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EUROPEAN ORGANIZATION FOR NUCLEAR RESEARCH

Addendum 2 to the ISOLDE and Neutron Time-of-Flight Committee

IS528 **Novel diagnostic and therapeutic radionuclides for the development of innovative radiopharmaceuticals**

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Abstract

We propose the exploration of novel radionuclides with diagnostic or therapeutic properties from ISOLDE. Access to such unique isotopes will enable the fundamental research in radiopharmaceutical science towards superior treatment, e.g. in nuclear oncology. The systematic investigation of the biological response to the different characteristics of the decay radiation will be performed for a better understanding of therapeutic effects. The development of alternative diagnostic tools will be applied for the management and optimization of radionuclide therapy.
We request 20 shifts to pursue our work with the quadruplet of diagnostic and therapeutic Tb isotopes, in particular ^{149}Tb and ^{152}Tb. We request 12 shifts to collect ^{140}Nd and ^{134}Ce which serve as long-lived *in-vivo* PET generators. We request 3 shifts for exploratory studies with other novel radioisotopes.

Requested shifts (in total): 35, thereof 33 shifts newly requested

Motivation, experimental setup and technique

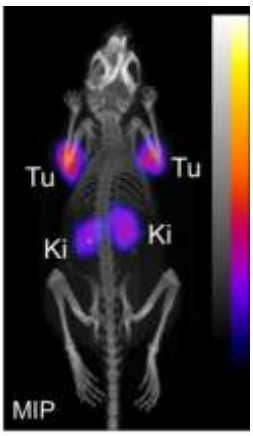
The enormous diversity of radioisotopes that are readily available at ISOLDE and the high quality of these mass-separated beams ("carrier-free", i.e. close to the ultimate specific activity) provide a unique toolkit for new applications in nuclear medicine and can overcome the bottleneck of radioisotope availability.
For general purpose applications the radioisotopes are collected at ISOLDE by implantation into a temporary matrix (e.g. Zn coated gold foils) or permanent matrix (e.g. mesoporous silicon), then shipped in shielded containers to the receiving laboratory. Upon arrival the temporary matrix is dissolved and the radionuclides are used either directly or after an additional radiochemical purification step for labeling of experimental radiopharmaceuticals. These serve for preclinical *in vitro* and *in vivo* studies.

Status report of experiments performed in 2014 and 2015

1) Production and Chemical Separation of Tb Radioisotopes

As in previous years, the Tb isotopes were produced by 1.4 GeV proton induced spallation of Ta foil targets. The 2014 target with higher tantalum mass gave record yields for ^{155}Dy/^{155}Tb, but the ^{149}Tb collections were plagued by several mishaps: malfunction of control system and stepping motor controller, sudden drop of target or line heating, etc. Therefore only a small part of the planned preclinical program using ^{149}Tb could be performed in 2014.
In 2015 a target with mixed 6 μm/25 μm foils was used. The RILIS dye lasers were not operational, instead a new Dy ionization scheme based on Ti-Sa lasers was tried. This scheme proofed to be very efficient and the laser ionization was very stable over the whole beam time. The combination of this target and the new Dy ionization scheme provided the best yields for ^{149}Dy/^{149}Tb so far.
The ISOLTRAP MR-TOF-MS was extremely useful in determining on-line the isobaric beam composition and understanding the optimum tune of target and line temperatures to maximize the ratio of Dy+Tb versus molecular oxide sidebands that dominate the overall dose rate.
Parallel collections of ^{149}Tb and ^{155}Tb were performed in GLM and GHM, but ^{149}Tb and ^{152}Tb could not be collected in parallel and had to be collected consecutively. Instead the beam-line occupation was optimized for parallel collections of ^{134}Ce, ^{140}Nd, ^{169}Yb as well as samples for nuclear solid state physics experiments.
In 2015 repeatedly excellent ^{149}Tb yields were achieved. With 1.5 hours of collection and 2 hours decay of co-implanted activities, up to 200 MBq ^{149}Tb could be transported to PSI. Collections of ^{152}Tb lasted 4 to 6 hours and up to 2 GBq ^{152}Tb could be shipped to PSI. The Tb radionuclides were extracted from the Zn foils by dissolving them in HNO_3/NH_4NO_3, loaded on to a macroporous strongly acidic cation exchange resin and the Tb radionuclides eluted using dilute α-hydroxyisobutyric acid (α-HIBA). The product eluent was used directly for the radiolabeling process. The separation of ^{152}Tb yielded activities of up to ~500 MBq, while ^{149}Tb separations yielded 100 MBq of highly pure (~99%) ^{149}Tb in α-HIBA solution.

2) Preclinical Studies with ^{152}Tb-DOTANOC at PSI



The aim of this study, was to estimate the potential of ^{152}Tb ($T_{1/2}$=17.5 h) for PET imaging using DOTANOC in mice with somatostatin receptor-positive tumor xenografts. ^{152}Tb-labeling of DOTANOC was performed directly in α-HIBA, which was used as an eluent of chromatography separation. ^{152}Tb-DOTANOC at a specific activity of 10 MBq/nmol and more than 95% radiochemical purity was obtained. PET/CT scans were performed at different time points after injection of mice with different activities of ^{152}Tb-DOTANOC using a Genisys8 benchtop camera. The resulting PET/CT images allowed excellent visualization of tumor xenografts (marked as "Tu" in the figure) for up to 32 h. This study confirmed the exceptional value of the β^+-emitting radiolanthanide, ^{152}Tb, for PET imaging, potentially allowing dosimetry before therapy with β^--emitting radiolanthanides, such as ^{177}Lu and ^{161}Tb and for non-invasive monitoring of therapy response.

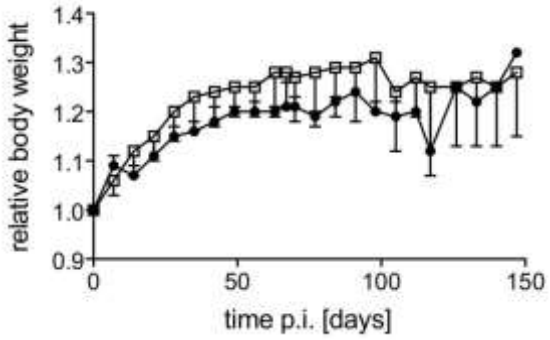
3) ^{149}Tb-DOTANOC for alpha-PET at PSI

Previously, we performed proof-of-concept studies using ^{149}Tb-folate for α-therapy of tumor-bearing mice (*Müller et al. 2014, Pharmaceuticals 7:353*). In another study, which took place in 2015, we focused on the

potentially unique characteristic of ^{149}Tb to be used for PET imaging due to its 7% positron branch, in addition to its usefulness for α-therapy. ^{149}Tb-DOTANOC was obtained with more than 98% radiochemical purity at 5 MBq/nmol specific activity which was never achieved before. A nude mouse bearing tumor xenografts was intravenously injected with about 7 MBq ^{149}Tb-DOTANOC. PET/CT scans were performed 2 h later using a preclinical Genisys8 bench-top camera. The quality of the obtained PET images was impressively high.

4) Preclinical Study with ^{149}Tb-Folate at PSI

As mentioned above, a preclinical proof-of-concept therapy study was previously performed with ^{149}Tb-folate in KB tumor-bearing mice (*Müller et al. 2014, Pharmaceuticals 7:353*). The results were very promising, as the tumor growth was significantly delayed in treated mice as compared to untreated control mice. In the study which was started in August 2015, the aim was to investigate potential damage to the kidneys after application of therapeutic doses of ^{149}Tb-folate. 6 female nude mice (without tumors) were injected with 5 MBq ^{149}Tb-folate and 3 additional mice received only α-HIBA as controls. Mice have been monitored by measuring the body weight and, with regard to potential damage to the kidneys, by determination of blood plasma parameters indicative for kidney function (blood urea nitrogen and creatinine) and by the performance of quantitative SPECT using ^{99m}Tc-DMSA, as previously reported for investigations with ^{177}Lu-folate (*Haller et al. 2015 Nucl Med Biol 42:770*). Mice were euthanized sequentially (2 treated and 1 control mouse) after 2 and 4 months. The last 3 mice are still alive and will be euthanized 6 months after therapy start. The tissue of the euthanized mice was harvested for histopathological investigations of the renal tissue and other potentially involved tissues (e.g. bone marrow). As the study is still on-going, the data has yet to be fully analysed. The graph shows the relative body weight of mice treated with ^{149}Tb-folate □ and mice which received only α-HIBA solution ●.



Submitted Publications and Abstracts to upcoming Conferences:

C. Müller, Ch. Vermeulen, K. Johnston, U. Köster, A. Türler, R. Schibli, N.P. van der Meulen: "Application of ^{152}Tb-DOTANOC in tumor-bearing mice: a radiolanthanide for PET imaging"; subm. to Eur J Nucl Med Mol Imaging Res.

C. Müller, Ch. Vermeulen, K. Johnston, U. Köster, A. Türler, R. Schibli, N.P. van der Meulen: "Alpha-PET with Terbium-149: Evidence and Perspectives for RadioTheragnostics"; subm. to Eur J Nucl Med Mol Imaging Radiopharm Chem.

N.P. van der Meulen, Ch. Vermeulen, U. Köster, K. Johnston, S. Haller, R. Schibli, A. Türler, C. Müller: "The use of ^{149}Tb and ^{152}Tb in preclinical investigations: an update on its mass separation and subsequent application for imaging and therapy" accepted for oral presentation at the ICTR-PHE 2016 Conference, Geneva, Switzerland

N.P. van der Meulen, Ch. Vermeulen, U. Köster, K. Johnston, R. Schibli, A. Türler, C. Müller: "The use of ^{152}Tb in preclinical investigations: its mass separation and subsequent application for imaging" abstract submitted for presentation at the EMIM 2016 Conference, Utrecht, The Netherlands

The preclinical pilot studies, which were performed in the past five years, generated considerable interest in terbium radionuclides for radiopharmaceutical and medical applications. The performance of more detailed studies and in-depth investigations of the therapeutic effects of ^{149}Tb using different targeting agents and tumor types is, thus, very important. One of the primary aims of MEDICIS is to produce radiolanthanides, including ^{149,152,155}Tb, for preclinical studies. Until Tb radioisotopes become routinely available from MEDICIS we want to continue our work with on-line collections at ISOLDE.

5) Preclinical study with ^{140}Nd and labeling studies with ^{134}Ce at Hevesy Lab, Risø

The purpose of this study was to assess the value of ^{140}Nd/^{140}Pr and ^{134}Ce/^{134}La as in vivo PET generators through kinetic evaluation of the pairs with somatostatin analogues in the neuroendocrine tumor-based somatostatin receptor 2 (sst2) system. By employing a known sst2 internalizing vector, DOTATATE, and a

known non-internalizing vector, DOTALM3, we attempted to determine in vivo diffusion kinetics of a freed positron-emitting daughter $^{140}Pr^{3+}$ in tumor-bearing mice.
In total 950 MBq of ^{140}Nd and 140 MBq of ^{134}Ce were collected at ISOLDE and shipped to Hevesy Lab. ^{140}Nd reactions with DOTATATE and DOTALM3 were efficient at 5 MBq/nmol (2 mice each). ^{134}Ce labeling was inefficient, and could only be achieved with receptor-saturating levels of the vectors, thereby precluding their use in vivo. The ^{140}Nd labeled vectors were i.v. injected into dual-flank H727 xenograft bearing mice (8 for each tracer). PET scans were taken at 1, 3, and 16 hours post injection. Following the last image, the animals were euthanized, and then imaged intact at 30 min post-mortem. The differences between the 16 h PET scan and the post-mortem scan were used to study the diffusion behavior of $^{140}Pr^{3+}$ following the parent ^{140}Nd EC decay. Three additional mice were scanned under the same protocol after injection of $^{140}Nd^{3+}$ in HEPES-buffered isotonic saline to investigate the free ion distributions in the tumor model.
The in vivo scans showed only a small difference in the tumor PET signal between pre- and post-mortem scans, with a slight increase in tumor signal post-mortem when DOTALM3 was used. Non-targeted organs, however, showed interesting source and sink behaviors illuminating some properties of the renal and hepatic interaction with neodymium and praseodymium.
Based upon the results of this study we conclude that ^{140}Nd imaging in preclinical models might be possible without designing an electron-capture-dislocation resistant chelate. In such cases, the imaging protocol established here is a useful test to determine how ^{140}Nd PET is altered by diffusion. Further, with careful experimental design it may be possible to exploit the diffusion effects to observe biological phenomena such as vector internalization.

6) In vitro experiments on mesoporous silicon in Helsinki

Mesoporous silicon (PSi) exhibits a number of properties that make it an attractive material in cancer therapy. PSi is a biocompatible and biodegradable material. In vivo, it dissolves mainly into silicic acid, which is a natural and non-toxic form of Si. The electrochemical synthesis of PSi enables production of PSi particles with an ordered pore network, tunable pore sizes and high pore volume, allowing fine control of drug load and release (J. Salonen and V.P. Lehto, *Chem Eng J* 2008, *137*, 162). The great advantage of PSi particles is their high drug loading capacity, which would allow delivery of high amounts of the drug in the target tissue without using impractically high amounts of the carrier. ^{32}P BioSilicon, which is comprised of nanoporous 20 μm polysilicon powder containing ^{32}P as a therapeutic radionuclide, is currently in clinical trials (Phase III) as brachytherapy agent for treating pancreatic cancer (K. Zhang et al. *Clin Cancer Res*, 2005, *11*, 7532).
In our previous work the PSi nanoparticles were labelled with ^{18}F using chemical methods (M. Sarparanta et al., *Mol Pharm* 2011, *8*, 1799). ^{18}F serves for tracing the particles *in vivo* and not for therapy. Here the radioactive label was covalently bound onto the surface of the particles. In vivo the PSi nanoparticles gradually dissolve, and the traceability of the particles is limited to the time the outer layers are staying intact. When considering therapeutic applications of PSi, the radioisotope should stay inside the particles as long as the isotope has decayed to its stable daughters. Premature release of the therapeutic radioisotope may cause accumulation of the isotope into non-target organs, which may lead to adverse side-effects. In our present approach, instead of chemical labelling, we use physical methods to get the radioactive label deep inside the silicon lattice, which makes it possible to avoid premature release of the radionuclide when administrated *in vivo*. This is realised by implanting radioactive metal ions directly into surface stabilized PSi wafers, which is then followed by processing the implanted, porous surface of the wafer into nanosized particles (100–200 nm) by pulse-etching. A suitable tracer nuclide will have long enough half-life (days to tens of days) and desired radiation properties (low-energy γ-rays for SPECT or β^+ emission for PET, with electron, Auger or α emission for therapy applications). The resulting radioactive nanoparticles are further modified with tumour targeting moieties and loaded with anti-cancer drugs, enabling tumour specific chemoradiotherapy of cancer. By selecting therapeutic radionuclides which are applicable for nuclear imaging, trafficking of the administrated chemoradiotherapy nanovectors is followed by non-invasive imaging and the chemotherapy is completed with radiation therapy.
So far we have concentrated our study in the dissolution properties of implanted PSi particles with different surface treatments at different physiologically relevant buffers. We profited of a short test implantation at ISOLDE in summer 2015 with two samples (pieces from fresh and oxidized PSi wafer) at mass 169 which

provided the longer-lived radiotracers ^{169}Yb and as molecular sideband ^{153}Gd. This turned out to be a successful proof-of-concept run: the activity was high enough for our tests, the wafers could be processed to particles and nearly a two-week dissolution study was run. PSi particles were divided to buffer solutions with three different pHs and the solutions were incubated at 37°C for 12 days. Samples of solutions were taken every second day and the activity dissolved in the buffer solution was measured. We could see the fresh and oxidized particles dissolving similarly at low pH values (< 7), but oxidized being somewhat more resistant at pH 7.41. These results should be validated and complemented by additional studies under different conditions.

Work plan for 2016 and 2017

A) Detailed studies with ^{152}Tb-based PET imaging

All of the studies mentioned above were performed with a limited number of test animals. Proper statistical analysis of the data was therefore not possible and publishing in high impact journals is difficult. Reviewers' comments to our article reporting on ^{152}Tb-based PET imaging were critical in this regard. They specifically requested more detailed investigations and more data that would also include stability experiments of ^{152}Tb-DOTANOC, testing radiolysis, biodistribution studies in tumor-bearing mice, as well as dynamic and quantitative PET. In order to be able to provide more data, it will be necessary to obtain several additional deliveries of ^{152}Tb.

B) Imaging studies with ^{149}Tb

The study, in which the possibility of PET imaging with ^{149}Tb was investigated, revealed exceptionally interesting characteristics of this radionuclide. It can be used not only for therapeutic purposes, but it offers the possibility to be used for nuclear imaging via PET, as shown by the first ever performed PET image of a tumor-bearing mouse using ^{149}Tb. In a subsequent study we would like to investigate ^{149}Tb further in this regard, but also with regard to the potential to use the radionuclide for SPECT. For this purpose, the facilities at PSI are unique as they allow the performance of animal studies and imaging with preclinical PET/CT and SPECT/CT scanners available at the same place.

C) Understanding radiotoxicity of alpha emitters

One of the main focuses of our research is to investigate renal toxicity after radionuclide therapy, since kidneys are particularly sensitive to radiation and commonly exposed to relatively high doses of radioactivity as a consequence of renal excretion of small-molecular-weight radiopharmaceuticals. In an attempt to investigate different radiation profiles, we recently investigated undesired side effects of ^{177}Lu-folate to the kidneys and compared them with those of ^{161}Tb-folate (*Haller et al. manuscript submitted to EJNMMI Research, Dec 2015*). ^{161}Tb and ^{149}Tb offer a unique opportunity to compare side effects after α- and β-radionuclide therapy using chemically identical radiopharmaceuticals. The study started in 2015, which is reported above, was initiated to obtain a first idea after which renal damage would become manifest. To allow a proper comparison that may reveal even minor differences in the damage pattern after the different treatments, more thorough investigations with a larger number of animals will be necessary. Such additional studies may allow drawing conclusions about the toxicity of α-therapy to the renal tissue in comparison to β-therapy. This would be unique as a comparison was only possible between application of different radionuclides and, thus, radiopharmaceuticals with different pharmacokinetic profiles.

D) PSMA-targeted therapy with ^{149}Tb

PSMA-targeted radionuclide therapy is one of the hot topics of nuclear medicine as it could provide new efficient ways to treat progressed prostate cancer. We are interested in PSMA-targeted therapy using Tb radionuclides, more specifically in the comparison of α- and β-radionuclide therapy using PSMA-targeted small molecules. PSMA-targeted compounds, such as PSMA617, are currently being used in clinical trials with ^{177}Lu. ^{149}Tb appears to be an excellent option for PSMA-targeted α-therapy, since the relatively short half-life of ^{149}Tb suits well with the short biological half-life of PSMA617. The effects of α- and β-emitters should be investigated in vitro using cell assays to determine double-strand breaks of DNA and other markers indicating damage of the tumor cells. At a later stage, therapies will be performed in vivo using

tumor-bearing mice. Tumor tissue samples will be investigated by immunohistochemistry using specific markers to characterize the profile of tumor cell damage in vivo.

Work packages A) and C) are really a major step in quality, from previously performed "proof-of-concept studies" (corresponding to "discovery experiments" in nuclear physics) to systematic studies (corresponding to e.g. precision measurements of lifetimes or branching ratios in nuclear physics). Consequently the number of animals injected has to be increased by about an order of magnitude and correspondingly more activity is required.
All work packages using Tb isotopes have in common that they require substantial activities of ^{149}Tb or ^{152}Tb respectively. A limited activity per batch not only reduces the number of injected mice more than pro rata (given that a minimum amount is set aside for specification and quality control), but frequently the effective specific activity (similar to a signal to background ratio in nuclear physics) is insufficient for quantitative labelling and consequently none of the activity can be used.
While the chemical separations proved to be very effective in 2015, it is the aim to further optimize the separation system, with improved logistics envisaged to produce a higher yield of product for preclinical purposes. For future the plan is to perform the chemical separation of the radionuclides from the dose-dominating oxide sidebands at CERN, allowing shipment of higher quantities of the desired radionuclide to PSI for preclinical investigations.

E) ^{140}Nd and ^{134}Ce for internalization and diffusion studies

For future tests ^{134}Ce is the highest priority because the 6 minute ^{134}La daughter widens the sensitivity window for diffusion times out of the tumors. In order to reach sufficient specific activity with ^{134}Ce labeling we need more activity from ISOLDE. Compared to production of ^{140}Nd and its precursors, the production of ^{134}Ce requires evaporation of six nucleons more in the spallation of ^{181}Ta. Consequently the production cross-sections drop significantly. We request use of the RILIS to ionize the precursor ^{134}Nd or ^{134}Pr since both together dominate the cumulative ^{134}Ce yield. Moreover, we will oxidize and then solvent extract Ce(IV) from the dissolved Zn matrix to improve its effective specific activity.
Additionally, we would like to continue with ^{140}Nd in two more models. One will be a highly perfused tumor model i.e. not a flank xenograft, but a semi-spontaneous lung metastases model. This will be targeted by an antibody, which will take advantage of the longer half-life of the parent and will provide a different kinetic model for the tracer distribution. The other will be a newly developed monoclonal antibodies for the diagnosis of life-threatening Aspergillus fumigatus (EU-FP7 MATHIAS project).
Ultimately, we hope to be able to use this technique to show the internalization status of targeted drug delivery vehicles. In cases of targeted Auger emitting radionuclides, or targeted lysosomal-degraded nanoparticles, the internalization status will have a large impact on the therapeutic effect.

F) In vitro and in vivo studies with mesoporous silicon

For continuing the development of radioactive metal implanted PSi particles we would need still 6 – 10 samples implanted with few MBq of activity. Besides ^{169}Yb also other radiotracers can be used that have long enough half-lives for transportation to Helsinki and suitable radiation properties, e.g. ^{155}Tb, ^{159}Dy, etc. After the particle processing has been tuned and the behavior of the implanted PSi particles is acceptable, we will need batches of activity for *in vivo* animal experiments, having activities in the range of tens of MBq.
Given that this application is not restricted to one specific radionuclide, the radionuclide will be selected so that collections can be performed in parallel (GLM or GHM respectively) with the planned collections of ^{149}Tb or ^{152}Tb respectively. Therefore no additional shifts are counted for this purpose.

For the same reason the required amounts of few MBq ^{155}Tb for the LOI submitted by T.E. Cocolios can be easily collected in parallel.

G) Exploratory studies with other promising radioisotopes

In addition to the radioisotopes discussed so far, there are other innovative radioisotopes with promising properties for imaging, as element-specific radiotracers or for targeted therapy. For a validation of the suitability of these radioisotopes initially basic studies are needed, namely phantom imaging studies and

image reconstruction optimization, radiochemical trials and *in-vitro* experiments. We intend to collect samples of ^{71,72,74}As, ^{73}Se, ^{84}Rb, ^{117m}Sn, ^{200,203}Pb, $^{203-206}$Bi, ^{211}At and ^{211}Rn allowing to perform initial tests. We ask for 3 shifts to perform these collections "opportunistically", i.e. to be scheduled when another experiment demands the respective target/ion source combination. In 2014/15 there was no suitable opportunity, therefore we reiterate our request to profit of test opportunities in the upcoming schedule.
We have explicitly added ^{211}At and ^{211}Rn (as generator isotope for ^{211}At) to this list, to determine their yields and purity achievable by 1.4 GeV proton induced spallation production and state of the art selective ion sources. ^{211}At is a promising therapeutic alpha emitter and one of the isotopes of interest in the TecHIBA-RITMI work package of ENSAR2. Following these yield measurements a separate proposal will be submitted on further use of these isotopes.

Off-line separation of ^{169}Er

The previously proposed (Point E in Addendum INTC-P-312-ADD-1) in vivo therapy study using off-line mass-separated ^{169}Er was not yet performed. As an off-line experiment it can be performed at MEDICIS once a RILIS scheme for Er has been validated. Therefore we did not reiterate our beam request for these 6 off-line shifts.

<u>Requested</u> shifts (including available shifts):

(i) Envisaged measurements and requested isotopes
A**)** 8 shifts for collection of 152Tb
B-D) 12 shifts for collection of 149Tb
E) 12 shifts for parallel collection of 134Ce and 140Nd
F) performed in parallel to A)-D)
G) 3 shifts for exploratory studies with other promising radioisotopes

(ii) Have these studies been performed in the meantime by another group? No.

(iii) Number of shifts (based on newest yields) required for each isotope
The given yields were observed in the last beam time, averaged over several hours of collection.

Isotope	Cumulative yield (/uC)	target – ion source	Shifts (8h)
149Tb	6E8	Ta foil + W surface ionizer and Dy RILIS	12
152Tb	1E10	Ta foil + W surface ionizer and Dy RILIS	8
140Nd	2E8	Ta foil + W surface ionizer	12
134Ce	≈2E8 (expected with RILIS)	Ta foil+W surface ionizer and Nd or Pr RILIS	
71,72,74As 73Se		ZrO2 or Y2O3 + VD5	3
84Rb		UCx+surface ionizer; Nb+surface ionizer; etc.	
117mSn		UCx + Sn RILIS	
200,203Pb 203-206Bi 211At		UCx or ThCx + Pb RILIS UCx or ThCx + Bi RILIS UCx or ThCx with At RILIS	
211Rn		UCx or ThCx + VD7	

Total shifts: 35
Remaining: 2
New request: 33

Appendix

DESCRIPTION OF THE PROPOSED EXPERIMENT

The experimental setup comprises: collection chambers at GLM and GHM

Part of the Choose an item.	Availability	Design and manufacturing
SSP-GLM chamber and SSP-GHM chamber	☒ Existing	☒ To be used without any modification

HAZARDS GENERATED BY THE EXPERIMENT

Hazards named in the document relevant for the fixed installation SSP-GLM chamber and SSP-GHM chamber.

Additional hazards:

Hazards	*[Part 1 of the experiment/equipment]*	*[Part 2 of the experiment/equipment]*	*[Part 3 of the experiment/equipment]*
Thermodynamic and fluidic			
Pressure	[pressure][Bar], [volume][l]		
Vacuum	About 1E-5 mbar in collection chambers		
Temperature	Room temperature [K]		
Heat transfer			
Thermal properties of materials			
Cryogenic fluid	[fluid], [pressure][Bar], [volume][l]		
Electrical and electromagnetic			
Electricity	[voltage] [V], [current][A]		
Static electricity			
Magnetic field	[magnetic field] [T]		
Batteries	☐		
Capacitors	☐		
Ionizing radiation			
Target material	Zn coated Au foil		
Beam particle type (e, p, ions, etc)	Ions		
Beam intensity	<few 1E10 per s		
Beam energy	30-60 keV		
Cooling liquids	[liquid]		
Gases	[gas]		
Calibration sources:	☐		
• Open source	☐		
• Sealed source	☐ [ISO standard]		
• Isotope			
• Activity			
Use of activated material:			
• Description	☐Shipping		
• Dose rate on contact and in 10 cm distance	<10[mSv/h] at contact of container		
• Isotope and activity	200 MBq 149Tb plus 133Ce, 133mCe, 133La		

	2 GBq 152Dy/152Tb 300 MBq 134Ce 300 MBq 140Nd Other isotopes are for test purposes and have lower activity and dose rate.		
Non-ionizing radiation			
Laser			
UV light			
Microwaves (300MHz-30 GHz)			
Radiofrequency (1-300MHz)			
Chemical			
Toxic	[chemical agent], [quantity]		
Harmful	[chemical agent], [quantity]		
CMR (carcinogens, mutagens and substances toxic to reproduction)	[chemical agent], [quantity]		
Corrosive	[chemical agent], [quantity]		
Irritant	[chemical agent], [quantity]		
Flammable	[chemical agent], [quantity]		
Oxidizing	[chemical agent], [quantity]		
Explosiveness	[chemical agent], [quantity]		
Asphyxiant	[chemical agent], [quantity]		
Dangerous for the environment	[chemical agent], [quantity]		
Mechanical			
Physical impact or mechanical energy (moving parts)	[location]		
Mechanical properties (Sharp, rough, slippery)	[location]		
Vibration	[location]		
Vehicles and Means of Transport	[location]		
Noise			
Frequency	[frequency],[Hz]		
Intensity			
Physical			
Confined spaces	[location]		
High workplaces	[location]		
Access to high workplaces	[location]		
Obstructions in passageways	[location]		
Manual handling	[location]		
Poor ergonomics	[location]		

0.1 Hazard identification

The dominant hazard is the ionizing radiation of the collected isotopes. They will be packed into Posisafe transport containers which are certified “type A” transport containers with 3cm tungsten shielding. Packing, labelling of the shipping containers and supervision of shipping is performed by CERN HSE-RP.

3.2 Average electrical power requirements (excluding fixed ISOLDE-installation mentioned above): *(make a rough estimate of the total power consumption of the additional equipment used in the experiment)*

No additional equipment besides fixed installations.