EUROPEAN ORGANIZATION FOR NUCLEAR RESEARCH

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

Terbium-149 for targeted alpha therapy

11 January 2023

Nick van der Meulen[1], Cristina Müller[1], Anzhelika Moiseeva[1], Colin Hillhouse[1], Pascal Grundler[1], Stuart Warren[1], Maryam Mostamand[1], Ana Katrina Mapanao[1], Avni Mehta[1], Karl Johnston[2], Ulli Köster[3]

[1] Paul Scherrer Institut, Villigen – ETH Zürich, Switzerland
[2] CERN, ISOLDE
[3] Institut Laue-Langevin, Grenoble, France

Spokespersons: Karl Johnston (karl.johnston@cern.ch)
Nick van der Meulen (nick.vandermeulen@psi.ch)
Local contact: Ulli Köster (koester@ill.eu)

CERN-INTC-2024-020 / INTC-P-593-ADD-2
10/01/2024

Abstract

We request additional shifts to continue the IS688 programme for ^{149}Tb preclinical studies towards Targeted Alpha Therapy. The campaign in 2023 resulted in significantly higher production of ^{149}Tb than was previously observed. This allowed for many of the aims of the previous addendum to be achieved, including the first-ever labelling up to 50MBq/nmol. Based on the possibility of the availability of higher activities of ^{149}Tb, this addendum is dedicated to the exploration of ^{149}Tb in combination with FAPI-49 for the targeted alpha therapy of sarcoma. This is the first time that this approach has been attempted and a demonstration of its success would be a major advance for targeted alpha therapy.

Requested shifts: 14 (split into 2-4 runs over 2 years)

Introduction

Terbium is a unique element in that it includes a quadruplet of radioisotopes suitable for diagnostics and therapy in nuclear medicine [1]. It is especially important with regard to the theragnostic concept, using chemically identical radioligands based on different Tb radioisotopes for diagnosis and therapy, respectively. The success of previous experiments by the current collaboration has been demonstrated in a variety of publications: the collection and purification of ^{149}Tb (α-emitter, $T_{1/2}$ = 4.1 h) and its use for preclinical therapy studies [2, 3] and PET imaging [4]. In addition, ^{152}Tb (β^+-emitter, $T_{1/2}$ = 17.5 h), has been applied to preclinical [5] and clinical [6] PET imaging, respectively. This versatility of the Tb radioisotopes has led to their being dubbed the "Swiss army knife for nuclear medicine", as shown in Figure 1 [1]. While ISOLDE can produce all four radioisotopes, the interest in this current addendum remains focused on ^{149}Tb.

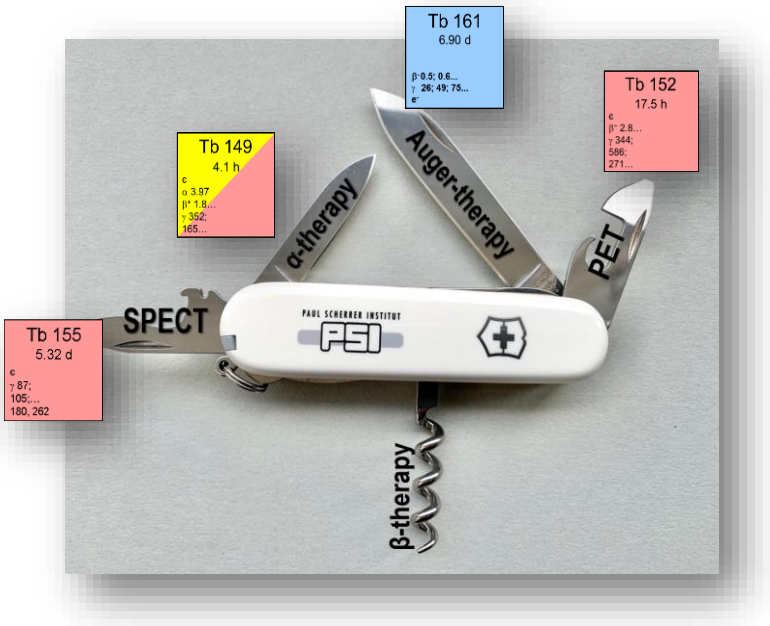

Figure 1 The quadruplet of theragnostic terbium radioisotopes.

This addendum is requesting additional shifts for the IS688 collaboration to continue the excellent progress which has been made in the last decade towards understanding the prospect of using ^{149}Tb as an isotope for Targeted Alpha Therapy (TAT). This is the **only radiolanthanide** that can be considered for alpha therapy. Its trivalency allows for the application of well-known labelling chemistry and can build on the experience gained from the use of ^{177}Lu in clinical environments. Although interest in the potential for the therapeutic

use of ^{149}Tb continues to grow, ISOLDE is still the only laboratory worldwide which is able to produce this radionuclide in sufficient quantities for preclinical studies.

In 2023 the production of this nuclide exceeded expectations. The use of a fresh target (#812) containing 25μm Ta rolls and exploiting so-called "back-of-the-line heating" allowed for the production of up to 4 times the previous levels of ^{149}Tb. This resulted in significantly more activity arriving at PSI, opening up new possibilities in the types of studies which can now be considered. The current addendum summarises the results from 2023 and discusses the programme of experiments which are to be undertaken before LS3.

Implantation method and purification

The required neutron-deficient lanthanides have been produced by 1.4 GeV proton-induced spallation in tantalum foil targets. The cumulative yield of ^{149}Tb is boosted by resonantly laser-ionising the ^{149}Dy precursor. The mass-separated beam will be ion-implanted into a temporary matrix (e.g. Zn-coated gold/platinum/tantalum foils), and shipped in shielded containers to PSI. In addition to ^{149}Tb, impurities such as sideband oxides are also collected, leading to high ambient dose rates. The use of a dedicated, well-shielded compact chamber has removed the concerns about high doses during implantation and the redevelopment of the GLM area has simplified the logistics of carrying out such collections at ISOLDE. The compact chamber and an example of the Zn-coated foil are shown in Figure 2. The chamber has now received its full safety clearance, as detailed in the safety appendix below.

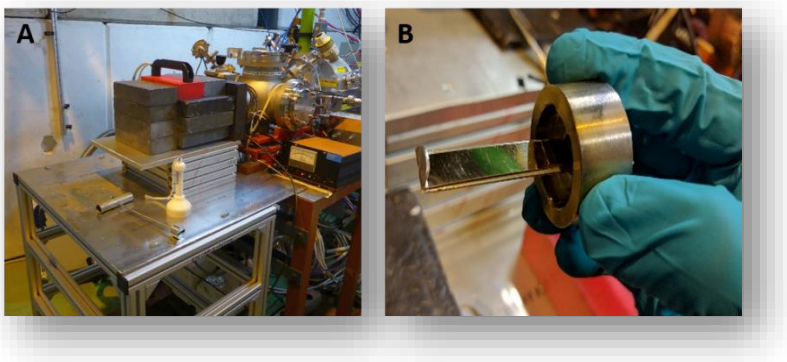

Figure 2 The compact chamber where the collections are performed (A), and the Zn coated Au foil into which the beam is deposited (B).

Summary of results and discussion from 2023

Two one-week campaigns for the production of ^{149}Tb took place in May and July 2023, respectively. Collections were performed overnight using Zn-coated gold/platinum foils. The foils, containing the desired product and its A=149 (pseudo-)isobars were transported to PSI for processing. The chemical separations were performed using an adjusted/updated method.

Usable products (with yields of 180-290 MBq) were produced using a two-column separation system in a hot cell, allowing the labelling of ^{149}Tb to somatostatin analogues and its use for preclinical studies.

Excellent results in terms of chemical separation and preclinical studies were obtained in these campaigns; however, these results require corroboration along with therapy studies using other somatostatin-based ligands. Up to **288 MBq** ^{149}Tb was separated from the collection material, with a radiochemical separation efficiency of >90% and a final radionuclidic purity >99.9%. The product was labelled to DOTA-derivatized peptides at up to 20 MBq/nmol molar activity, even **50 MBq/nmol** was achieved when attempted: the first time that this quality was obtained. *In vitro* cell viability assays using AR42J tumour cells were performed using ^{149}Tb-DOTALM3 and ^{149}Tb-DOTATATE (Figure 3), along with *in vivo* PET/CT imaging of AR42J tumour-bearing mice with these ligands.

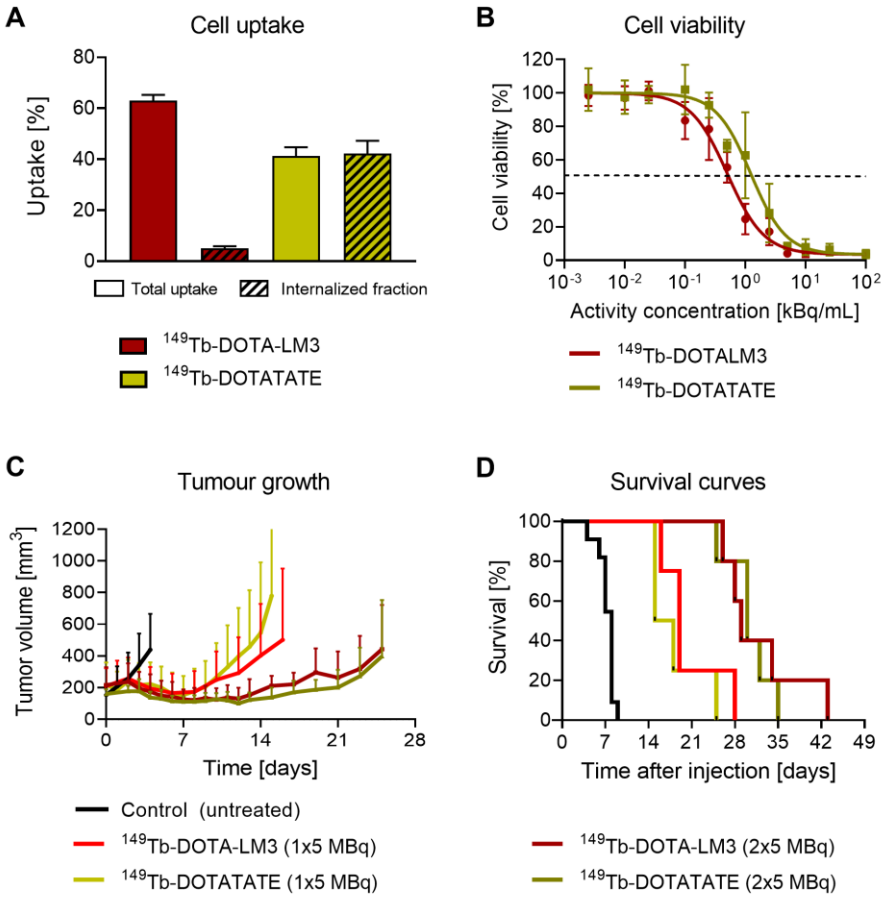

Figure 3 Initial data extracted from in vitro and in vivo experiments performed with AR42J tumour cells and respective xenograft mouse models. (A) Cell uptake and internalization of [^{149}Tb]Tb-DOTA-LM3 and [^{149}Tb]Tb-DOTATATE; (B) Cell viability of cells after exposure to various activity concentrations of [^{149}Tb]Tb-DOTA-LM3 and [^{149}Tb]Tb-DOTATATE; (C/D) Tumour growth and survival curves of mice injected with 1x5 MBq or 2x5 MBq [^{149}Tb]Tb-DOTA-LM3 and [^{149}Tb]Tb-DOTATATE.

Therapy studies were performed with these radioligands to investigate the efficacy to delay the tumour growth. Tolerability studies of these radiopeptides were performed over a 2-months period. The data of these studies are still being processed and analysed.

Aims until LS3

To date, ^{149}Tb has been investigated with folate conjugates [2], with PSMA ligands [3] and somatostatin analogues ([4] and unpublished data from campaigns 2022/23), respectively. For the next campaign of ^{149}Tb production as a collaborative effort between ISOLDE/CERN and PSI, we propose to investigate ^{149}Tb in combination with FAPI-49 for the targeted alpha therapy of sarcoma.

The fibroblast activation protein (FAP) is a membrane-bound enzyme which is highly expressed in reactive stromal fibroblasts of more than 90% of human epithelial cancers and malignant cells of bone and soft tissue sarcomas. FAP holds promise as a pan-cancer target due to its overexpression in the vast majority of cancers.

Several approaches of FAP-targeting are currently being tested, including the use of low-molecular-weight inhibitors to deliver diagnostic and therapeutic radionuclides for molecular imaging and potential therapeutic applications of cancer diseases [8]. Preliminary data on PET/CT using FAPI radiotracers are highly encouraging. The therapeutic application of FAPI labelled with β^-- and α-particle-emitting radionuclides has been proposed and initial (pre)clinical studies were performed [9].

FAPI-46 is a quinoline-based FAP-targeting ligand suitable for labelling with trivalent radionuclides through a DOTA chelator. FAPI-46 has higher tumour uptake and prolonged tumour accumulation and can, thus, be used for tumour imaging of a multitude of different cancers. It has been investigated in combination with ^{177}Lu and ^{225}Ac for β^-- and α-therapy, respectively, in a preclinical model of pancreas cancer [10].

We believe that the use of FAPI ligands would be particularly interesting in combination with ^{149}Tb. The commonly fast pharmacokinetics of FAPI molecules would perfectly match the short half-life of ^{149}Tb. We, therefore, propose the labelling of FAPI-46 with ^{149}Tb and subsequent testing of ^{149}Tb-FAPI-46 using FAP-expressing sarcoma cells *in vitro*. We will perform cell viability and survival assays to investigate the potency of ^{149}Tb-FAPI-46 to kill sarcoma cells *in vitro*. Furthermore, initial therapy studies in a small number of tumour-bearing mice will be initiated to investigate the therapeutic efficacy of ^{149}Tb-FAPI.

We therefore request 14 shifts in order to initiate the study of ^{149}Tb-FAPI-46 for TAT. Based on 2 runs per year until LS3 this will allow us to gain valuable insights into the feasibility of this concept and whether it can be exploited in a more general manner in the future.

Requested shifts:

(i) Envisaged measurements and requested isotopes
14 shifts for the collection of ^{149}Tb.

(ii) Number of shifts (based on newest yields) required for each isotope
The given yields were observed in the 2023 campaign: the upper values during the first run in May, the lower values in July.

Isotope	Cumulative yield (/uC)	Target – ion source	Shifts (8h)
^{149}Tb	8E8 – 2E9	Ta foil + Ta surface ionizer (same specifications as target #812) and Dy RILIS	14

Total shifts: 14

References:

[1] Müller et al., J Nucl Med 53, 1951 (2012).

[2] Müller et al., Pharmaceuticals 7, 353 (2014).

[3] Umbricht et al., Scientific Reports 9, 17800 (2019).

[4] Müller et al., EJNMMI Radiopharmacy and Chemistry 1,5 (2016).

[5] Müller et al., EJNMMI Research 6, 35 (2016).

[6] Baum et al., Dalton Transactions 46, 14638 (2017).

[7] Beyer et al., Eur J Nucl Med Mol Imaging 31, 547 (2004).

[8] Chandekar et al., Diagnostics 13, 2018 (2023).

[9] Sidrak et al., Int J Mol Sci. 24(4), 3863 (2023).

[10] Liu et al., Eur J Nucl Med Mol Imaging 49, 871 (2022).

Appendix

DESCRIPTION OF THE PROPOSED EXPERIMENT

Please describe here below the main parts of your experimental set-up:

Part of the experiment	Design and manufacturing
Chamber for high dose rate collections of medical radioisotopes https://edms.cern.ch/document/1756267/2	☒ To be used without any modification ☐ To be modified

HAZARDS GENERATED BY THE EXPERIMENT

Additional hazard from flexible or transported equipment to the CERN site:

Domain	Hazards/Hazardous Activities		Description
Mechanical Safety	Pressure	☐	[pressure] [bar], [volume][l]
	Vacuum	☐	
	Machine tools	☐	
	Mechanical energy (moving parts)	☐	
	Hot/Cold surfaces	☐	
Cryogenic Safety	Cryogenic fluid	☐	[fluid] [m^3]
Electrical Safety	Electrical equipment and installations	☐	[voltage] [V], [current] [A]
	High Voltage equipment	☐	[voltage] [V]
Chemical Safety	CMR (carcinogens, mutagens and toxic to reproduction)	☐	[fluid], [quantity]
	Toxic/Irritant	☐	[fluid], [quantity]
	Corrosive	☐	[fluid], [quantity]
	Oxidizing	☐	[fluid], [quantity]
	Flammable/Potentially explosive atmospheres	☐	[fluid], [quantity]
	Dangerous for the environment	☐	[fluid], [quantity]
Non-ionizing radiation Safety	Laser	☐	[laser], [class]
	UV light	☐	
	Magnetic field	☐	[magnetic field] [T]
Workplace	Excessive noise	☐	
	Working outside normal working hours	☐	
	Working at height (climbing platforms, etc.)	☐	

	Outdoor activities	☐	
Fire Safety	Ignition sources	☐	
	Combustible Materials	☐	
	Hot Work (e.g. welding, grinding)	☐	
Other hazards			