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CERN-MEDICIS: A UNIQUE FACILITY FOR THE PRODUCTION OF NON-CONVENTIONAL RADIONUCLIDES FOR THE MEDICAL RESEARCH

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Abstract

CERN-MEDICIS (MEDical Isotopes Collected from ISolde) is a facility at CERN (Switzerland) dedicated to the production of non-conventional radionuclides for research and development in imaging, diagnostics and radiation therapy done at partner institutes. It exploits, in a controlled radiation area suited for the handling of unsealed radioactive sources, a target irradiation station positioned between the High Resolution Separator (HRS) ISOLDE target station and its beam dump, a target remote handling system and a dedicated isotope separator beam line. It irradiates targets with the 1.4 GeV Proton Synchroton Booster (PSB), and also receives activated target materials from external institutes, notably during CERN's Long Shut-Downs. The irradiated target is heated to high temperatures (up to 2300°C) to allow for the release of the isotopes of interest out of the target which are subsequently ionized. The ions are accelerated and the beam is steered through an offline mass separator. The radionuclide batches are, this way, extracted through mass separation and implanted into a thin metallic collection foil up to an energy of 60 keV. After collection, the isotope source is prepared to be dispatched to biomedical research centers (Figure 1).

Since its commissioning in December 2017, the CERN-MEDICIS facility has provided non-conventional medical radionuclides such as Tb-149, Tb-152, Tb-155, Tm-165, Er-169 and Yb-175 with high specific activity, some for the first time, to research institutes and hospitals, being part of the MEDICIS collaboration, for R&D in imaging or treatment [1].

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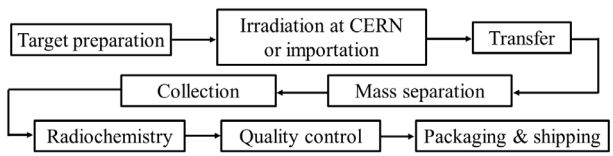

Figure 1: CERN-MEDICIS' steps from target preparation to radioisotopes shipping.

THE CERN-MEDICIS COLLABORATION

The research program at CERN-MEDICIS is driven by a collaboration agreement between CERN and several partners which includes research institutes, hospitals and universities [1]. The installation has been built as an extension of the ISOLDE facility [2] for research purposes on medical isotopes in view of providing the collaborating institutes with radioisotopes of high specific activity for their research programs [3]. The CERN-MEDICIS scientific program is shaped from the biomedical projects submitted by the members to the Collaboration Board which evaluates the needs of the community and the technical feasibility. The first collection of radionuclides took place in December 2017 at the end of the commissioning period. Since then, the collaboration board approved already 25 proposals. The list of radionuclides of interest once defined is thus re-evaluated at each board, mostly for applications in theranostics, combining diagnosis and therapy. Among them we can find scandium isotopes such as Sc-44 and Sc-47 [4-6]. Sc-44 is of interest for Positron Emission Tomography (PET) and Sc-47 for use in both, therapy and Single Photon Emission Computed Tomography (SPECT). As for Sc-47, Cu-67 is a radionuclide of interest for theranostic

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applications [7]. CERN-MEDICIS has already demonstrated the possibility of producing three out of the four terbium isotopes of high interest for nuclear medicine [8], which include the alpha emitter Tb-149 [9], the positron emitter Tb-152 [10], the gamma and Auger emitter Tb-155 [11]. Completing this so-called "swiss army knife" of nuclear medicine [12], is Tb-161 which is available from nuclear reactors. CERN-MEDICIS is also focusing on the collection of Sm-153, Tm-167, Er-169, Yb-175 and the alpha emitter Ac-225 [1]. These radionuclides are produced either by using the PSB beam [13], or using target materials irradiated at external partner institutes, such as the high flux reactor at Institut Laue Langevin (ILL) in Grenoble (France) [14] and at the high power cyclotron at ARRONAX (Accélerateur pour la Recherche en Radiochimie et en Oncologie à Nantes Atlantique) in Nantes (France) [15].

IRRADIATION AT ISOLDE WITH THE CERN PROTON BEAM

Before each irradiation a dedicated target unit is built, which is compatible with both ISOLDE and MEDICIS facilities. It is composed of a water-cooled aluminium vacuum vessel which encloses a tubular tantalum oven inside of which a target material is placed. As can be seen in Figure 2, the MEDICIS target is larger (50 mm diameter) than the ISOLDE one (20 mm diameter). The oven is connected to an ion source via a transfer line [16]. The target is brought from the CERN-MEDICIS laboratory to the ISOLDE target area via an automatic rail conveyor system (RCS). The MEDICIS target is installed for irradiation between the HRS target station onto which the proton beam is directed for the online mass separation performed at ISOLDE, and the beam dump. The MEDICIS target is irradiated by the fraction of the primary proton beam which did not interact with the ISOLDE target and by the secondary particles generated from the ISOLDE target's irradiation. FLUKA simulations [17, 18] have been performed in order to assess the number of primary protons and their energy spectrum that reach the MEDICIS target with ISOLDE targets made of different materials. The geometry [19] includes the full representation of the ISOLDE and MEDICIS targets (see Figure 2) with the beam dump located downstream of the MEDICIS target. Analytically, the number of hadrons $N(x)$ that reach the end of an ISOLDE target (x=19.6 cm) without being subject to any inelastic interaction can be expressed as [20]:

$$N(x) = N_0 .\exp(-x/\lambda) \quad (1)$$

with N_0 the initial number of primaries entering the volume, x the length of the target in cm and λ the inelastic interaction length at beam energy in cm, which is characteristic for each target material.

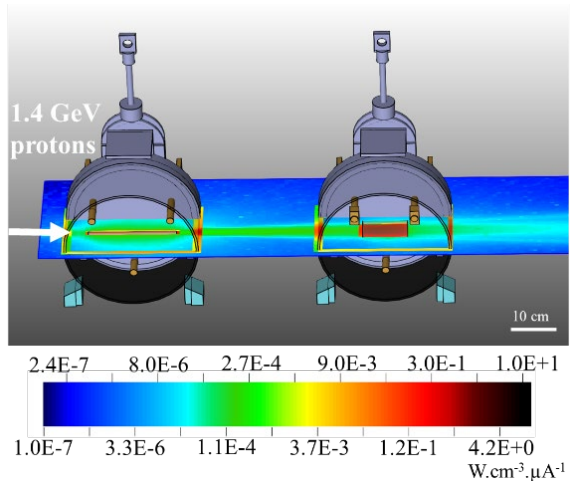

Figure 2: Visualisation of the ISOLDE (left) and MEDICIS target (right) irradiated by the 1.4 GeV proton beam. The deposited energy is represented in $W.cm^{-3}.\mu A^{-1}$.

The first column in Table 1 gives a summary of the ISOLDE target materials with their apparent density in the second column. Column 3 gives the fraction F of hadrons $N(x)/N_0$ using equation (1), while column 4 provides F obtained by FLUKA simulations (star density, a star being defined as a hadronic inelastic interaction occurring at an energy higher than 50 MeV). It should be noted that ISOLDE uses UC_2-2C targets with an apparent density of 3.5 $g.cm^{-3}$ [3] for about 60% of its physics program. Consequently, the MEDICIS target can exploit about 2/3 of the PSB's primary protons (see Table 1).

Table 1: Fraction F of primary protons leaving the ISOLDE target unit without inelastic interaction.

ISOLDE target material	Density ($g.cm^{-3}$)	F – equation (1)	F – Monte Carlo
UC_2-2C [3]	3.5	64%	69%
Ta [3]	2.0‡	80%	83%
UC_2-2C (nano) [21]	1.4	85%	86%
Ti [3]	0.8	88%	89%
CaO [22]	0.4	93%	93%
None§	-	97%	97%

Figure 3 shows the proton fluences in lethargy representation, expressed in $cm^{-2}.primary^{-1}$, at the entrance and at the exit of an ISOLDE UC_2-2C target, and at the entrance of the MEDICIS target. This figure illustrates that for 60% of ISOLDE's beam time, the protons impinging on the MEDICIS target have an energy spectrum ranging between 1.3 and 1.4 GeV.

Once the target has been irradiated, it is transported back to MEDICIS with the same rail conveyor system (RCS). From this point onward, a KUKA® robot handles the target (see Figure 4) and is used to connect it to the target station to start the isotope collection [23]. It should be noted that, when no MEDICIS target is placed downstream of the

‡ Ta target densities can vary between 0.8 and 4 g/cm^3

§ The beam is passing through the target vessel only

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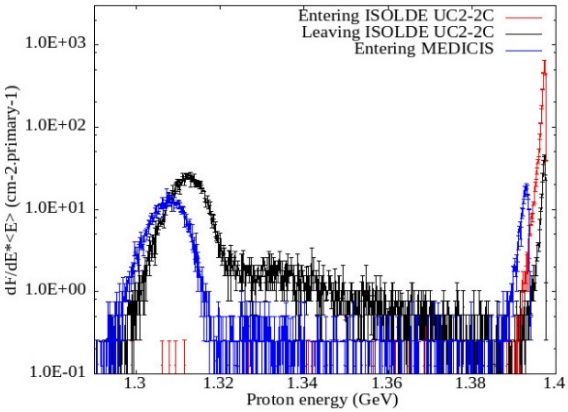

Figure 3: Lethargy representation of the proton fluence spectra at the entrance and the exit of an ISOLDE UC_2-2C target and at the entrance of a MEDICIS target.

Figure 4: KUKA® robot manipulating a MEDICIS target placed on the rail conveyor system (RCS).

ISOLDE target, the beam is directly stopped in the beam dump. The MEDICIS target takes advantage of these unused protons without impacting the physics program at ISOLDE and acts as a parasitic facility.

Due to an efficient remote handling system, the MEDICIS facility can collect and provide its partner institutes with short-lived medical radionuclides of only a few hours half-lives. After the irradiation it takes on average: (i) 12 min for the RCS to bring the target back from the irradiation point, (ii) 15 min to measure the target's dose rate and install it with the KUKA® robot on the MEDICIS frontend, and finally, (iii) 3 hours to condition the target unit for extraction (vacuum, high voltage and heating). Thus, the MEDICIS facility can start extracting radioisotopes after about 3.5 hours after irradiation of the target. Additionally, in synergy with ISOLDE, targets can also be parasitically irradiated at the MEDICIS irradiation point to produce long-lived radioisotopes and used afterwards on the ISOLDE frontends, thus extending the program with so-called winter physics into CERN's shutdown period, as demonstrated in the recent study of RaF molecules [24].

USE OF EXTERNAL SOURCES

At the end of 2018 CERN started its Long Shutdown 2 (LS2) for a duration of 2.5 years, during which the CERN accelerators are closed for maintenance. As a consequence, no proton beams are accelerated for the diverse experimental program until 2021 and, in particular, no targets can be irradiated. CERN-MEDICIS is one of the very few facilities at CERN still operating during LS2, performing offline mass separation of radionuclides from materials irradiated by external partner institutes such as ARRONAX and ILL.

Feasibility tests with $^{168}Er_2O_3$ targets irradiated at ILL for the separation of Er-169 [25] were performed in 2018, during which a first high specific activity batch of 18 MBq was collected. ARRONAX possesses a high-power cyclotron capable of delivering proton, deuteron and alpha particle beams. To provide CERN-MEDICIS with externally irradiated sources, thin Gd foils are irradiated by 30 MeV protons offering the maximum production cross-section for the generation of Tb-155 through Gd-nat(p,xn) reactions [26]. However, other radioisotopes such as Tb-154 and Tb-156 are co-produced. These radionuclides can only be purified by mass separation in order to supply the research institutes with pure and high specific activity collections of Tb-155. Before being shipped to CERN-MEDICIS the irradiated Gd foils are dissolved and the solution is evaporated on a dedicated sample holder, developed to be rapidly and securely transferred into the target tantalum oven, from which the isotopes are evaporated in order to be ionized and mass separated. In 2019 irradiated target materials were also received from the high flux reactor of the Institut Laue Langevin (ILL) in Grenoble. Prior to the irradiation quartz vials were filled with enriched target materials such as Er-168, Yb-174 and Pt-194. The vials were sealed and irradiated at the ILL high-flux nuclear reactor for the production of radioisotopes via neutron activation. The stable isotopes of the same chemical element present in the enriched material and co-produced impurities, justify the need to perform mass separation to collect the radionuclide of medical interest with the highest purity and specific activity. The decontamination, opening and transfer into the tantalum oven was performed at CERN-MEDICIS, with a dedicated automatic transfer system developed in 2019 to reduce the dose received by the operator and avoid any risk of contamination.

OPERATION IN 2018 AND 2019

Prior to a collection the target unit is coupled to the MEDICIS target station. The target is heated to very high temperatures, typically above 2000 °C, to allow for the diffusion and effusion of the radionuclides of interest out of the target to an ion source for subsequent ionization. The ions are then accelerated and sent through a mass separator. The MEDICIS target station includes a coupling flange held at a potential usually ranging from 30 kV to 60 kV and a grounded extraction electrode, placed after an acceleration gap ranging from 50 to 100 mm from the ion source exit. An Einzel lens is used to shape the ion beam downstream of the extraction electrode. More information regarding the MEDICIS beam line can be found in Ref. [23]. In addition, the MELISSA (MEDICIS Laser Ion Source for Separator Assembly) laser laboratory [27, 28], in service since April 2019, helps to increase the separation efficiency

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and the selectivity. The radioisotopes are extracted in the form of Radioactive Ion Beams (RIB) and implanted into one-sided zinc-coated gold foils (0.5 mm thick). Once the implantation is completed the samples are retrieved from the collection chamber using a shielded trolley. This trolley can be directly connected to a shielded fume hood, under which the samples are retrieved and conditioned to be measured by γ-spectrometry, for subsequent transport to the partner institutes or for further radiochemistry manipulation.

Operation with CERN Proton Beam in 2018

In 2018, the first year of operation after the facility's commissioning, the targets consisted mostly of 20 mm diameter tantalum rolls as used at ISOLDE, while the nominal 50 mm targets were under development. In total the MEDICIS program exploited 1.8E19 of the delivered protons, which represents 33% of the protons sent to the HRS target station. An additional 6.0E18 protons were sent to MEDICIS by deflecting the proton beam below the ISOLDE target while the latter was setting up for physics runs. This so-called direct irradiation mode increased the production rate considerably in the 20 mm diameter MEDICIS targets. Five radionuclides of medical interest were collected in 2018: Er-169 as feasibility tests, Tb-149, Tb-152, Tb-155 and Tm-165 as a generator of the Er-165 Auger emitter, with activities from 1 to 137 MBq and separation efficiency ε up to 1.6% (see Table 2). Four radioisotope batches were shipped: two were delivered to the University Hospital in Lausanne (CHUV, CH) and two others to the National Physical Laboratory (NPL, UK) [11]. MEDICIS has successfully collected and shipped Tb-149 within less than 7 hours after the end of irradiation. That year the facility provided 235 MBq (End of Collection) suitable for medical applications out of a total of 1.7 GBq, including tests and isobaric molecular activities. The facility was operated with a total of 12 target units, including prototypes, some being reused up to four times, thereby reducing operational costs and generated radioactive waste. Including machine development runs, the total radioisotope collection time amounted to about 220 hours.

Operation with External Sources in 2019

In 2019 during LS2, ILL and ARRONAX provided CERN-MEDICIS with external sources. Three radionuclides of medical interest were collected after mass separation: Tb-155, Er-169 and Yb-175 (see Table 2). Four research institutes received activity, including NPL (UK), KU Leuven/SCK CEN (BE), Hopitaux Universitaires de Genève (HUG) and the Paul Scherrer Institute (PSI) in Switzerland. The latter could perform first preclinical tests with high specific activity Yb-175. Fifteen collections were performed for a total of 870 MBq and with separation efficiency of up to 6%, exploiting the Resonance Ionization Laser Ion Source (RILIS) laser ionization from MELISSA. It should be noted that using external irradiated material and in contrast to the mode of operation that involves irradiation with PS Booster protons, there is no activation of the target unit itself. Operation in 2019 was achieved with eight new target units, some of them re-used up to three times.

The selection of the target and the ion source, both critical elements for the optimisation of isotope separation, is under constant development. It is based on the combined expertise available from the ISOLDE facility and the ISOL community, as well as the specific experience gained from the batch mode offline separation performed at MEDICIS. To this end, radiochemistry is also included in the radioisotope delivery chain and will soon be available at CERN-MEDICIS.

Table 2: Overview of the collected radioisotopes (ε: separation efficiencies)

Radio-nuclide	Target	Ion Source	Collection (MBq)	ε (%)
Tb-149	^{nat}Ta	W/Re	8	-
Tb-152	^{nat}Ta	Re	1	-
Tb-155	^{nat}Gd/^{nat}Ta	W/Re/ MELISSA	71	1.2
Tm-165	^{nat}Ta	Re	137	1.6
Er-169	$^{168}Er_2O_3$	W/Re/ MELISSA	369	0.5
Yb-175	$^{174}Yb_2O_3$	W/Re/ MELISSA	519	6.0

CONCLUSION AND OUTLOOK

After a successful first commissioning phase in 2017, CERN-MEDICIS has shown its capability of delivering radionuclides with high specific activity to partner institutes of the MEDICIS collaboration. Radioisotopes of medical interest were collected using both, production with the proton beam delivered by the CERN PS Booster and using external sources. The latter mode of operation allows CERN-MEDICIS to be one of the few facilities operating during CERN's Long Shutdown 2. After a period of maintenance and upgrades at the end of 2019, the facility resumed operation in March 2020. CERN-MEDICIS will restart its program throughout LS2 to deliver mass-separated medical radionuclides using external irradiated material. Besides ARRONAX with gadolinium target irradiation for the collection of Tb-155, PSI will provide its first external sources to CERN-MEDICIS this summer to proceed with the mass-separation of the Auger emitter Tm-167. Sm-153 will be mass separated from enriched Sm-152 irradiated at the SCK CEN BR2 reactor. The Pakistan Atomic Research Reactor, which has recently joined the collaboration, will also provide external irradiated materials notably from neutron activation of enriched Pt-194 for the production of Pt-195m. In addition, studies will be performed for assessing the feasibility of separating Ac-227 from Ac-225, an alpha emitter of high interest for targeted alpha therapy. Extracting radionuclides with long half-lives from targets previously operated at ISOLDE before LS2 will finally be explored further. This already allowed ISOLDE to extend its physics program in 2018, and will continue providing parasitically-irradiated targets for offline studies at ISOLDE.

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Based on the experience and lessons learnt during its 1st year, MEDICIS will resume operation with protons in 2021 and continue providing its partner institutes with high specific activity radionuclides, some of them for the first time.

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