EUROPEAN ORGANIZATION FOR NUCLEAR RESEARCH

Letter of Intent to the ISOLDE and Neutron Time-of-Flight Committee

Radium and Francium beam tests to produce ^{225}Ac/ ^{213}Bi generators at CERN-MEDICIS

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Abstract

In this Letter of Intent, we propose to test ^{225}Fr/Ra beam intensities achieved with UCx and ThCx targets and surface ion sources at Isolde, as possible isotope sources to build generators of ^{225}Ac/^{213}Bi for targeted alpha therapy trials within the forthcoming CERN-MEDICIS facility. The present LoI brings together a long-standing expertise in the manufacturing of ^{225}Ac/^{213}Bi generators at JRC-ITU and the capabilities of producing intense beams of ^{225}Fr/Ra at CERN, with 1.4GeV proton from PSB and thick uranium and thorium refractory targets.

Diagnosis and treatment with radioisotopes has been a common practice in medicine for more than a century. Imaging protocoles using the PET emitter ^{18}F with the glucose analog FDG are now routinely performed in a wide range of prescriptions across a network of large hospitals and clinics. This field of medicine is today experiencing important developments, with for instance the marketing of alpha-emitting radiopharmaceuticals, Xofigo® based on $^{223}RaCl_2$ salt for hormone resistant prostate cancers with bone metastasis [1]. With the progress of imaging techniques such as micro-PET/SPECT CT suitable to scan small animals, the development of new radiopharmaceuticals passes through the test of new compounds on animal models before undertaking clinical trials to test the efficacy, toxicity, side effects and precise prescription dose of the candidate drug on patients.

In the field of systemic radiotherapy, both the identification of a biological receptor or target in the tissue, the synthesis of suitable compounds and the synthesis and purification of a suitable radioisotope is required for a successful marketing of radiopharmaceuticals with diagnosis and treatment potential. Emerging radioisotopes, such as low range beta emitters like ^{177}Lu, alpha emitters like ^{149}Tb and Auger emitters such as ^{117m}Sn have the potential to provide curing capabilities for difficult medical applications that up to now did not find suitable solutions, from chemotherapy, surgical resection, external radiotherapy, and targeted radiotherapy.

CERN-MEDICIS is a new facility under construction which will build upon the expertise gained for over fifty years to produce radioactive beams at ISOLDE, where more than 1000 radioisotope beams from 73 different chemical elements are available today [2,3]. In particular, a wide range of alpha emitting radioisotopes can be produced from actinide targets such as ThO_2, ThC_x or UC_x, or from Tantalum foils [3]. Biomedical activities based on the isotopes produced at ISOLDE were reported in the 1990's when Beyer et al., investigated the influence of EDTMP (EthyleneDihamineTetraMethylenePhosphonic acid) chelator concentration on bio-distribution of simultaneously injected different radio-lanthanides and ^{225}Ac in mice bearing carcinoma tumor [4]. Sources of ^{225}Ac were again collected at Isolde from a thick ThC_x target in 2001 during 5 days, leading to 2.10^{15} atoms collected from a combined beam of ^{225}Ra/Fr, decaying into ^{225}Ac [5].

The group at JRC-ITU has developed expertise in the production of ^{225}Ac, e.g. extraction of ^{225}Ac from ^{229}Th sources or via ^{226}Ra(p,n)^{225}Ac cyclotron irradiation. The group has created ^{225}Ac-^{213}Bi-generators that can be used for tests on cell lines at ITU and be dispatched to hospitals for preclinical and clinical trials [6-8].

Up to now clinical trials treating glioblastoma, hormone resistant prostate cancer with metastasis, neuroendocrine tumors (GEP_NET) resistant to chemo- or radiation therapy have been performed with promising outcomes. Tumor-depending doses up to several GBq of ^{213}Bi are used in the protocols with clear results of longer survival rates with no short term toxicity. The study of long term toxicity is ongoing [9]. A clear advantage of the mass-separated ^{225}Ac source over other methods of production is the purity of the final sample, for instance with the suppression of the ^{227}Ac fraction.

In this letter, we ask to monitor the rate of ^{225}Ra/Fr production from the different UCx, ThO_2 or ThCx target units that are operated throughout the year at ISOLDE. This can be done with little or no impact on the approved physics program since this can be done by Faraday cup measurements; this can be completed with tape station measurements, for instance when the target unit is set-up or at the end of the physics run. Different conditions and typical variability can thus be documented, which will become extremely valuable data collected for the future CERN-MEDICIS offline mass-separation.

References:

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Appendix

DESCRIPTION OF THE PROPOSED EXPERIMENT

The experimental setup comprises: *(name the fixed-ISOLDE installations, as well as flexible elements of the experiment)*

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

HAZARDS GENERATED BY THE EXPERIMENT

(if using fixed installation) Hazards named in the document relevant for the fixed [COLLAPS, CRIS, ISOLTRAP, MINIBALL + only CD, MINIBALL + T-REX, NICOLE, SSP-GLM chamber, SSP-GHM chamber, or WITCH] installation.

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			
Temperature	[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	Ta		
Beam particle type (e, p, ions, etc)	225Ra, 225Fr		
Beam intensity	1e8pps		
Beam energy	30kV		
Cooling liquids			
Gases			
Calibration sources:	☐		
• Open source	☐		
• Sealed source	☐ [ISO standard]		
• Isotope			
• Activity			
Use of activated material:			

• Description	☐		
• Dose rate on contact and in 10 cm distance			
• Isotope			
• Activity			
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

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)*