CERN-MEDICIS

MEDical Isotopes Collected from ISolde

Production of radionuclides for medical research

Charlotte DUCHEMIN, CERN, SY-STI-RBS

MEDICIS experimental program coordinator & PRISMAP technical manager

On behalf of the MEDICIS local dream-team, collaboration and all contributors

29 Nov 2023

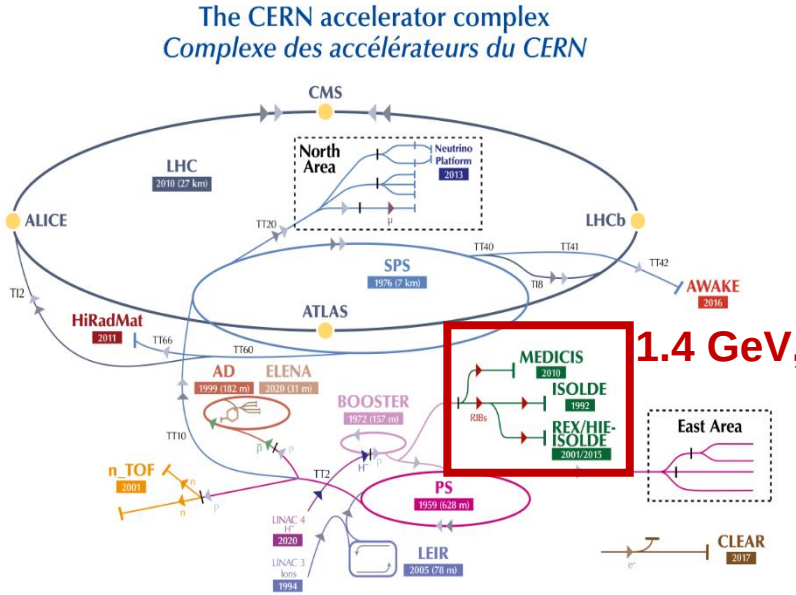
ISOLDE WORKSHOP 2023

CERN-MEDICIS - presentation of the facility

MEDICIS - **MED**ical **I**sotopes **C**ollected from **IS**olde

- Facility built for research purposes for **medical radionuclide production by mass separation**
  - Commissioned with Radioactive Ion Beam **in December 2017**
  - **Integrated into the CERN accelerator complex**

- Collaboration between CERN and 14 research institutes managed by MoU
  - Two collaboration boards per year
  - Receive external sources from reactors/cyclotrons taking part, allowing for running during Long Shutdowns !



**Upgrade to 2 GeV, 6 µA under discussion*

CERN-MEDICIS is one of the pillar of **PRISMAP, the European medical isotope program**

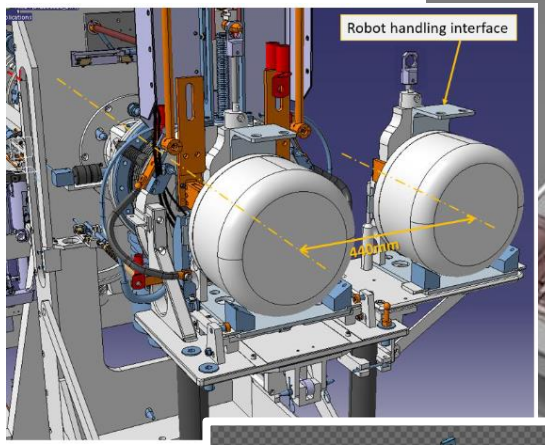
A single entry-point for external user to get access to medical radionuclides

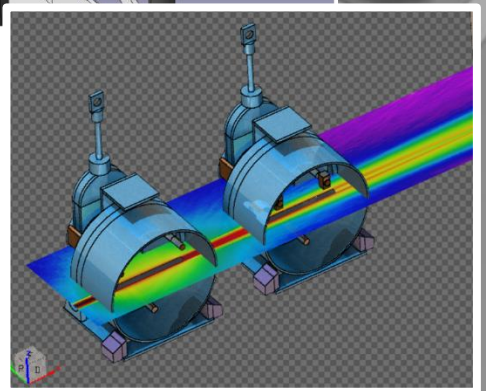
INFRA-2-2020 European Commission www.prismap.eu

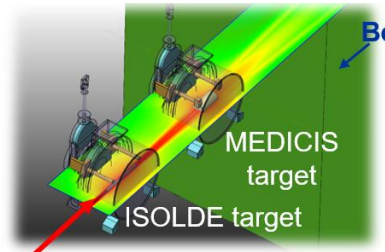
CERN-MEDICIS - integration within the ISOLDE complex

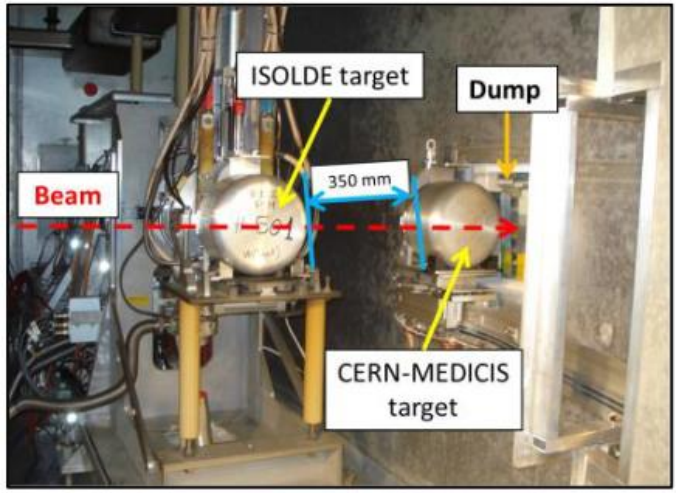
Since 2021

GPS
Irradiation Station





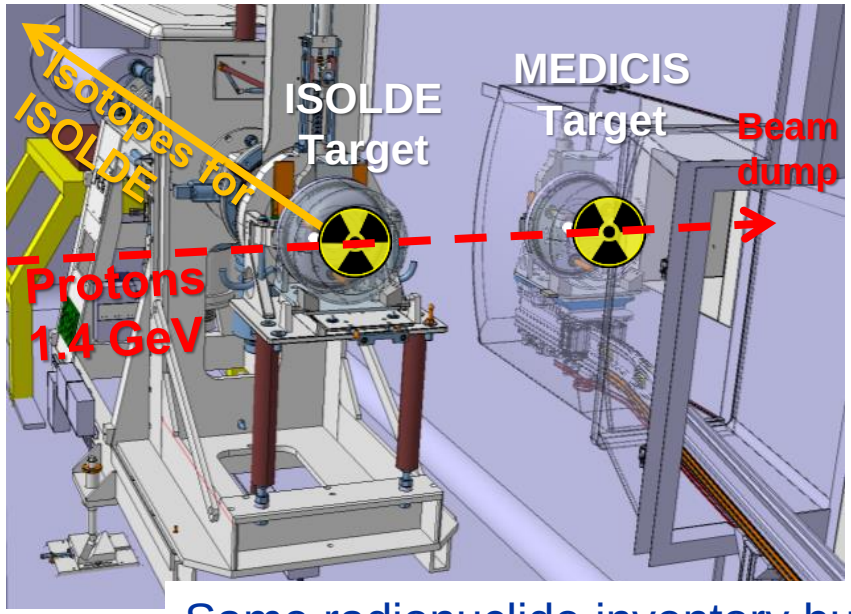




CERN-MEDICIS - irradiation possibilities

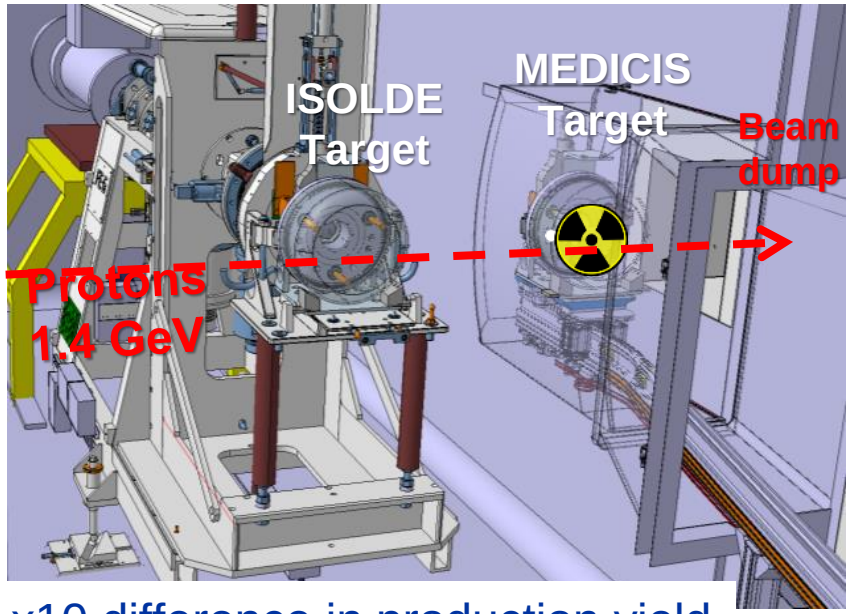
Indirect irradiation at ISOLDE (1.4 GeV)

Recycle the protons

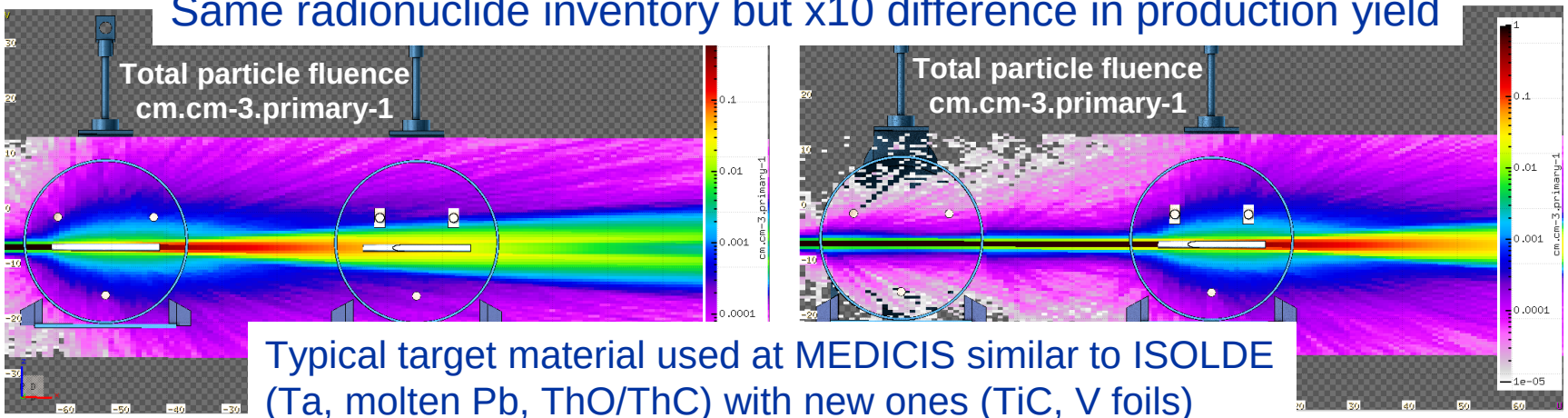


Direct irradiation at ISOLDE (1.4 GeV)

1st time tested already in 2018

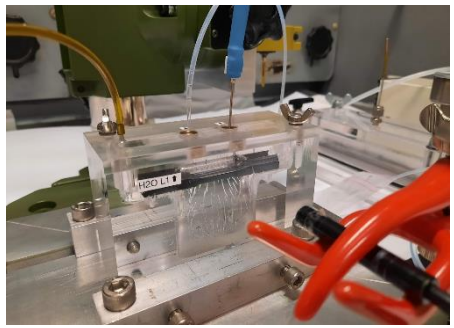


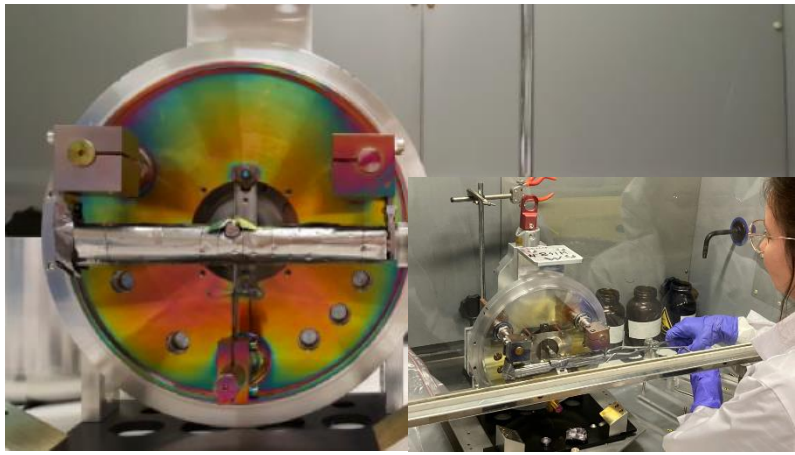
Same radionuclide inventory but x10 difference in production yield



Typical target material used at MEDICIS similar to ISOLDE (Ta, molten Pb, ThO/ThC) with new ones (TiC, V foils)

External sources produced at partner institutes





CERN-MEDICIS – workflow (one prod. per week)

End-user waiting to receive his MEDICIS radionuclide

!! During LS/when no protons at CERN: strong interaction with external collaborators to receive externally irradiated target materials

Irradiation defined and scheduled
3 to 6 months in advance

Interaction between MEDICIS coordinator, ISOLDE physics coordinator and ISOLDE operators

Completely dependent on ISOLDE events & schedule

Involvement of logistics and shipping service to find the best means of transport

HSE-RP, SCE-SSC

Planification of the shipping & EDH request
2 months in advance

G-spectrometry request via TREC
2 months in advance
HSE-RP

Work and dose planning established with RP
2 months in advance
HSE-RP

Request sent to remote handling team to handle the target before and after irradiation
1 month in advance and regular updates
BE-CEM

Operation planning
2 to 6 months in advance
2 x 40% full time equivalent operators (STAFF SY-STI)
1 x operator for the laser laboratory (PJAS) since 2019*
**in 2023 RILIS(ISOLDE) ensuring operation*

CERN-MEDICIS – workflow (one prod. per week)

Preparatory operation file
& meeting with operators
1 to 2 weeks in advance
+ regular meetings
SY-STI MED-OP
MED-Coordinator

Irradiation
1 to several days

Mass separation performed
1 to 5 days
SY-STI – MED OP
(including laser op as well since 2019)

Since 2018
Radiochemistry step (if required)
Glovebox available **since 2021**
Day D
HSE-RP, SY-STI

Sample characterized & transport documentation established
Day D
HSE-RP, SCE-SSC

Sample shipped to partner institute
Day D to Day 1
HSE-RP, SCE-SSC
COLLABORATION

Operation report published
Day 1 to Day 3
SY-STI – MED Coord.

Weekly review & preparation of next mass separation
Once a week
SY-STI MED-OP, MED-Coordinator

Project completed
COLLABORATION

F. Deligne, dessinateur

"It does not look like it, but it seems that I have a lot of influence"

*In chaos theory, the **butterfly effect** is the sensitive dependence on initial conditions in which a small change in one state of a deterministic nonlinear system can result in large differences in a later state.

DETAILED VIEW OF THE INFRASTRUCTURE

CERN-MEDICIS – detailed view of the infrastructure

Available since 2021

First use for Ac-225/Ac-227 sample transfer

Now regularly used for radiochemistry and handling of alpha emitters

CERN-MEDICIS – MELISSA laser laboratory

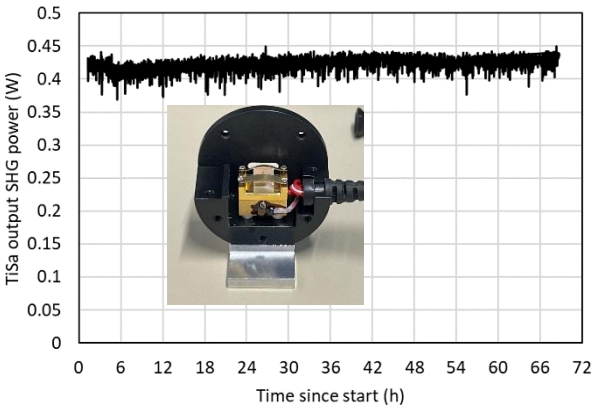
(C. Bernerd presentation this morning)

- MEDICIS-dedicated laser laboratory for ionization **commissioned in 2019**
- Used for more than 80% of the collected isotopes
- **In 2023 : operation supported by the ISOLDE-RILIS team**

+ strong support from KU Leuven (PJAS & PhD Students) and RILIS, since commissioning

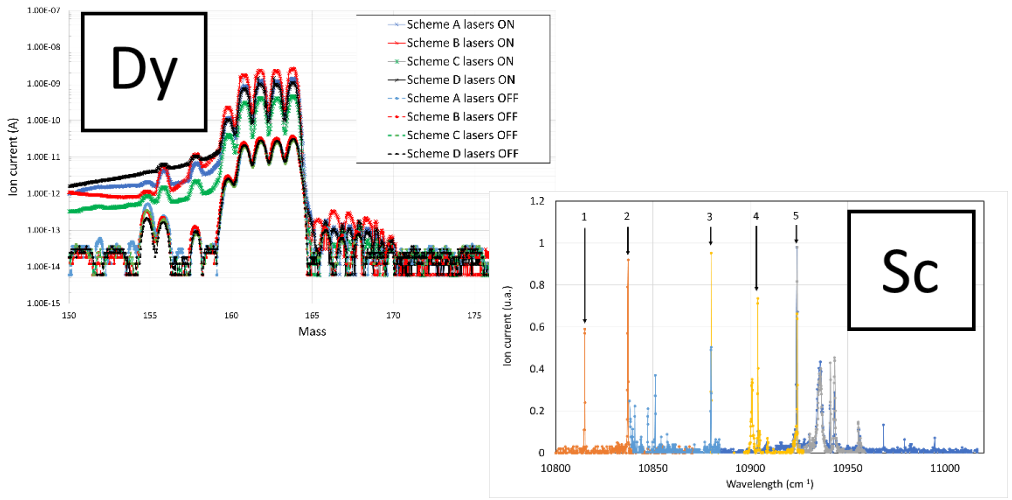
Not only used for regular operation but also a development lab for both MEDICIS and ISOLDE

Long-term laser stability



Now standard in RILIS

Laser scheme development/comparison



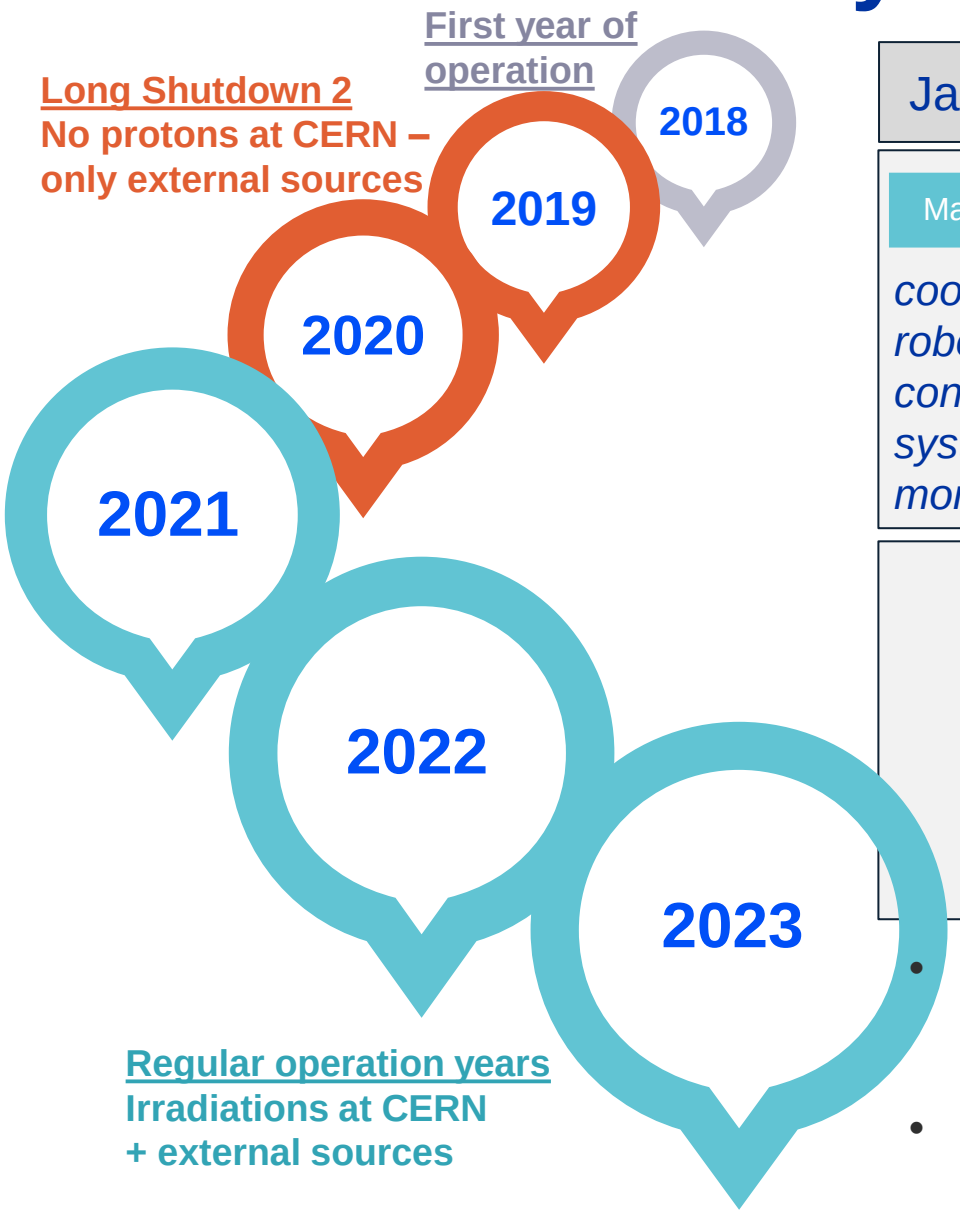
Raman Z-fold laser using diamond for wavelength extension

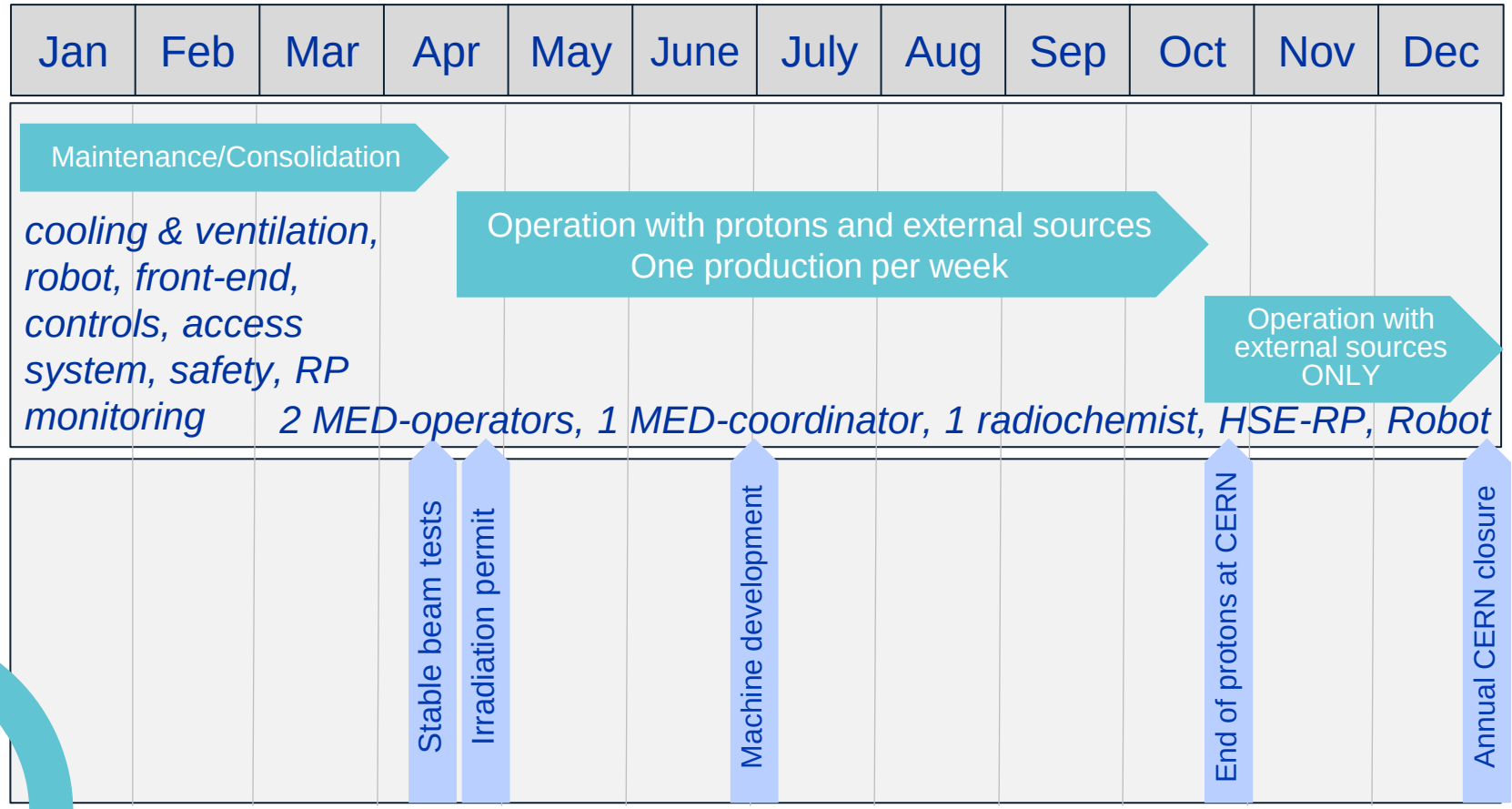
=> First-ever use online for Radium ionization in MEDICIS last September

Go have a look at C. Bernerd poster !

A typical MEDICIS yearly schedule

CERN-MEDICIS – yearly schedule (example of 2023)



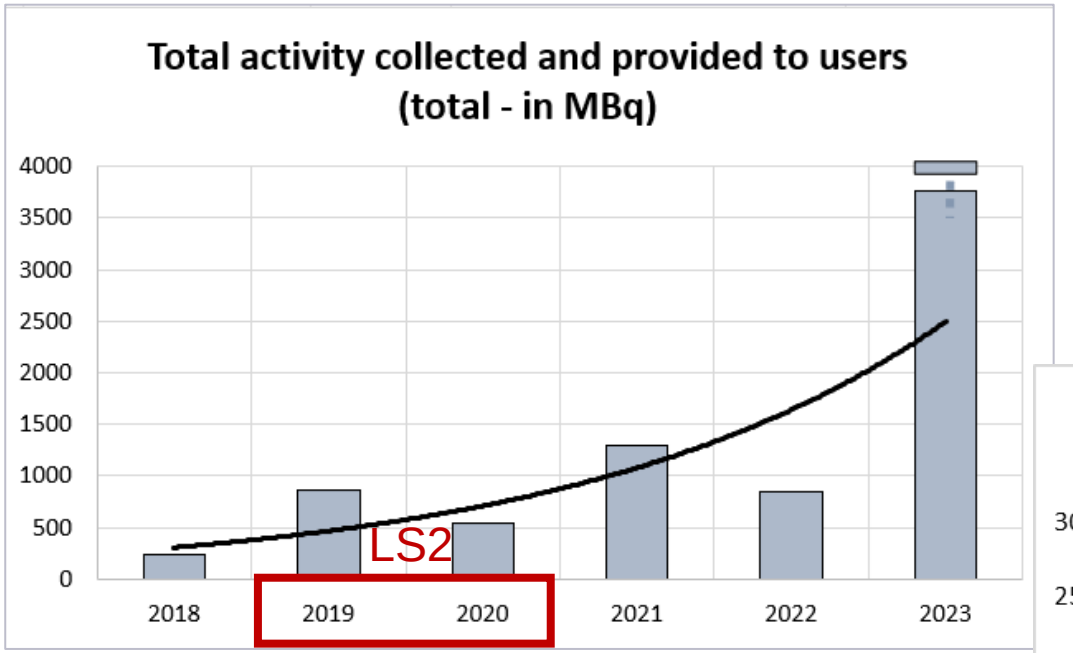


- About **10 targets built per year**
  - **Target parameters fully traced (EAM light, JIRA, Wiki, yearly summary file …)**
- Target are re-used to **optimize the process, ressources and minimize waste production** : up to 12 times so far with external sources !

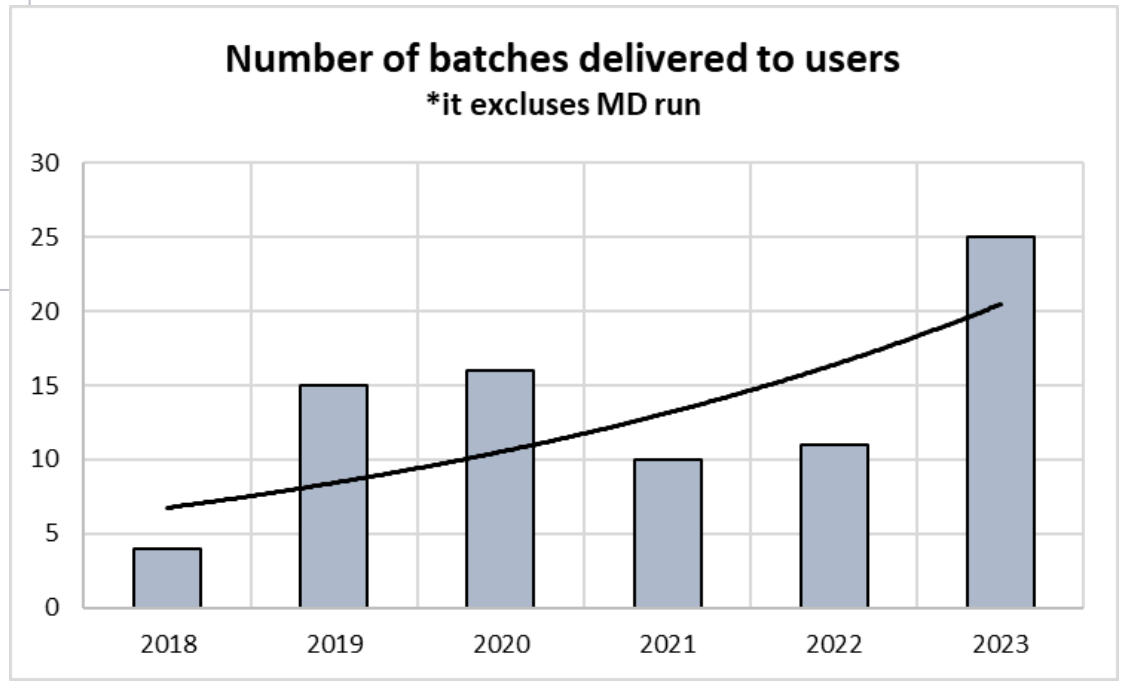
An overview since commissioning

CERN-MEDICIS – an overview since commissioning

Year	Mode of operation
2018	CERN PSB External sources
2019	External sources (Long shutdown)
2020	External sources (long shutdown)
2021	CERN PSB External sources
2022	CERN PSB External sources
2023	CERN PSB External sources



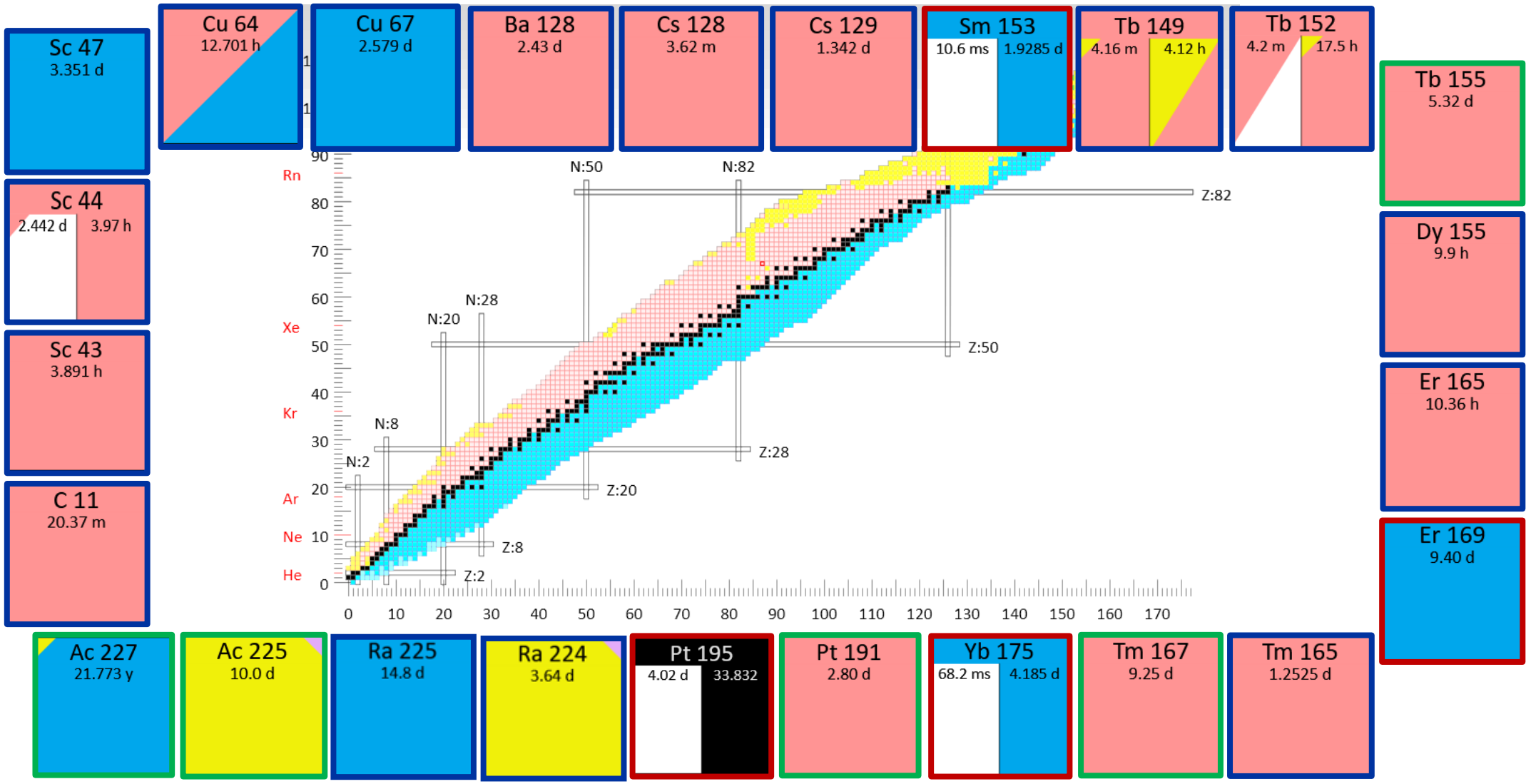
3.8 GBq collected until now in 2023
… and we are still in operation !



Intervention doses remain low despite significant increase of activity collected (ALARA)

MEDICIS radionuclides so far …

CERN-MEDICIS – our list of radionuclides



External sources

Produced at CERN PSB

Both production modes

CERN-MEDICIS within PRISMAP

European project PRISMAP

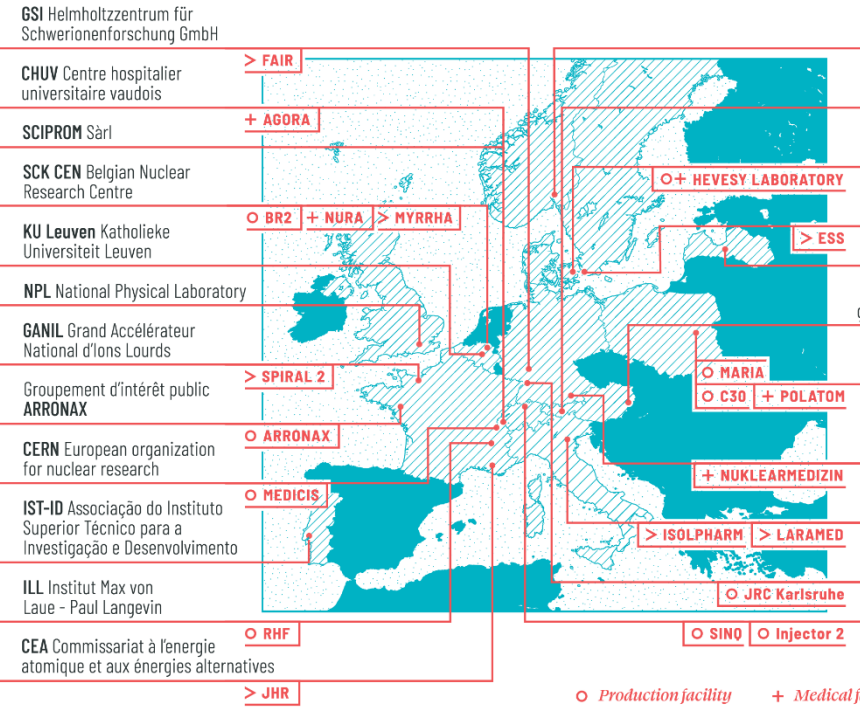
"A network of world-leading European facilities (…) has been established to offer the broadest catalogue of radionuclides for medical research."

Established

Under development

Our portfolio of medical radionuclides

43 Sc Scandium	44 Sc Scandium	47 Sc Scandium	52 Mn Manganese	64 Cu Copper	67 Cu Copper	103 Pd Palladium																	
111 Ag Silver	128 Ba Barium	128 Cs Caesium	135 La Lanthanum	153 Sm Samarium	149 Tb Terbium	152 Tb Terbium																	
155 Tb Terbium	161 Tb Terbium	165 Tm Thulium	165 Er Erbium	169 Er Erbium	175 Yb Ytterbium	199 Au Gold																	
203 Pb Lead	211 At Astatine	213 Bi Bismuth	223 Ra Radium	224 Ra Radium	225 Ac Actinium	227 Th Thorium																	



2023 overview and highlights

CERN-MEDICIS – view of 2023 productions so far

Cs-129
1x 91 MBq
1x 140 MBq
1x 1 GBq

Ba-128
1x 60 MBq
1x 340 MBq

CHUV, Lausanne, CH

Ra-224/Pb-212*
1x 50 MBq

1x 80 MBq
*M.Inzamam project

DTU, Denmark

Ra-225/Ac-225*
1x 60 MBq Ra-225
+
1x 11 MBq Ac-225

PAEC, Pakistan
KUL, Belgium
IRA, Lausanne, CH

1x 35 MBq Ra-225
+
1x 4 MBq Ac-225

KUL, Belgium

1x 15 MBq Ra-225

NPL,UK

1x 140 MBq Ra-225

*J.Johnson PhD thesis

PAEC, Pakistan

40% efficiency repeated twice for elemental Ra !

Tm-167
1x 20 MBq
1x 92 MBq

NPL,UK
PSI, CH

Tm-165
1x 12 MBq
1x 180 MBq

NPL,UK
DTU, Denmark

Er-169
1x 150 MBq
1x last separation about to start

PSI, CH

Sm-153
1x 130 MBq
1x 1.2 GBq

Heidelberg Hospital, GE

In development:

Univ. Bordeaux, FR
NPL, UK

Tb-155
1x 4 MBq
1x 2 MBq*
W. Wojtaczka PhD thesis

Sc-47 (+Sc-44m)
1x 4 MBq
1x 3 MBq

Sc-46
1 x 2.5 MBq
(>2% eff. ! *)
E.Mamis PhD thesis

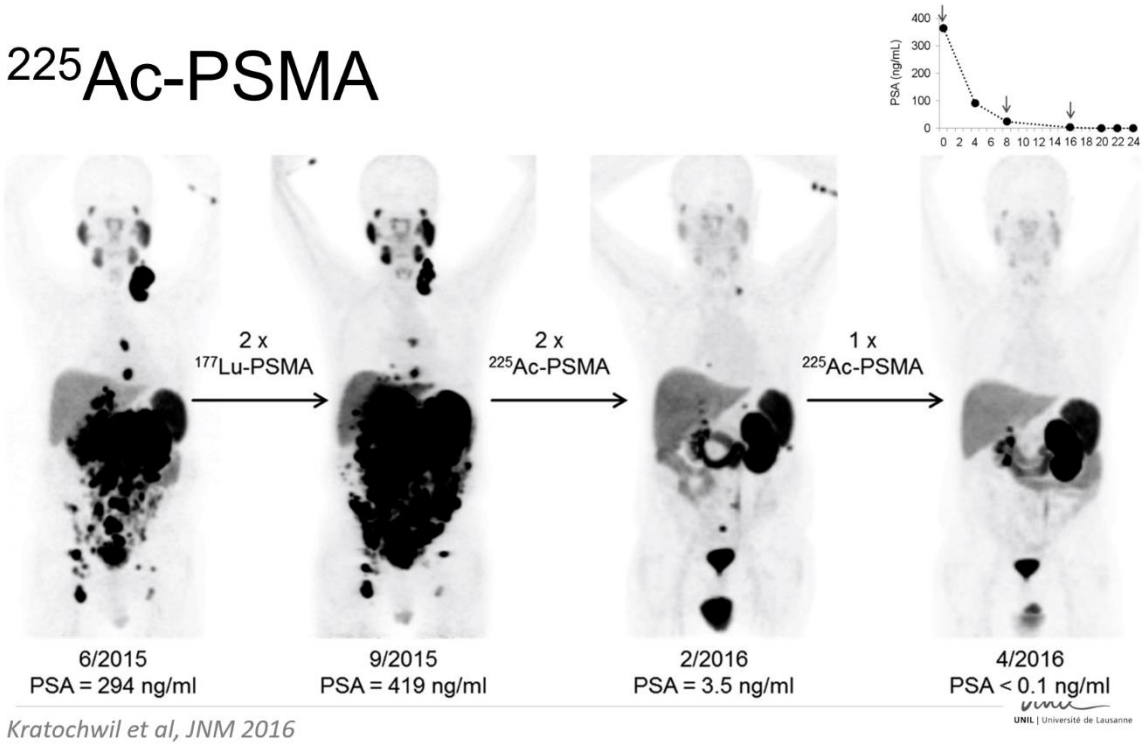
All values presented are at the time of the End Of Collection (EOC)

Status on 24/11/2023

CERN-MEDICIS: radionuclides and research projects

Alpha emitters: Ra/Ac-225 and Ra-224/Pb-212

^{225}Ac-PSMA

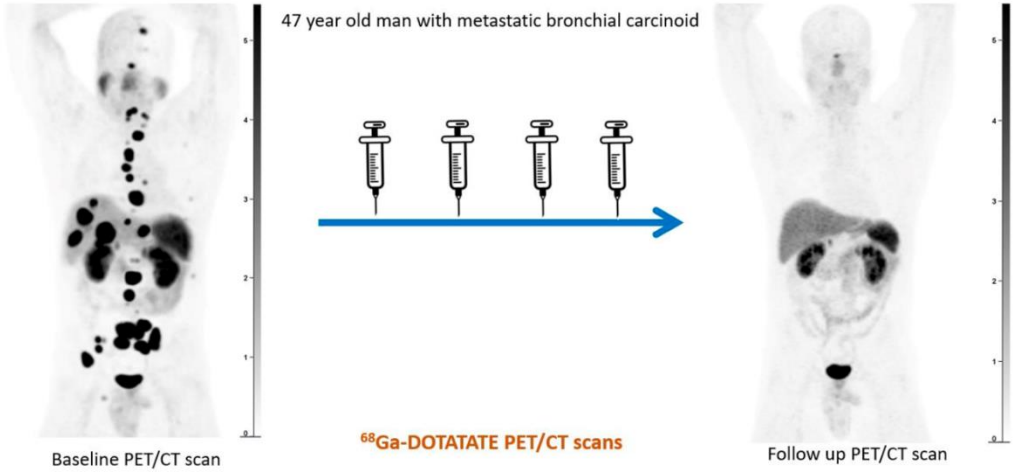


Kratochwil et al, JNM 2016

40% separation efficiency achieved and repeated for elemental Ra at MEDICIS !

^{212}Pb-DOTAMTATE

Phase 1 clinical trial of Alpha particle PRRT with ^{212}Pb-DOTAMTATE



Delpassand et al JNM 2022

*Kratochwlill et al. Journal of nuclear medicine, 2016
**Delpassand et al. Journal of nuclear medicine, 2022

Courtesy of Prof. John Prior (CHUV)

CERN-MEDICIS: radionuclides and research projects

Cs-129, Ba-128/Cs-128

THE IN-VIVO GENERATOR ^{128}BA/^{128}CS : A NEW CALCIUM SURROGATE FOR TREATMENT OF OSTEOSARCOMA

Results:
Ba-128/Cs-128 accumulates in bones
BUT also in the kidneys

Question:
Is it due to Ba or Cs?

→ MEDICIS provided pure Cs-129 to solve this question

→ Strong uptake of Ba-128 in the bones confirmed

→ Strong uptake of Cs-129 in the kidneys

Preclinical PET images & Dosimetry

- ^{128}Ba/^{128}Cs strongly accumulates in the bones of mice, but also in the kidney according to the physiological status of the animal (Figure1). It is important to understand this undesirable kidney accumulation as it will severely impact the dosimetry of ^{128}Ba/^{128}Cs in patient

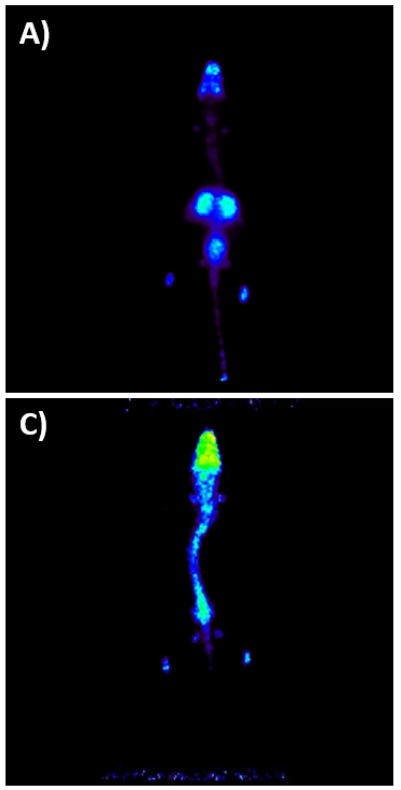
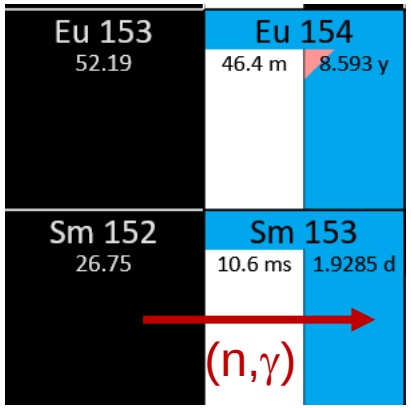


Figure 1: Preclinical PET images of mice 24 hours post injection of ^{128}Ba/^{128}Cs. A) anesthetized with isoflurane. B) anesthetized with xylazine/ketamine and c) sacrificed (same condition as biodistribution)

"Bone cancer"

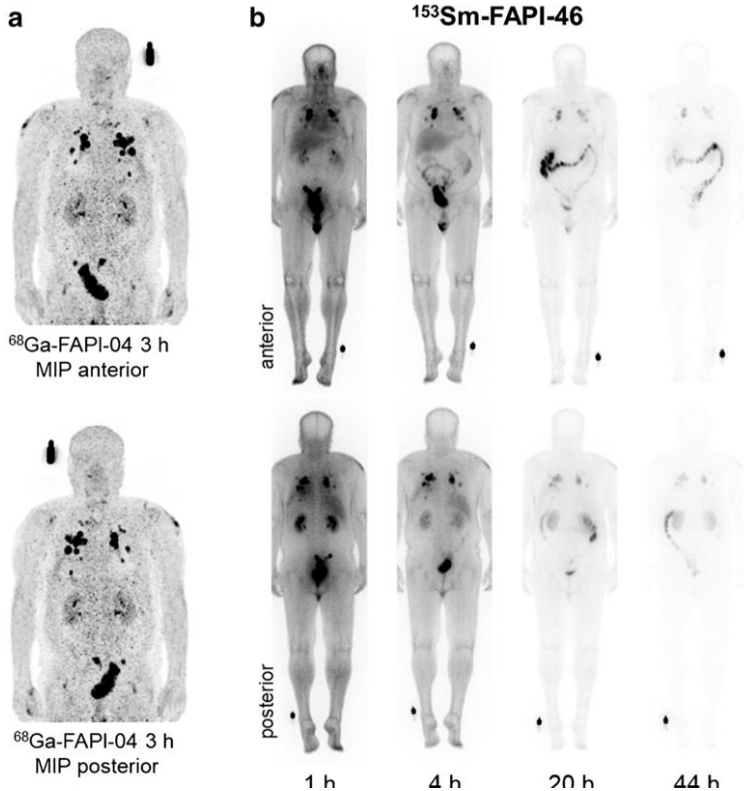
CERN-MEDICIS: radionuclides and research projects

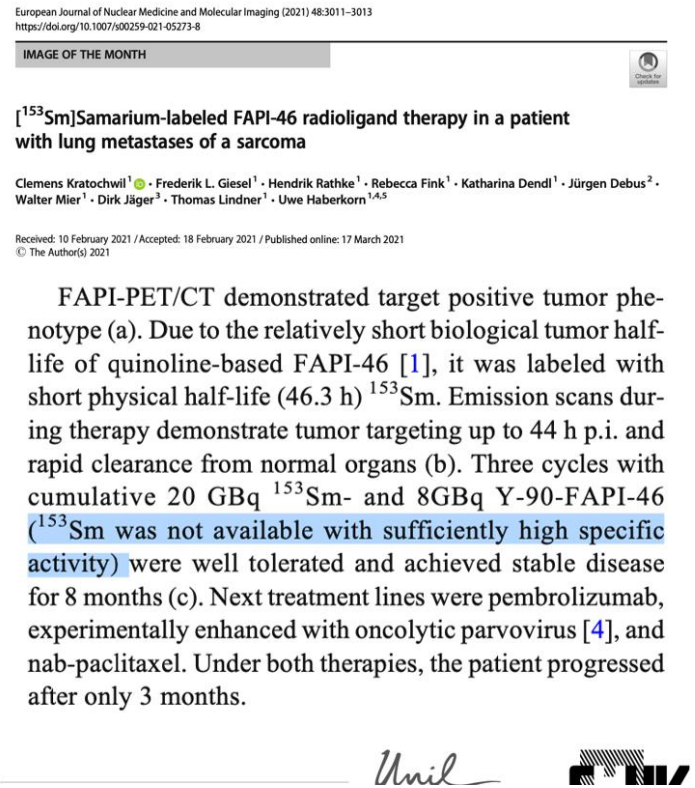
Sm-153



- Currently used for **pain palliation** of advanced bone metastasis **(Quadramet©)**
- Low specific activity of the carrier-added production route Sm-152(n,γ)Sm-153 **due to the high ratio Sm-152 (stable) / Sm-153 (radioactive)**

^{153}SM-FAPI-46 RADIOLIGAND THERAPY WITH HIGH-MOLAR ACTIVITY ^{153}SM





European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:3011–3013
https://doi.org/10.1007/s00259-021-05273-8

IMAGE OF THE MONTH

[^{153}Sm]Samarium-labeled FAPI-46 radioligand therapy in a patient with lung metastases of a sarcoma

Clemens Kratochwil[1] · Frederik L. Giesel[1] · Hendrik Rathke[1] · Rebecca Fink[1] · Katharina Dendl[1] · Jürgen Debus[2] · Walter Mier[1] · Dirk Jäger[3] · Thomas Lindner[1] · Uwe Haberkorn[1,4,5]

Received: 10 February 2021 / Accepted: 18 February 2021 / Published online: 17 March 2021
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FAPI-PET/CT demonstrated target positive tumor phenotype (a). Due to the relatively short biological tumor half-life of quinoline-based FAPI-46 [1], it was labeled with short physical half-life (46.3 h) ^{153}Sm. Emission scans during therapy demonstrate tumor targeting up to 44 h p.i. and rapid clearance from normal organs (b). Three cycles with cumulative 20 GBq ^{153}Sm- and 8GBq Y-90-FAPI-46 (^{153}Sm was not available with sufficiently high specific activity) were well tolerated and achieved stable disease for 8 months (c). Next treatment lines were pembrolizumab, experimentally enhanced with oncolytic parvovirus [4], and nab-paclitaxel. Under both therapies, the patient progressed after only 3 months.

Courtesy of Prof. MD John Prior (CHUV)

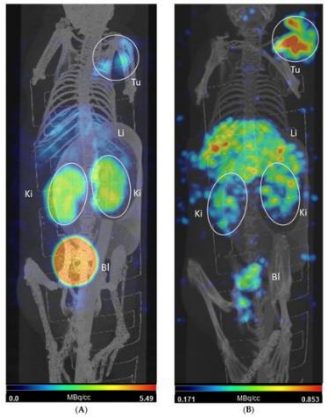
CERN-MEDICIS: radionuclides and research projects

Sm-153

Use of Sm-153 for Targeted Radionuclide Therapy only possible if Sm-153 is produced with higher specific-activity (higher ratio Sm-153/Sm-152)

Need to pass by mass-separation → CERN-MEDICIS **!**

- Up to 13% separation efficiency, with MELISSA laser ionization
  - **Final product suitable for radiolabelling** at SCK CEN (BE)



Production of Sm-153 With Very High Specific Activity for Targeted Radionuclide Therapy

Michiel Van de Voorde [1*], Charlotte Duchemin [2,3], Reinhard Heinke [2,3], Laura Lambert [3], Eric Chevallay [3], Thomas Schneider [4], Miranda Van Stenis [4], Thomas Elias Cocolios [2], Thomas Cardinaels [1,5], Bernard Ponsard [1], Maarten Ooms [1], Thierry Stora [3] and Andrew R. Burgoyne [1*]

pharmaceutics — MDPI

Article

Exploring the Potential of High-Molar-Activity Samarium-153 for Targeted Radionuclide Therapy with [153Sm]Sm-DOTA-TATE

Koen Vermeulen [1], Michiel Van de Voorde [1], Charlotte Segers [1], Amelie Coolkens [1], Sunay Rodriguez Pérez [1], Noami Daems [1], Charlotte Duchemin [2,3], Melissa Crabbé [1], Tomas Opsomer [1], Clarita Saldarriaga Vargas [4], Reinhard Heinke [2,3], Laura Lambert [3], Cyril Bernerd [2,3], Andrew R. Burgoyne [1], Thomas Elias Cocolios [2], Thierry Stora [3] and Maarten Ooms [1,*]

"The Belgian Nuclear Research Centre and the MEDICIS research branch of CERN joined forces to produce high-A_m ^{153}Sm"

This proof-of-concept is now opening doors **towards therapy using Sm-153 mass separated at MEDICIS** → clinical translation from 2024 at the Medical Hospital of Heidelberg in Germany

MED-035

153SM-FAPI-46 RADIOLIGAND THERAPY WITH HIGH-MOLAR ACTIVITY 153SM

UNIVERSITÄT HEIDELBERG ZUKUNFT SEIT 1386

"5 patients pre-selected to have metastatic FAP-positive tumor diseases who already exhausted all approved treatment will be offered to receive experimental therapy according to German Law ("Heilversuch" = compassionate care)"

CERN-MEDICIS – conclusions, milestones & outlooks

One of the few facilities at CERN to run during Long Shutdowns

already proven in 2019 and 2020 with great achievements !

2017

Facility commissioning
1st Radioactive Ion Beam produced !

2018

First board meeting and projects approved

First year of operation
- First direct irradiation at ISOLDE

Start of radiochemistry

2019

Commissioning of MELISSA laser laboratory
First laser ionized beam

First full year of operation with external sources only

1 GBq total collected and shipped

2020

2nd year successful year of operation with external sources only
Despite Covid Crisis

Record efficiency of 53% !

Online g-spec monitoring
Enabled the detection of sputtering effect/issue
Evolution of implantation layers

2021

Restart with proton at CERN-ISOLDE

Glovebox purchase

Introduction of KPIs

First irradiation on new irradiation station (GPS ISIS)

Start of the PRISMAP European Project

2022

Double collection system in place

Successful first double collection !

Use of glovebox for Ac-227 manipulation

On-site HP Ge detector for shipping optimization

2023

34 projects approved so far

Optimization of beam position for direct irradiation

First double Ra-224/225 collection

- First proof of concept of Ra-224/Pb-212 generator
- First Raman laser ionization study for radium

1 GBq collected in a single batch from irradiated target
1 GBq collected in a single batch from external target

2024

First clinical translation of mass separated Sm-153 !

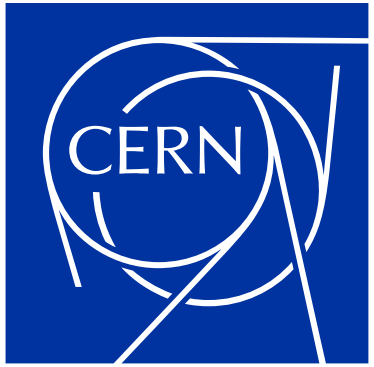
New collimator system to avoid early saturation of online-γ-spectrometer

First Ra-223 collection will be tested

A BIG THANKS TO ALL THE PEOPLE, GROUPS, SERVICES, INSTITUTES, COLLABORATION … INVOLVED IN MEDICIS!

THE Dream-Team

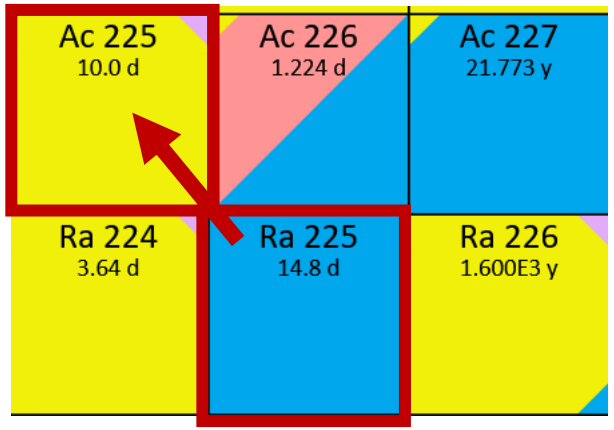
THANK YOU FOR YOUR ATTENTION !



home.cern

CERN-MEDICIS: radionuclides and research projects

Ra-225/Ac-225



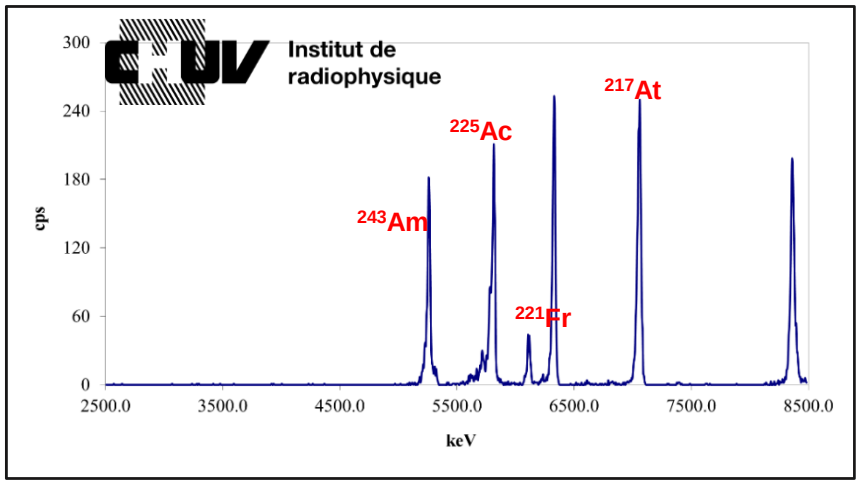
Collaboration CERN-MEDICIS, JRC Karlsruhe, KU Leuven → reach the highest Ac-225 efficiency

- Ac-225 collected from an **external** sample: **10%** reached* (measured)
- Ra-225/Ac-225 collected from **Th target** irradiated at ISOLDE: up to **40%** reached via Ra-225** (in-target production yield simulated with FLUKA)
  - Ac-225 labelled with PSMA-617 with efficiency of >97% (INMOL Cancer Hospital, Lahore)

- **Intercomparison KU Leuven (BE) / CHUV-IRA (CH) / NPL (UK)**
  "to determine the amount (if any) of Ac-227 impurities in Ac-225 produced at MEDICIS"

  Recent results: two ^{225}Ac productions (May 2023 / June 2023) were characterized at CHUV/IRA
  Outcome:
  no ^{227}Ac impurity (< mBq) was identified in both ^{225}Ac samples

- **Dosimetric and radiochemistry study by CERN & CHUV-IRA (CH)**

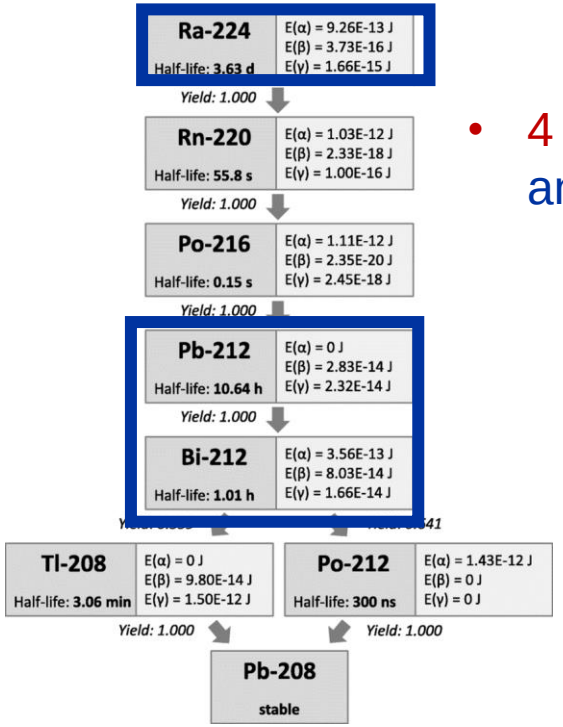


Alpha spectrum of a ^{225}Ac aliquot from a June 2023 production showing no trace of Ac-227. Measured after > 100 days (courtesy of R. Cusnir)

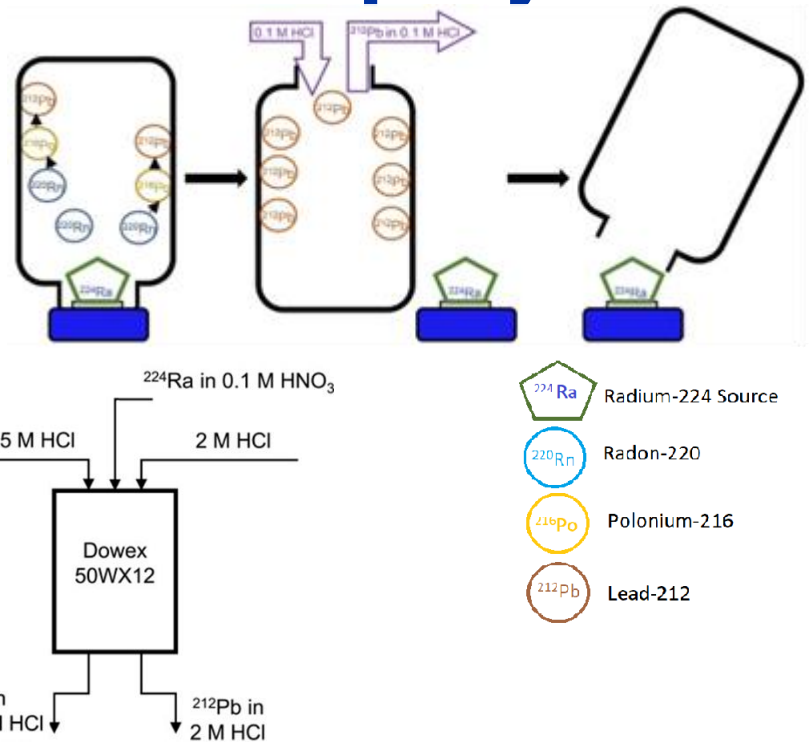
*Johnson, *et al. Sci Rep* **13**, 1347 (2023)
**Radchenko et al. Journal of nuclear medicine, 62, 11 (2021)*

CERN-MEDICIS: radionuclides and research projects

Ra-224



- 4 collections performed in 2023 up to 80 MBq for R&D and feasibility tests
  - 3 collections and generators produced using the "gas collection method": collection of emanated Rn-220
  - 1 collection used to produce a generator by using the chromatographic separation of the radionuclides.



- 80 MBq generator dispatched to DTU, Hevesy Lab, DK (PRISMAP partner institute)
  - Very successful first elution and labelling with DOTATATE combined with stability study in mouse serum
- Chromatographic generator at CERN: the **efficiency is up to 60%**
  - Working on further optimization

Li, R.G., Stenberg, V.Y. and Larsen, R.H. (2022) 'An experimental generator for production of high-purity212pb for use in radiopharmaceuticals', *Journal of Nuclear Medicine*, 64(1), pp. 173–176. doi:10.2967/jnumed.122.264009.
M. Pruszyński *et al*. (2021) 'Radiochemical separation of ^{224}Ra from ^{232}U and ^{228}Th sources for ^{224}Ra/^{212}Pb/^{212}Bi Generator', Applied Radiation and Isotopes, 172, pp. 109655. doi:10.1016/j.apradiso.2021.109655

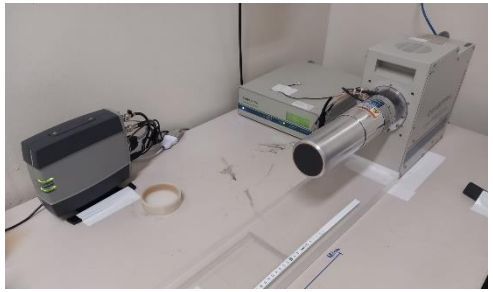
Ongoing project
Scandium thermal release studies from irradiated nat-Ti and nat-V foils

Goal is to understand the thermal release of Sc from nat-Ti and nat-V for subsequent efficient mass separation at CERN-MEDICIS to produce high specific activity Sc-44m/g and Sc-47 for medical applications.

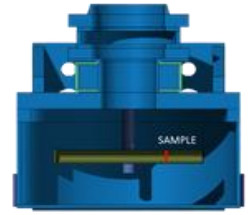
1 g of nat-Ti or 3.4 g of nat-V*

*the mass difference is to compensate from the lower production yield in V in comparison with Ti

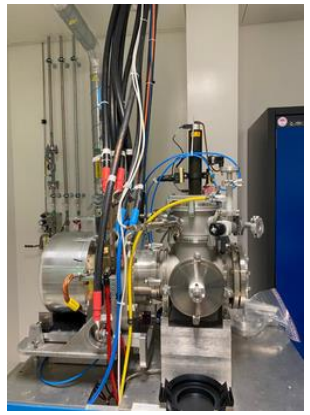
Irradiation at CHARM facility by the secondary neutrons produced from the impact of 24 GeV protons impinging on a metallic target with an average intensity of 5E10 protons/second over 5 days



Gamma spectrometry to determine sample activity before and after heating



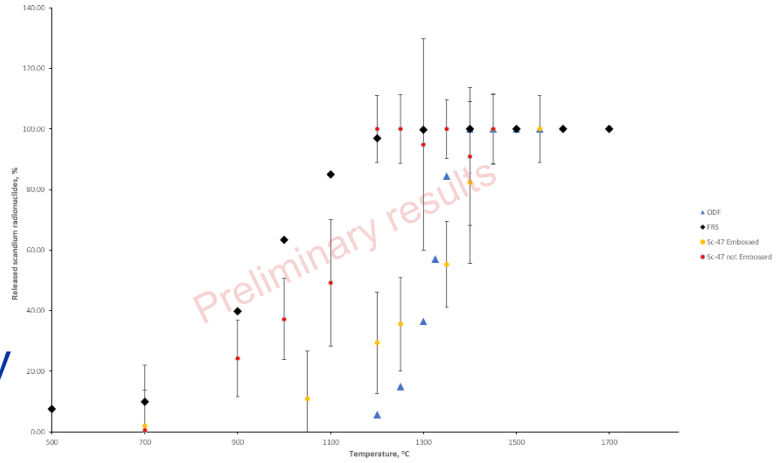
View of a sample placed inside the target container of a typical ISOL target unit. The vacuum and heating is controlled. Temperature up to 2000 degrees Celsius can be reached with a vacuum around 1E-6 mbar

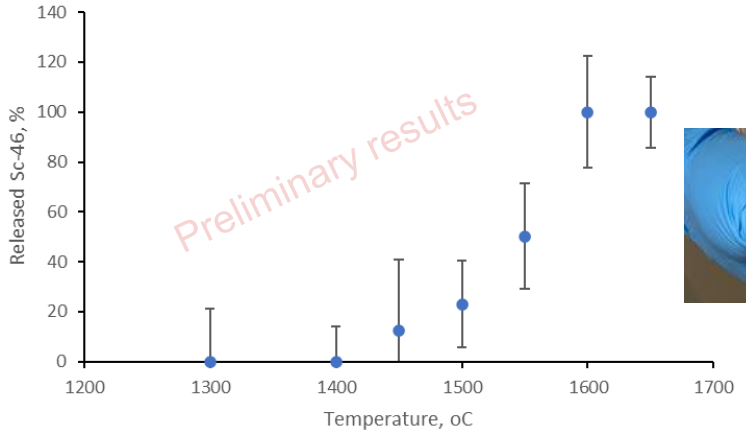


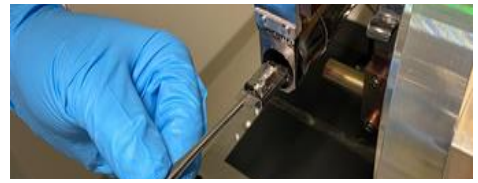
Experimental setup for scandium thermal release studies

Led to a positive impact on the Sc mass separation efficiency increase !

Systematically do this study for non-easy-to-release radionuclides !!!







Sample retrieval after heating

Courtesy of P. Kalnina, E. Mamis.
Strong support from HSE-RP for irradiation opportunities at CHARM and experiments