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Development of Radionuclides for Theragnostic Applications at the Paul Scherrer Institut (PSI)

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Abstract –*The Paul Scherrer Institut (PSI) is the largest research institute for natural and engineering sciences in Switzerland, focusing on cutting-edge research in four fields, namely, Future Technologies, Energy and Climate, Health Innovation and Fundamentals of Nature. PSI develops, builds and operates complex large research facilities, in particular, one of the most powerful proton accelerators worldwide. An important component of innovative radiopharmaceuticals, especially in oncology, is the availability of various radionuclides with optimal decay properties for the improvement of diagnostic or therapeutic efficacy. The Laboratory od Radiochemistry (LRC) at PSI, in collaboration with the Center of Radiopharmaceutical Sciences (CRS), produces and further develops a variety of accelerator, reactor (or Spallation Neutron Source) and spallation-induced radionuclides via its vast networks. Medical radionuclides must be available with high-specific activity and purity. Here, the choice of nuclear reaction and subsequent radiochemical isolation strategy play a key role.*

Keywords: Theragnostics, radiopharmaceuticals, spallation target

I. Introduction

The Paul Scherrer Institute (PSI) is the largest research institute for natural and engineering sciences in Switzerland. PSI conducts basic as well as applied research in four main fields, namely, Future Technologies, Energy and Climate, Health Innovation and Fundamentals of Nature.

To support the Swiss research community, PSI develops, builds and operates complex large research facilities (Fig. 1). The site hosts facilities such as the Swiss Light Source (SLS), the Swiss X-ray Free-Electron Laser (SwissFEL), the High Intensity Proton Accelerator (HIPA) facility - which also feeds the spallation neutron source (Swiss Neutron Source, or SINQ), the muon source (SμS) and the Swiss Research Infrastructure for Particle physics (CHRISP). More than 2500 scientists per year from all over the world use these large facilities for research and development.

In the area of Health Innovation, PSI researchers focus on the causes of illnesses and explore different potential treatment methods. PSI founded the Center for Proton Therapy (CPT), for the treatment of specific malignant tumors, and is famous for its eye therapy program and treatment of children. The federal research facility has also made a substantial contribution to the world of nuclear medicine over the years by producing radionuclides, as well as radiopharmaceuticals.

Fig. 1. Aerial view of the PSI premises

The facilities used towards this program have evolved over the last five decades and its historical development has established radionuclide development as a major education and research driver towards radiochemistry in Switzerland.

II. RADIONUCLIDE PRODUCTION

PSI operates a High Intensity Proton Accelerator (HIPA) amenity as part of its Large-Scale Facilities, where three accelerators are connected in series to increase proton beam energy. A Cockroft-Walton accelerator accelerates protons at 870 keV to the Injector II separated-sector cyclotron, where the protons are accelerated to 72 MeV at high intensity (>2 mA) to the Ring cyclotron. The Ring cyclotron accelerates the protons further to 590 MeV, which are then sent down the beamline to various experimental vaults, before the remainder of the beam is collected in a lead beam dump, which serves as a neutron spallation source for the Swiss Neutron Source (SINQ).

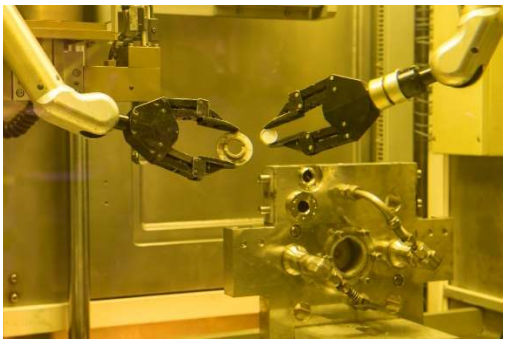

Fig. 2. Reception hot cell at IP2 irradiation station, where target capsules are loaded/unloaded from the target holder (bottom right). (https://www.psi.ch/en/media/our-research/in-the-focus-of-the-protons).

Along the beam line between Injector II and the Ring cyclotron, up to 100 µA protons are split from the high-intensity 72 MeV protons from Injector II into an irradiation station, known as IP2 [1]. These protons irradiate various targets towards the production of exotic radionuclides intended for medical purposes. The IP2 irradiation station was designed and built in the early 1980s and was put into service in 1986 [2]. The station was brought into service in 1985 and took over the lead role in the radionuclide production, and subsequent development program. The target holders used at IP2 are large, heavy and constructed using stainless steel. They were designed to hold large targets such that they could be irradiated at high proton energies and obtain high production yields. The station has a rail transport system such that targets can be loaded and unloaded from a hot cell adjacent to the irradiation station (Fig. 2).

With the increased popularity of PET for the diagnosis of cancer, as a result of its superior image resolution over Single Photon Emission Computed Tomography (SPECT), the strategy of the station's use was adjusted to meet the growing demand for new positron-emitting radionuclides. To meet the revised strategy of IP2's use, it was necessary to degrade from 72 MeV to the desired energy of the radiometal to be produced using Niobium discs. Currently, IP2 gleans 50 µA protons from Injector II, by means of a beam splitter placed along the beam line between Injector II and the Ring cyclotron. Once developed, these proofs-of-principle can then be put into practice at partner facilities. Examples of this include 44Sc [3] and 165Er [4]. Target material is irradiated, extracted from its Al capsule and a chemical separation process performed to obtain radionuclidically and chemically pure product. An example, featuring 44Sc, is described below.

44-Scandium is seen as a potentially ideal radiometal for PET, as its half-life ($T_{1/2}$ = 4.04 h) [16] is longer and resolution is better than that of 68Ga (currently the most popular radiometal in use for PET; $T_{1/2}$ = 68 min). It can be produced at a cyclotron via the 44Ca(p,n)44Sc nuclear reaction [5,3]. Irradiated targets are dissolved in nitric acid and loaded onto a column containing DGA extraction resin, where the 44Sc is retained and the Ca target material passed through the system. This is collected separately and subsequently recycled to make new targets. The desired 44Sc is eluted with dilute hydrochloric acid and concentrated onto a second, smaller, resin column. The final product is eluted from this second column in a small volume such that it could be used effectively for preclinical [6] and clinical studies [7].

Other than the beam used in various experimental vaults, the remainder thereof (>70 %) from the 590 MeV Ring cyclotron is deflected into an extended beam line towards a final target designed to stop the proton beam – a lead "beam dump", which is the spallation target for SINQ (the Swiss Neutron Source). SINQ houses a pneumatic "rabbit" system for neutron irradiation of materials inserted into a beam tube. The pair of tubes closest to the target (PNA) is utilized for radionuclide production and development, which includes the production of radioactive tracers towards

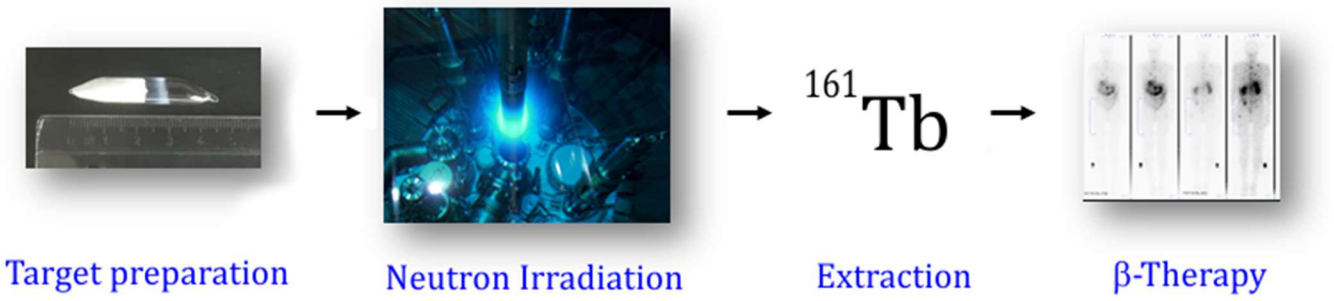

Fig. 3. The 161-Terbium production route from bench to bedside.

developing chemical separation methods (thermal neutron flux: $2 \cdot 10^{13}$ n cm^{-2} s^{-1} mA^{-1}). Over the last decade, however, PNA was predominantly used for the development and upscale of 161Tb production [4] (Gracheva et al., 2019). Enriched Gd target material is sealed in a quartz ampoule, and is placed in an Al capsule, which is welded closed before irradiation.

Terbium-161 ($t_{1/2}$ = 6.95 d [8]) is produced by the irradiation of enriched gadolinium with neutrons via the 160Gd(n,γ)161Gd→161Tb nuclear reaction. While neutron irradiation of target material generally yields carrier-added product (it produces a radioisotope of the target material), the 161Gd produced has a short half-life ($t_{1/2}$ = 4 min), decaying to 161Tb. In this way, carrier-free product is obtained following chemical separation. The target material, in oxide form, is dissolved in acid and evaporated, before being collected with ammonium nitrate and passed through a long cation exchange resin column at a slow pump speed. As for most lanthanides, Tb and Gd are separated using α-HIBA (alpha-hydroxyisobutyric acid). The desired 161Tb is eluted from the long column and concentrated on a small extraction resin column, before finally being removed as product in a small volume of dilute HCl [4].

161-Terbium decays with the emission of β^--particles of medium energy (E_{β^-av} = 154 keV), comparable to the β^--particles emitted by 177Lu (E_{β^-av} =134 keV). 161Tb closely resembles 177Lu chemically, as well as by physical decay and, thus, can be used for β^--therapy using DOTA-functionalized tumor-targeting ligands. 161Tb is of particular interest for radionuclide therapy of disseminated disease, due to the co-emission of conversion and Auger electrons that may be advantageous for the treatment of single-cancer cells. 161Tb also emits photon radiation (E_γ= 45–53 keV (39%), 75 keV (10%)) suitable for SPECT imaging. The production of 161Tb has been established to make this radionuclide available in GBq-quantities and in high quality, which enabled multiple preclinical studies [9] (Mueller et al., 2019) as well as a first-in-human application [10] (Baum et al., 2021). The nuclide is poised to be prepared as a GMP-compliant radiopharmaceutical for clinical trials (Fig. 3).

III. Further developments at PSI

IMPACT (Isotope and Muon Production using Advanced Cyclotron and Target technologies) is a new Swiss Research Infrastructure proposal recently submitted by PSI [11]. It entails the construction of two new target stations and beamlines at the high-intensity proton accelerator (HIPA) facility. The first aims to increase current muon rates by up to 100-fold for experiments in particle physics and materials science (HIMB), while the second (Targeted Alpha Tumour Therapy and Other Oncological Solutions - TATTOOS) aims to create difficult-to-produce radionuclides suitable for advanced cancer treatments in the required quantities towards potential clinical studies.

The TATTOOS concept is based on the technology currently operated at ISOLDE at CERN [12]. Some radionuclides attractive for medical purposes are difficult to produce and, currently, are collected and mass-separated following a high-energy spallation reaction (ISOL) using a tantalum target. The desired radionuclides were subsequently chemically separated from their zinc collection material, as well as their isobars, such that it could be utilized for radiolabelling [13, 14].

In the desire to capitalize on PSI/ISOLDE-CERN's successes with these basic-research experiments, the TATTOOS concept [15] germinated and an initial design was devised (Fig. 4).

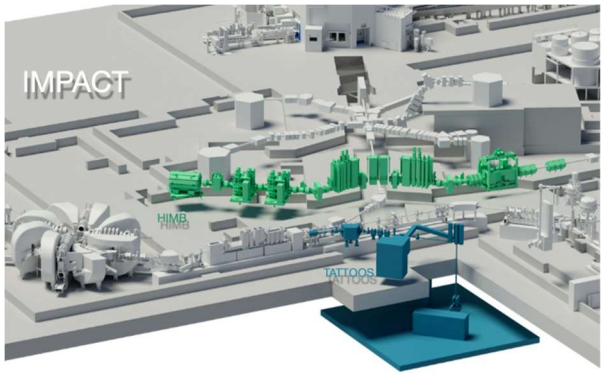

Fig. 4. The IMPACT project proposal concept, as part of PSI's HIPA complex

The Ring Cyclotron, as part of the High Intensity Proton Accelerator (HIPA) facility at PSI, will be utilized for this purpose, where 100 μA of the high-energy 590-MeV protons will be guided to an online spallation target connected to an ISOL facility.

TATTOOS is proposed to produce unprecedented activities of isotopically and radiochemically pure exotic radionuclides for radiopharmaceutical use. Radiochemical separation processes, as part of a shielded-cell facility where the mass-separated ion sample is collected, will ensure that the quality of the desired nuclide will meet the standard required for such use, while also used for fundamental research.

Radionuclides for theragnostics can be produced using the envisaged ISOL procedure, with attractive radionuclides regarded as hot topics, such as the α-emitters 149Tb, 225Ra/225Ac and 211At, as well as β^--emitters and nuclides relevant for diagnostic purposes, being envisaged.

IV. Conclusions

The IP2 irradiation station at PSI is an effective tool towards proof-of-concept development of exotic radionuclides in Switzerland. Its effectiveness has resulted in enabling PET radiometal production by irradiation at medical cyclotrons. Its effectiveness has resulted in upgrades planned to improve irradiation conditions. A new target holder with a revised degrader system and a thermocouple collimator system has been designed and is under construction, with initial tests planned within the next year. SINQ has also proven to be an effective tool for the development of 161Tb, with the irradiation being up-scaled at network partner facilities towards first clinical trials.

A novel irradiation station with high-energy protons at PSI, in the view of enlarging the radionuclide production portfolio in Switzerland as well as Europe, referred to as TATTOOS, is proposed. The spallation process induced by high-energy protons, utilising various target material, will provide access to a plethora of exotic radionuclides not otherwise accessible with great scientific potential for nuclear physics, astrophysics and fundamental radiochemistry.

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