EUROPEAN ORGANIZATION FOR NUCLEAR RESEARCH

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

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

11 October 2018

Anu Airaksinen[9], Martina Benesova[1], Thomas Cocolios[10], David Cullen[13], Gilles de France[8], Andrew Fenwick[11], Kelly Ferreira[11], Hanna Frånberg[8], Catherine Ghezzi[2], Nadezda Gracheva[1], Ferid Haddad[3], Roger Hasler[1], Kerttuli Helariutta[9], Peter Ivanov[11], Ulrika Jakobsson[9], Mikael Jensen[4], Steven Judge[11], Christian Kesenheimer[6], Ulli Köster[5], Gilles Montavon[3], Cristina Müller[1], Andrew Pearce[11], Bernd Pichler[6], Jean-Pierre Pouget[7], Andrew Robinson[11], Anna-Maria Rolle[6], Gregory Severin[4], Jill Tipping[12], Christoph Umbricht[1], Stefan Wiehr[6], Nicholas van der Meulen[1]

[1] Paul Scherrer Institut, Villigen, Switzerland
[2] CHU – INSERM – Université Grenoble, France
[3] ARRONAX – INSERM – CRCNA – Subatech Nantes, France
[4] Risø National Laboratory, Roskilde, Denmark
[5] Institut Laue-Langevin, Grenoble, France
[6] Universitätsklinik Tübingen, Germany
[7] Institut de Recherche en Cancérologie de Montpellier, France
[8] GANIL, Caen, France
[9] University of Helsinki, Department of Chemistry, Finland
[10] KU Leuven, Belgium
[11] National Physical Laboratory, Teddington, United Kingdom
[12] Christie Medical Physics and Engineering, The Christie NHS Foundation Trust, Manchester, United Kingdom
[13] School of Physics & Astronomy, The University of Manchester, Manchester, United Kingdom

Spokesperson: Ulli Köster (koester@ill.eu)
Local contact: Karl Johnston (karl.johnston@cern.ch)

CERN-INTC-2018-030 / INTC-SR-059
12/10/2018

Abstract

The concept of the collection of novel radionuclides for use in nuclear medicine, with diagnostic or therapeutic properties, from ISOLDE was explored. Access to such unique isotopes has enabled fundamental research in radiopharmaceutical sciences towards proposed superior cancer diagnosis and treatment. The systematic investigation of the biological response to the different characteristics of the decay radiation has been performed towards better understanding of potential therapeutic effects. The development of alternative diagnostic tools has been investigated for the management and optimization of radionuclide therapy.
Work was performed with the neutron-deficient isotopes of the quadruplet of diagnostic and therapeutic terbium isotopes, namely ^{149}Tb, ^{152}Tb and ^{155}Tb.

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 can provide a unique toolkit for new applications in nuclear medicine utilizing the ISOL concept. Initial results of these experiments (performed at ISOLDE) have been met with great interest and ISOL facilities have since been planned with this idea in mind.

For applications, the radioisotopes were 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 was dissolved and the radionuclides used either directly or following additional radiochemical purification. The purified product was labeled to ligands, which served for preclinical *in vitro* and *in vivo* studies.

Status report of experiments performed in 2017 and 2018

1) Production and Chemical Separation of Tb Radioisotopes

As previously reported, the Tb isotopes were produced by 1.4 GeV proton induced spallation of Ta foil targets and collected via their Dy precursors. The yield of the latter was significantly enhanced following the implementation of resonant laser ionization in 2016.

System updates were implemented at the ISOLDE collection chamber in 2017 and the campaign was utilized to test and demonstrate its efficiency and safety. The update ensured that only one radioisotope collection could be performed per shift. As a result, ^{152}Tb was chosen for collection towards the demonstration, due to its longer half-life and higher yields for collection. The chemical separation system was redesigned and built for use in a hot cell. Good yields were recorded in 2017. Two collections runs took place (due to logistical issues) and up to 500 MBq ^{152}Tb could be shipped to PSI over a single collection (in September 2017). Sputter deposited Zn coatings on Au foils were used for this collection (allowing the production of thinner and more reproducible Zn coatings). As in the May 2017 campaign, the beam was too well focused, resulting in the collection of a major fraction of the activity in the gold foil itself. The chemical separation method, as a result, was again adjusted, with the top layer of the gold foil being dissolved in *aqua regia*, before being diluted and loaded on to the cation exchange resin. The rinsing and elution of the product was performed as before. The product quality was suitable for labeling purposes.

A single campaign to produce ^{149}Tb took place in June 2018. Initially, collections were performed using 0.2 mm thick Zn foils and the chemical separations performed using an updated method. The results were erratic, with low yields being obtained due to the tardiness of the separation process and poor labeling capability of the product. Similar yields were obtained when switching to Zn-coated gold foils as before, however, the product could label to PSMA – albeit poorly. Usable product (and yields around 100 MBq) were finally produced when reverting to the previously-used chemical separation method (which consisted of a smaller column). Again, the beam was too focused, however, this did not prevent ^{149}Tb from being produced and subsequently labeled to PSMA-617 for use in preclinical studies.

2) ^{149}Tb-PSMA for therapy studies at PSI

In our previous study which took place in 2015, we demonstrated a potentially unique characteristic of ^{149}Tb to be used for “alpha-PET”, i.e. PET imaging due to its 7% positron branch, in addition to its usefulness for α-therapy. In 2018, ^{149}Tb-PSMA-617 was obtained with more than 98% radiochemical purity at up to 6 MBq/nmol specific activity. Groups of 6 mice bearing tumor PC-3 PIP xenografts were intravenously injected with ~6 MBq ^{149}Tb-PSMA-617 or 2 x 3 MBq ^{149}Tb-PSMA-617 at Day 1 and 2 or at Day 1 and 4, respectively. The mice were monitored over several weeks with regard to the tumor growth and body weight. The tumor growth delay was more pronounced in the groups that received 2 x 3 MBq than in mice that received the whole activity in just one injection. The median survival time was 26 days in the group that received 1 x 6 MBq, hence, significantly longer than in untreated control mice (median survival time 20 days). Mice which received 2 x 3 MBq at Day 1 and 2 or Day 1 and 4, respectively, had a median survival of 36 days and 32 days, respectively. Detailed data analysis is on-going and a manuscript to publish these results is in preparation.

Accepted Publications in 2017/8:

Cristina Müller, Nicholas P. van der Meulen, Martina Benesová, Roger Schibli. Therapeutic Radiometals Beyond ^{177}Lu and ^{90}Y: Production and Application of Promising α-Particle, β-Particle, and Auger Electron Emitters. *J.Nucl.Med.* 58 (2017), 91S.

Richard Baum, Aviral Singh, Martina Benesova, Christiaan Vermeulen, Silvano Gnesin, Ulli Koester, Karl Johnston, Dirk Mueller, Stefan Senftleben, Harshad Kulkarni, Andreas Tuerler, Roger Schibli, John Prior, Nicholas van der Meulen, Cristina Müller. Clinical evaluation of the radiolanthanide terbium-152: First-in-human PET/CT with ^{152}Tb-DOTATOC. *Dalton Trans.* 46 (2017), 14638.

Cristina Müller, Katharina A. Domnanich, Christoph A. Umbricht, Nicholas P. van der Meulen. Scandium and Terbium Radionuclides for Radiotheranostics: Current State of Development Towards Clinical Application. *Br J Radiol* 91 (2018), 20180074.

Oral Presentations in 2017/8:

Nicholas P. van der Meulen, Cristina Müller: *"Tb radionuclides separated at ISOLDE; processed and used for radiolabelling and imaging experiments at PSI"*, Radiochemistry lecture (31 May 2017), University of Bern, Switzerland.

Nicholas P. van der Meulen, Ulli Köster, Karl Johnston, Christoph Umbricht, Martina Benesova, Roger Hasler, Nadezda Gracheva, Christiaan Vermeulen, Cristina Müller: *"An update on the chemical separation of ^{152}Tb and its subsequent application for PET imaging"*, ISOLDE Workshop and Users Meeting 2017, Geneva, Switzerland.

Nicholas P. van der Meulen, Ulli Köster, Karl Johnston, Christiaan Vermeulen, Christoph Umbricht, Martina Benesova, Roger Hasler, Nadezda Gracheva, Roger Schibli, Aviral Singh, Richard P. Baum, Cristina Müller: *"The use of ^{149}Tb and ^{152}Tb in preclinical and clinical investigations: its mass separation and subsequent application for imaging and therapy"*, 255th ACS Meeting, New Orleans, USA.

Cristina Müller, Christoph A. Umbricht, Martina Benešová, Christian Vermeulen, Ulli Köster, Karl Johnston, Aviral Singh, Dirk Müller, Richard P. Baum, Andreas Türler, Rorger Schibli, Nicholas P.van der Meulen: *"Proof-of-Concept Study using ^{152}Tb-PSMA-617 for Imaging of Prostate Cancer*" International Symposium on Radiopharmaceutical Sciences (ISRS), May 2018 Dresden, Germany

Cristina Müller: *"Prostate Cancer Theranostics – New Radioisotopes for Imaging and Therapy"* – invited lecture at WARMTH 2017, Vienna, Austria.

Cristina Müller: *"Theranostic Application of Exotic Radionuclides in Cancer Research* – invited lecture at Summer School June 2018, Lisbon, Portugal.

Cristina Müller & Nicholas P. van der Meulen: *„Preclinical Development and Application Using Exotic Radionuclides"* – invited lecture, Sept 2018, Montpellier, France.

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 PSMA-617 and other, new tumor-targeting ligands are very important.

One of the primary aims of MEDICIS is to produce radiolanthanides, including ^{149,152,155}Tb, for preclinical studies. However, until Tb radioisotopes become routinely available from MEDICIS it is felt necessary to continue developmental work with on-line collections at ISOLDE.

Note: this third section will not be presented at the INTC open session. The written report has been considered sufficient for this part of the proposal.

3) Radioisotope implanted porous silicon nanoparticles for theranostic applications

Ulrika Jakobsson[1], Ermei Mäkilä[2], Antti Rahikkala[3], Sanjeev Ranjan[1], Jarkko Lampuoti[1], Ulli Köster[4], Jarno Salonen[2], Helder Santos[3], Mirkka Sarparanta[1], Anu Airaksinen[1] and Kerttuli Helariutta[1]

[1]University of Helsinki, Department of Chemistry, Finland
[2]University of Helsinki, Faculty of Pharmacy, Finland
[3]University of Turku, Department of Physics and Astronomy, Finland
[4]Institut Laue-Langevin, France

Two foils of thermally hydrocarbonised nanoporous silicon (THCPSi) (∅ = 1 cm, 40 μm thickness) were implanted at ISOLDE with ^{155}Tb ions. After that, the foil was transported to Helsinki, Finland, where it was further processed to particles by milling and sonicating. A fraction of nanoparticles with size less than 300 nm was separated by centrifugation and washed with HNO_3 to remove any loose ^{155}Tb. After that, a part of the particles was coated with a solid lipid (SL) layer to improve their stability. Both coated and uncoated particles were finally surrounded by a red blood cell membrane (RBC) whose aim was to improve the blood circulation time of the particles.

After processing, the in-vitro stability of three batches of particles (bare THCPSi, THCPSi-RBC and THCPSi-SL-RBC) was tested in two physiologically relevant pH values (5.6 and 7.4) and in human plasma at +37˚C. In these tests it was found that the particles are quite stable against dissolution over a long time period (over 80% of ^{155}Tb was bound to particles up to 60 hours). There were also no major differences observed between the stability of RBC and SL-RBC treated particles, so the THCPSi-RBC particles were selected for the in-vivo experiment due to their simpler manufacturing process.

The in-vivo experiment involved injecting 200 μl of THCPSi-RBC particle suspension (average activity 9.6 kBq) in the tail vein of a group of five female BALB/c mice. Blood samples were taken at 20, 60, 120 and 240 minutes after injection. The animals were sacrificed at 480 minutes from injection, and the organs were harvested. The activity of the blood samples and the organs was measured.

In the in vivo experiment, it was found that the RBC coating improves significantly the circulation time of the THCPSi particles in blood, which is good when targeting is aimed for. Also we saw that the particles stayed intact inside the body since they were mostly cleared out via liver and spleen. It was also proven that the body recognizes the RBC coated particles as blood cells because they were specially concentrated to spleen whose function is to clear out the defect blood cells.

The experiment was a proof-of-principle of our method for preparing radioisotope-implanted porous silicon nanoparticles via direct implantation of radionuclides. After optimizing the process, the particles can further be modified to improve selectivity by adding targeting moieties. Ultimately the properties of the implanted radionuclide will be selected to support both the imaging and therapeutic applications.

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-GHM chamber (only for parallel collection of low dose-rate ^{155}Tb)	☒ Existing	☒ To be used without any modification
Shielded ENSAR2 collection chamber (for high dose rate ^{149}Tb and ^{152}Tb collections)	☐ Existing	☐ To be used without any modification ☐ To be modified
	☒ New	☐ Standard equipment supplied by a manufacturer ☒ collaboration responsible for the design and manufacturing

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	1 GBq 149Tb plus 133Ce, 133mCe and 133La 2 GBq 152Dy/152Tb 100 MBq 155Tb		
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. For the high dose rate collections of ^{149}Tb and ^{152}Tb a new dedicated collection chamber will be constructed that provides local shielding during the collection and the transfer into the transport container.

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): < 3kW