PAUL SCHERRER INSTITUT

PSI

RADIONUCLIDE DEVELOPMENT

CRS

CENTER FOR RADIOPHARMACEUTICAL SCIENCES

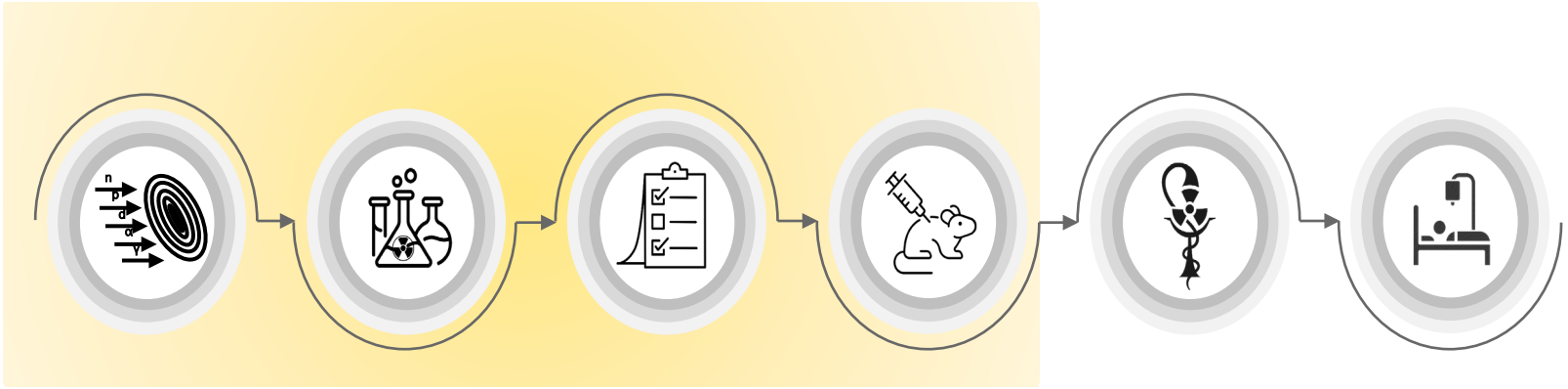
ETH PSI USZ

^{149}Tb for Targeted Alpha Therapy

Nicholas P. van der Meulen, Anzhelika Moiseeva, Pascal V. Grundler, Ulli Köster, Karl Johnston, Colin C. Hillhouse, Ana Katrina Mapanao, Avni Mehta, Stuart Warren, Maryam Mostamand, Cristina Müller

ISOLDE IS688

Process of Radionuclide Development: a multidisciplinary affair



TARGET IRRADIATION

Target development and optimization of irradiation conditions

RADIOCHEMISTRY

Radiochemical separation from target material

QUALITY CONTROL

Chemical purity, radiochemical purity, radionuclidic purity, pH, identity, bacterial endotoxins

PRECLINICAL STUDIES

In-vitro and in-vivo imaging studies

GMP PROCESS DEVELOPMENT

Introduction into the GMP concept for radiopharmaceutical production

CLINICAL STUDIES

Clinical trials to confirm preclinical results

RADIONUCLIDE DEVELOPMENT

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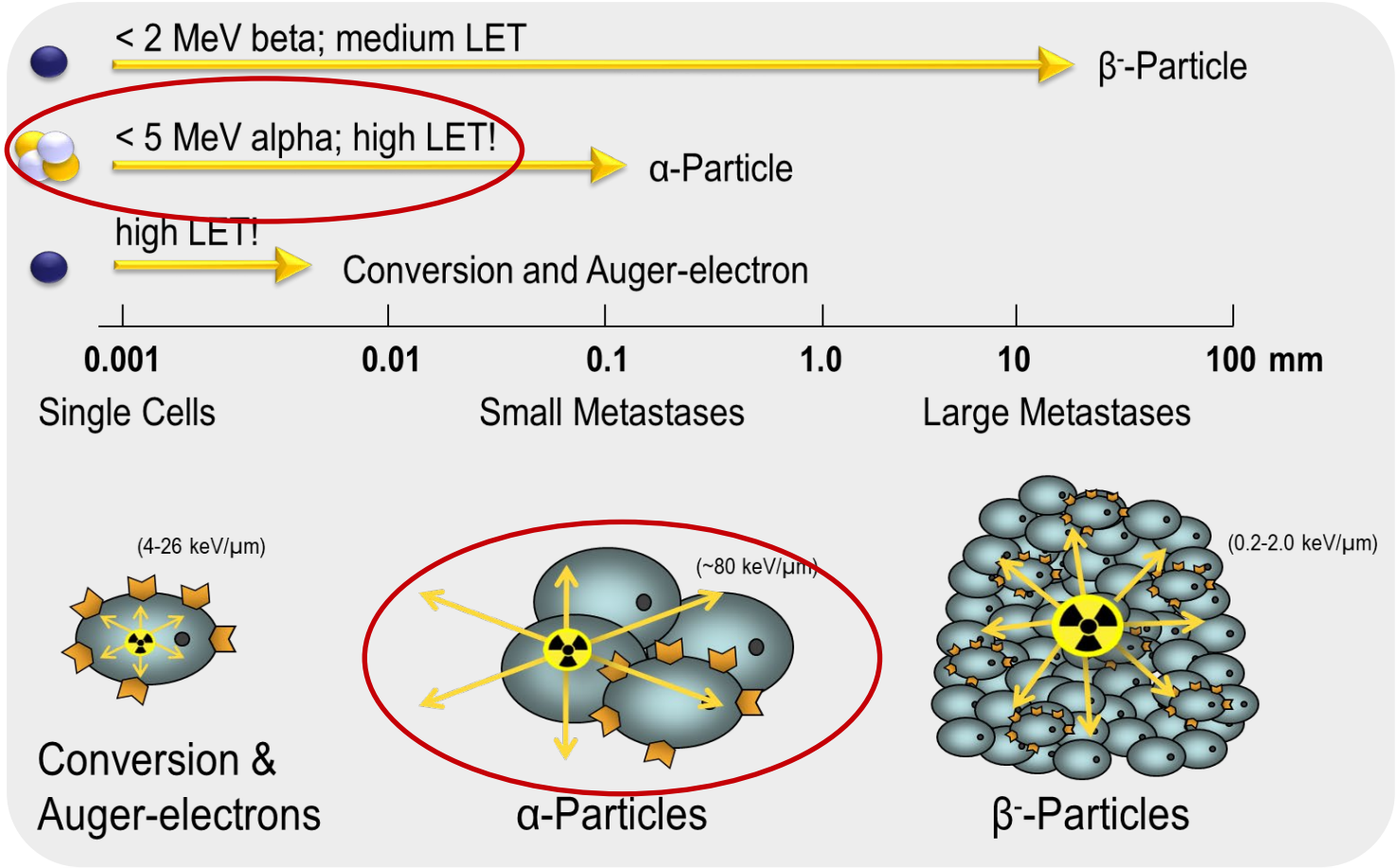
Tissue Range of Therapeutic Radiation



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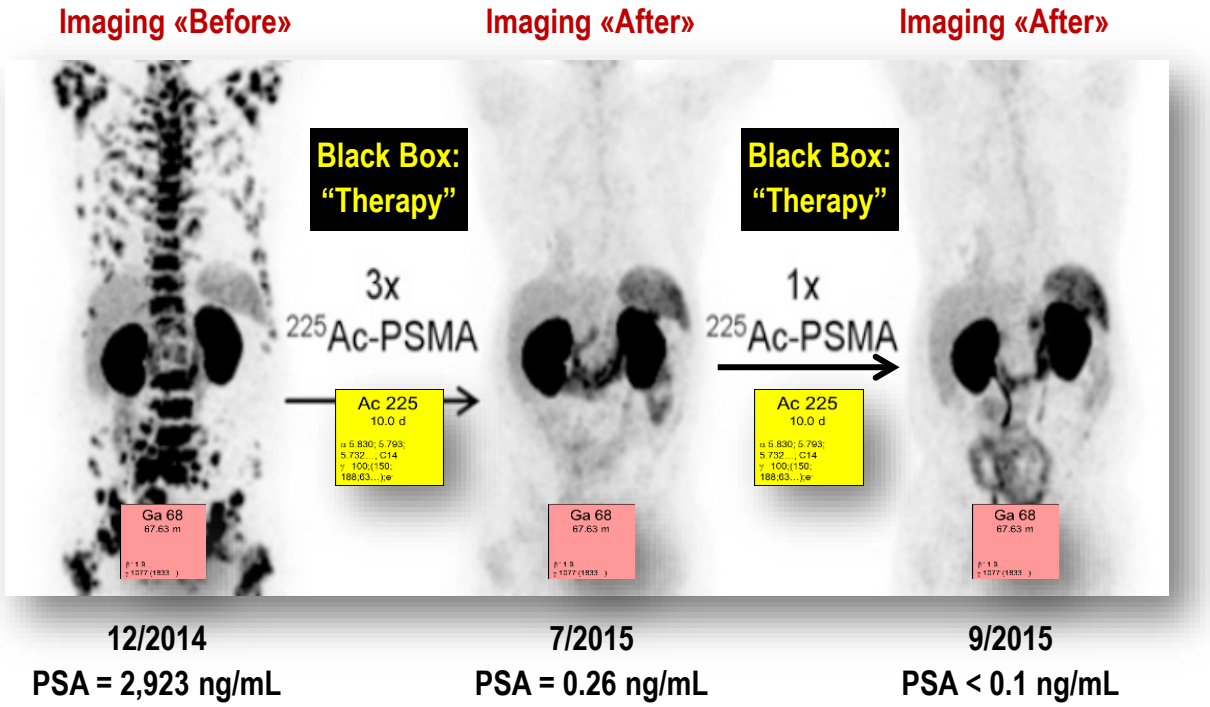
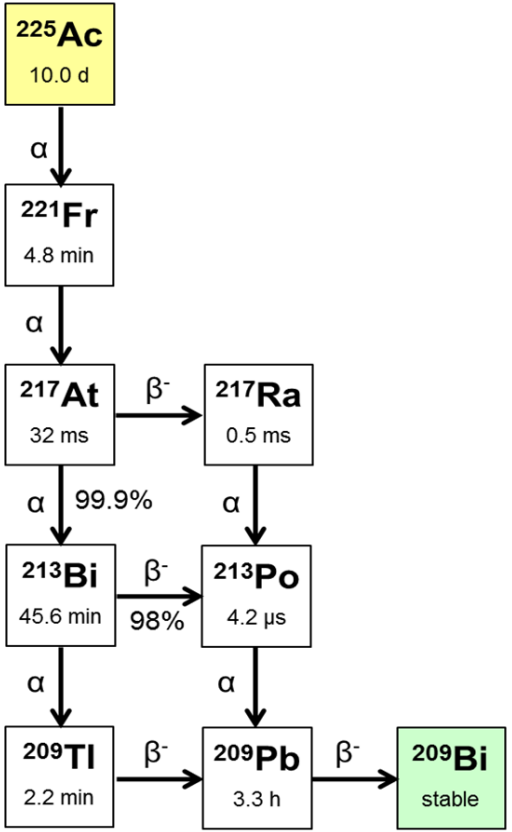
^{225}Ac-PSMA-617: α-Radionuclide Therapy

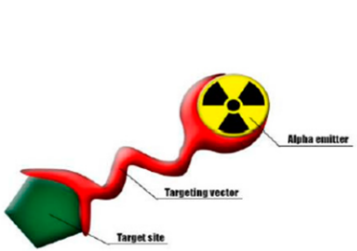


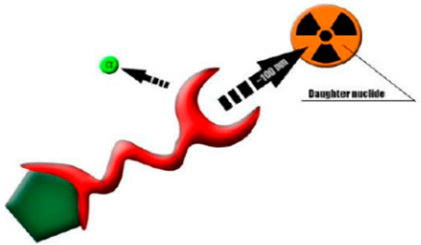
Kratochwil et al. **2016** J Nucl Med 57:1941.

Potential Concern about Actinium-225



Recoiling daughter radionuclide detaching from a targeting agent as a consequence of alpha decay:





Released daughter nuclides are radioactive!

They accumulate in healthy tissue (bones and kidneys)

Kruijff et al. **2015** Pharmaceuticals 8:321-336.

The Terbium “Sisters”

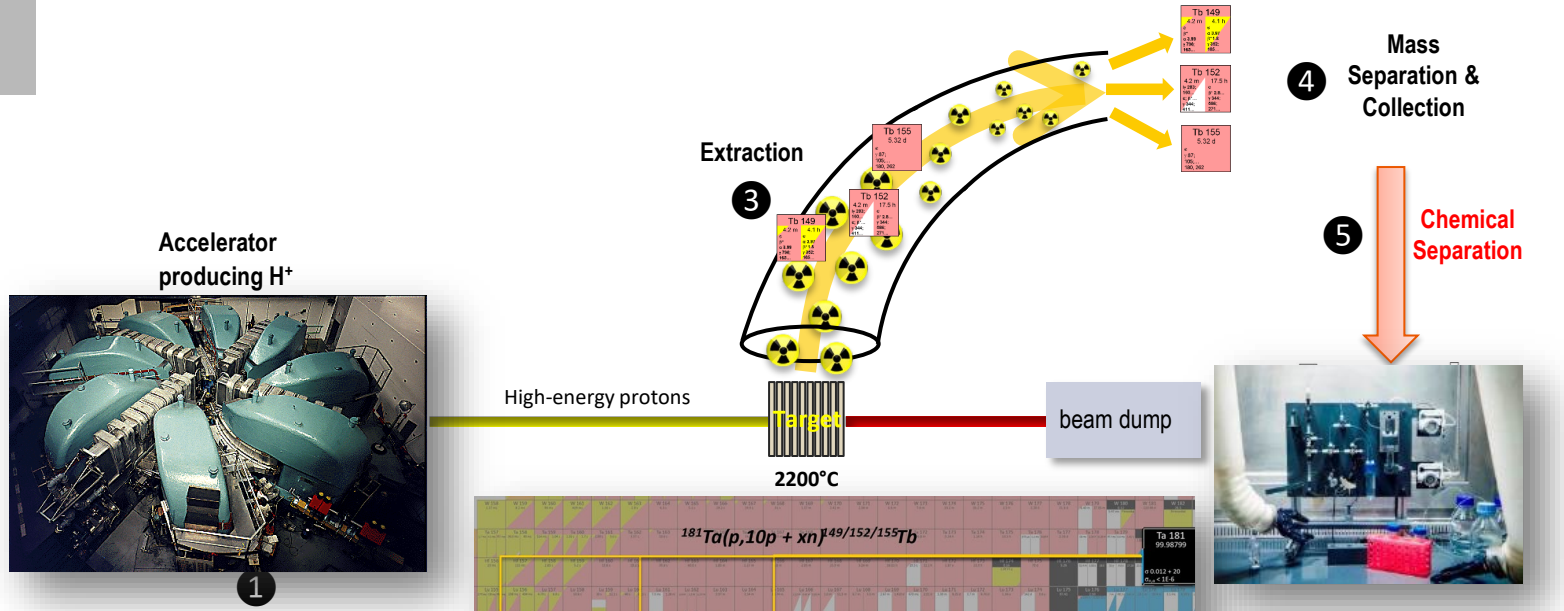
^{149}Tb: PSI's collaboration with ISOLDE

History:

- Began with Beyer et al. in late 90's;
- Resurrected by PSI members in 2011;
- ISOLDE-PSI the only collaboration currently working on ^{149}Tb;
- Many groups desire to produce it, but currently do not have the means.
- Switzerland became a member state in 2023/4

RADIONUCLIDE DEVELOPMENT

Radionuclide Development using Isotope Separation OnLine (ISOL)



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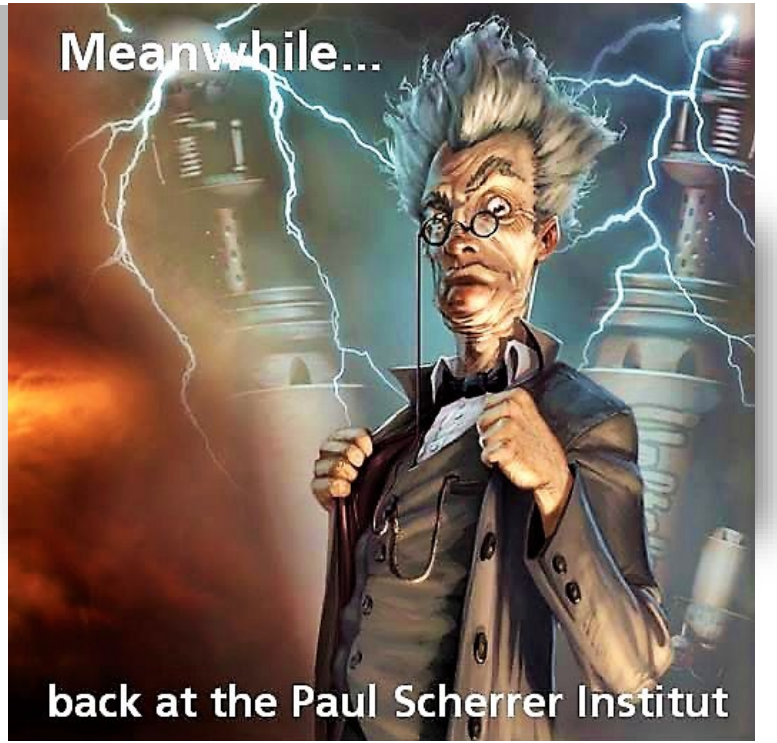
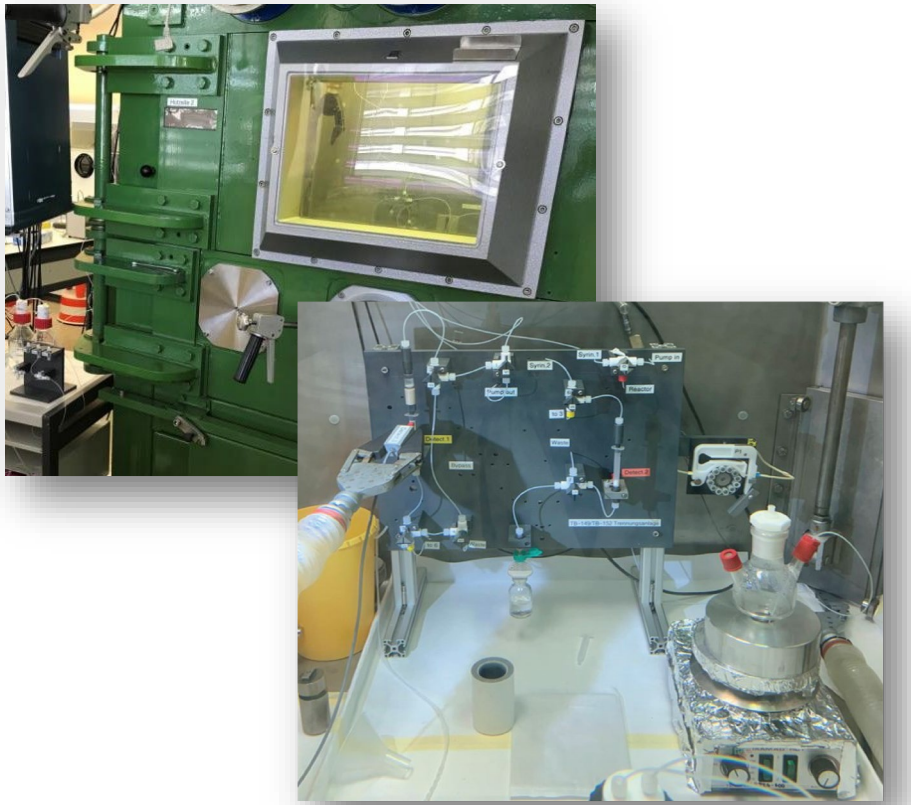
^{149}Tb: The Logistics Challenge

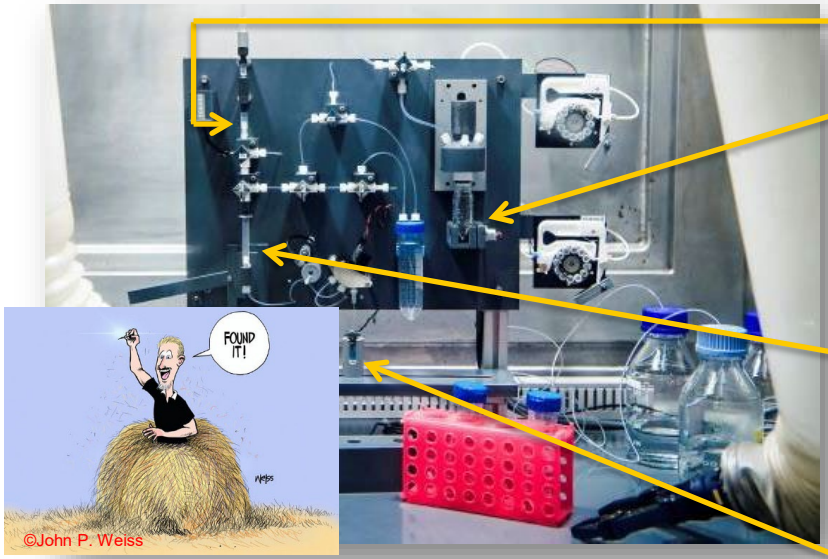
Collection & Separation

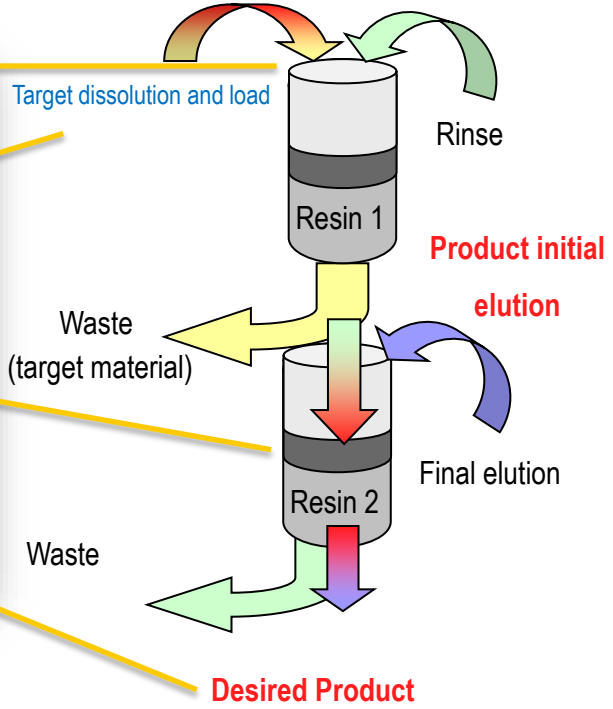


© C. Grünewald



Chemical Separation Process Application





van der Meulen et al., Nucl Med. Biol. (2015)
Domnanich et al., EJNMMI Radiopharm. Chem. (2017)
van der Meulen et al. Molecules (2020)

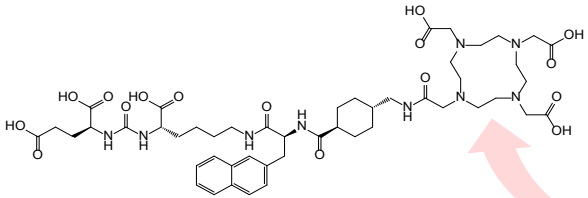
ng product from **mg** target material!

RADIONUCLIDE DEVELOPMENT

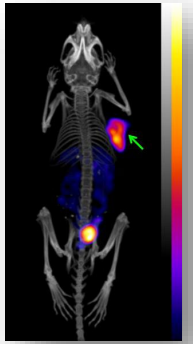
Importance of Product Purity for Preclinical Application

Biomolecule

- Chemical synthesis: metal-free working environment
- Preparation of stock solution: in metal free environment (no metal spatula)

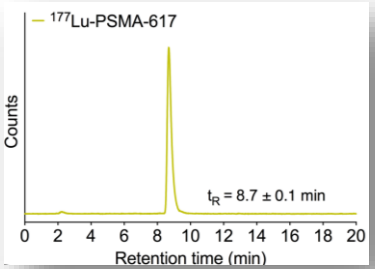


The macrocyclic Chelator is NOT selective for the Radiometal of interest, but will coordinate other (cold) metal ions.



Radionuclide

- **Radionuclidic purity:** >99.9%
- **Chemical purity:** no metal ions (i.e. absence of Fe, Co, Cu, Zn, Gd, Pb etc.)



RADIONUCLIDE DEVELOPMENT

^{149}Tb Production and Radiochemical Separation

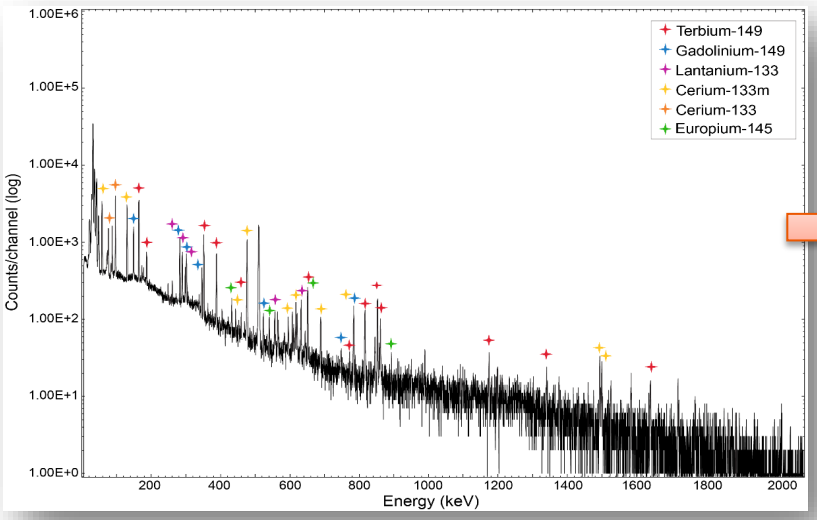
Three 1-week campaigns desired in 2024/5

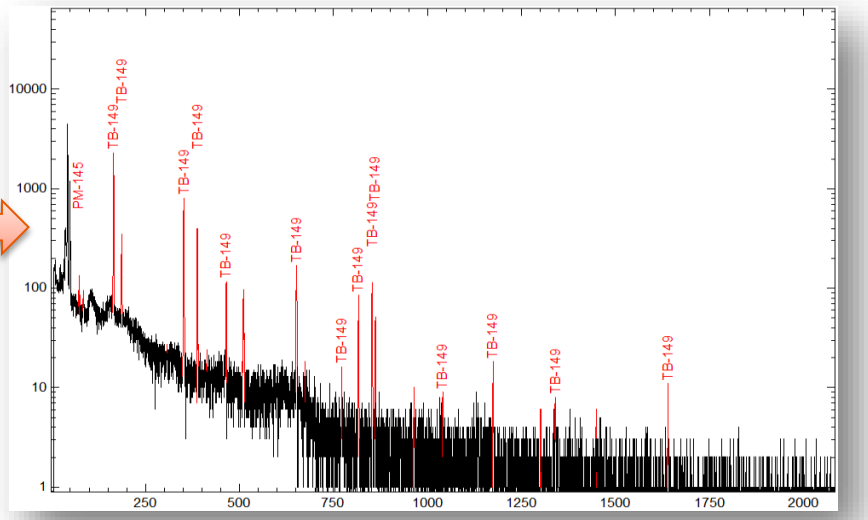
Favaretto et al., Scientific Reports, accepted for publication

ACCEPTED

Campaign results:

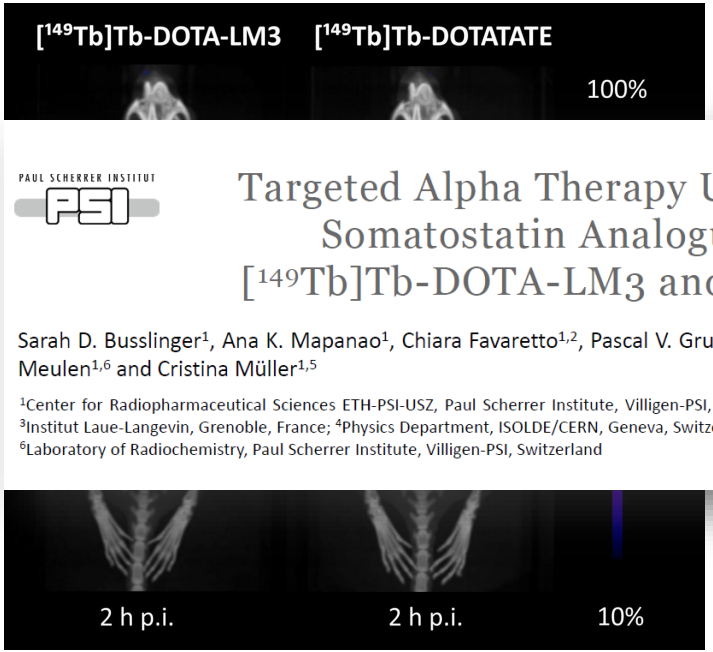
- Up to **260 MBq** ^{149}Tb produced
- Radiochemical separation efficiency **>90%**
- Final radionuclidic purity **>99.9 %**
- **50 MBq/nmol** radiolabelling achieved (began with 3-5 MBq/nmol)





^{149}Tb: In Vitro & In Vivo Studies

PET/CT images



α-PET demonstrated for the first time in 2015/6

In vitro cell viability

DOTA-LM3 used in a clinical study with ^{161}Tb in 2023

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Targeted Alpha Therapy Using Terbium-149 with Somatostatin Analogues: Comparison of [149Tb]Tb-DOTA-LM3 and [149Tb]Tb-DOTATATE

CRS CENTER FOR RADIOPHARMACEUTICAL SCIENCES

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[1]Center for Radiopharmaceutical Sciences ETH-PSI-USZ, Paul Scherrer Institute, Villigen-PSI, Switzerland; [2]Division of Nuclear Medicine, University Hospital Basel, Basel, Switzerland; [3]Institut Laue-Langevin, Grenoble, France; [4]Physics Department, ISOLDE/CERN, Geneva, Switzerland; [5]Department of Chemistry and Applied Biosciences, ETH Zurich, Zurich, Switzerland; [6]Laboratory of Radiochemistry, Paul Scherrer Institute, Villigen-PSI, Switzerland

^{149}Tb *In Vitro* & *In Vivo* Studies: what's next?

Next Campaigns/Desires

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

- ***Three 1-week campaigns desired in 2024/25***
- Investigate labelling at **higher molar activity**. (This will determine the quality of ^{149}Tb, requires higher activity).
- investigate ^{149}Tb in combination with **FAPI-46** 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.

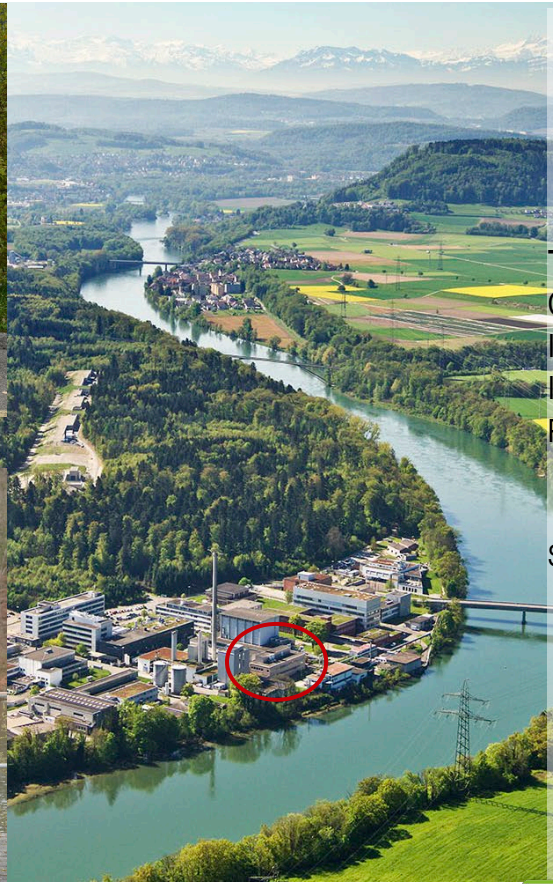
Next Campaigns/Desires

- Determine survival assays (different type of *in vitro* treatment/analysis).
- Determine cell viability assays (to investigate potency of ^{149}Tb-FAPI-46).
- Perform initial therapy studies in a small number of tumour-bearing mice to investigate the therapeutic efficacy of ^{149}Tb-FAPI-46).

Ongoing

- Data processing, analysis and preparation of images and figures

Thank You For Your Attention!



RADIONUCLIDE DEVELOPMENT

Thanks to:
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ISOLTRAP-MR-TOF-MS team
PSI Radiation Safety & logistics

Support: ENSAR2 (EU H2020 project Nr. 654002)