a laser ion source could be performed in the future to identify the most efficient ionization mechanism for silver.

Regarding the recovery efficiency from the deposition target, it is important to highlight that only one material, $NaNO_3$, was considered in this study. However, the development of other secondary target materials could be undertaken and potentially increase the efficiency of the harvesting process.

Finally, as general consideration, what makes reasonable to investigate the possibility to produce ^{111}Ag according to the patented ISOLPHARM method, is the fact that currently it is not routinely produced with traditional techniques, even if its decay properties are extremely interesting for a potential medical use. When the first ^{111}Ag beam will be extracted and collected from SPES, the first ^{111}Ag labelled high specific activity radiopharmaceuticals will be produced with the molecules developed in the framework of ISOLPHARM_Ag and the first *in-vitro* and *in-vivo* tests will be performed.

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