Production of innovative medical radionuclides by mass separation

Prof. Thomas Elias Cocolios
KU Leuven Institute for Nuclear and Radiation Physics
INPC 2025, Daejeon, South Korea

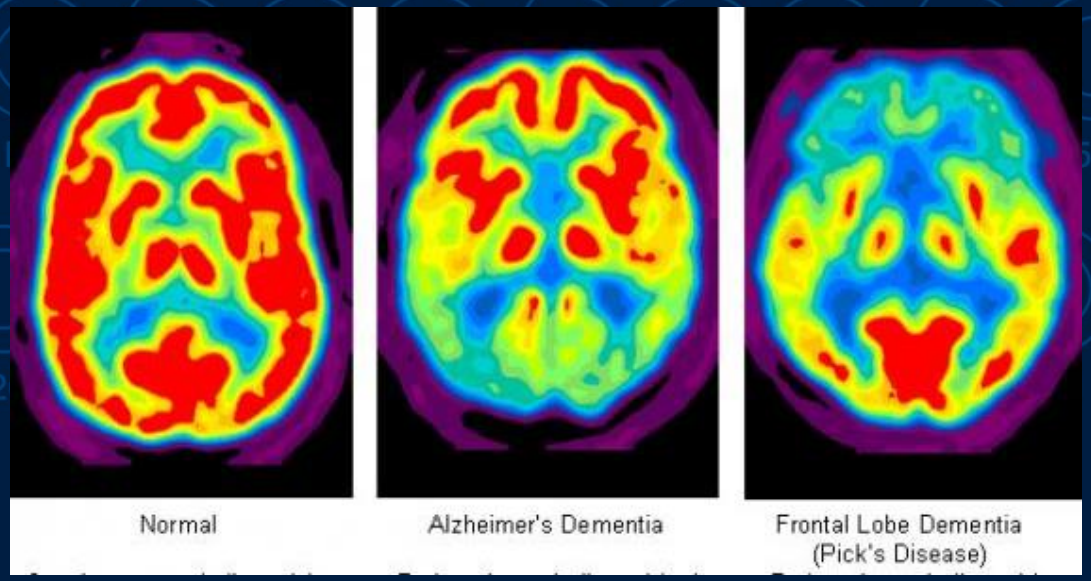
KU LEUVEN

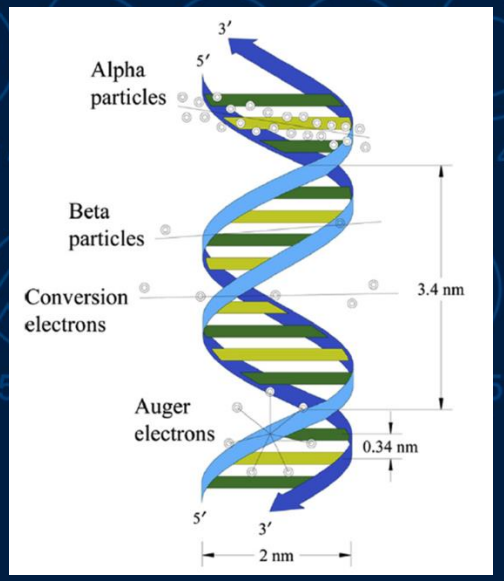
Overview

- Basic concepts of nuclear medicine
- The supply challenge
- Radionuclide mass separation
- PRISMAP *et plus si affinités…*

Medical radionuclides

Some basics of nuclear medicine





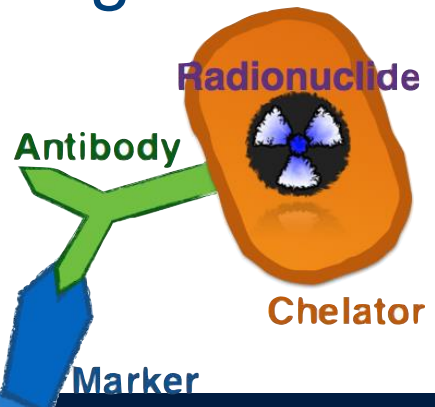
KU LEUVEN

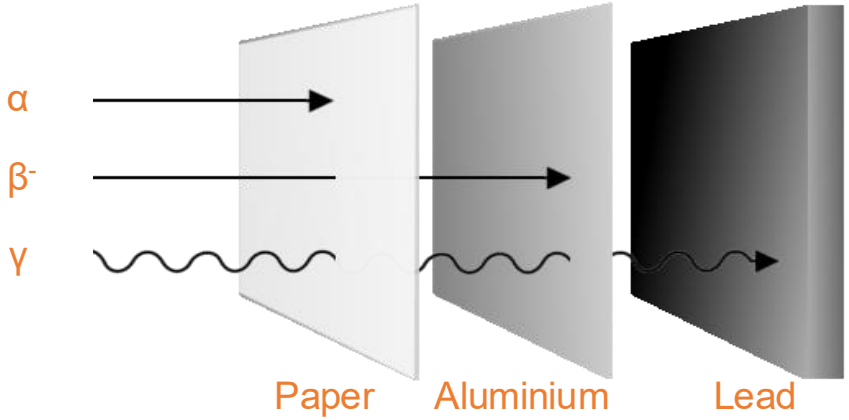
Molecular imaging

A radionuclide is transported to a specific location in the body where it decays with the emission of a γ ray.

The γ ray penetrates the tissues and exits the body so that it may be recorded externally to visualize where it decayed.

Multiple orientations yield a 3D tomographic reconstruction of the image.

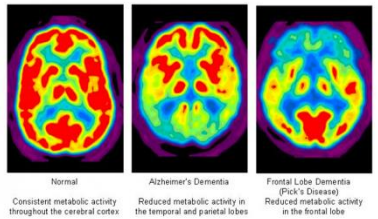




Targeted action

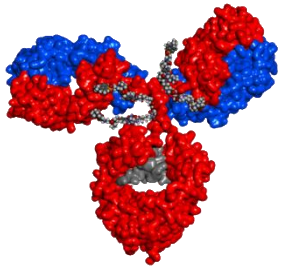
The body uses some trace elements for specific actions:

- iodine for thyroid functions
- calcium in the bones



A radioactive isotope can be included in a molecule involved in metabolic activities:

- sugar-equivalent FDG



Cells may display receptors that are specific and can be linked to by targeting m

- peptides
- hormones
- antibodies

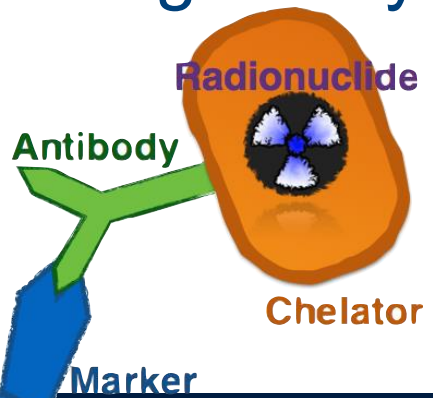
Important to match biodistribution to half-life!

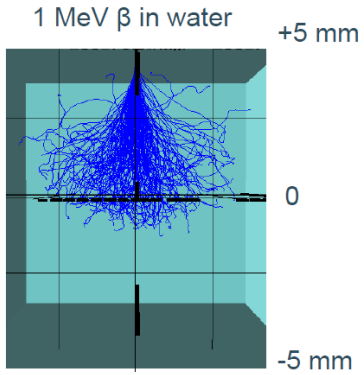
Switching to therapy

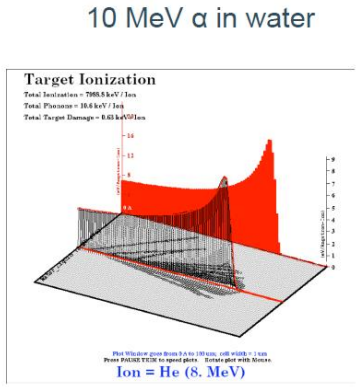
Replacing the γ-ray emission with charged particle emission yields therapeutic effect.

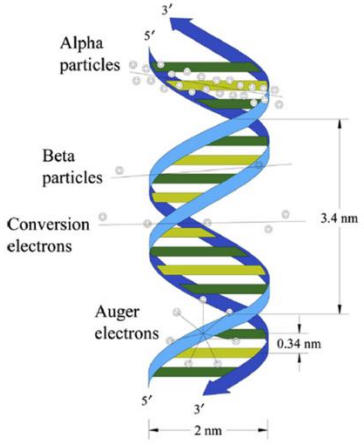
β^- particles may reach up to a few mm, α particles reach but a few cells, Auger electrons act within a cell.

For an efficient treatment, the DNA of the targeted cell must be damaged beyond repair









Theranostics

If a single vector molecule can be identified with interchangeable radioisotopes, then its efficacy and properties can be **tested with molecular imaging** and then **applied with therapy**.

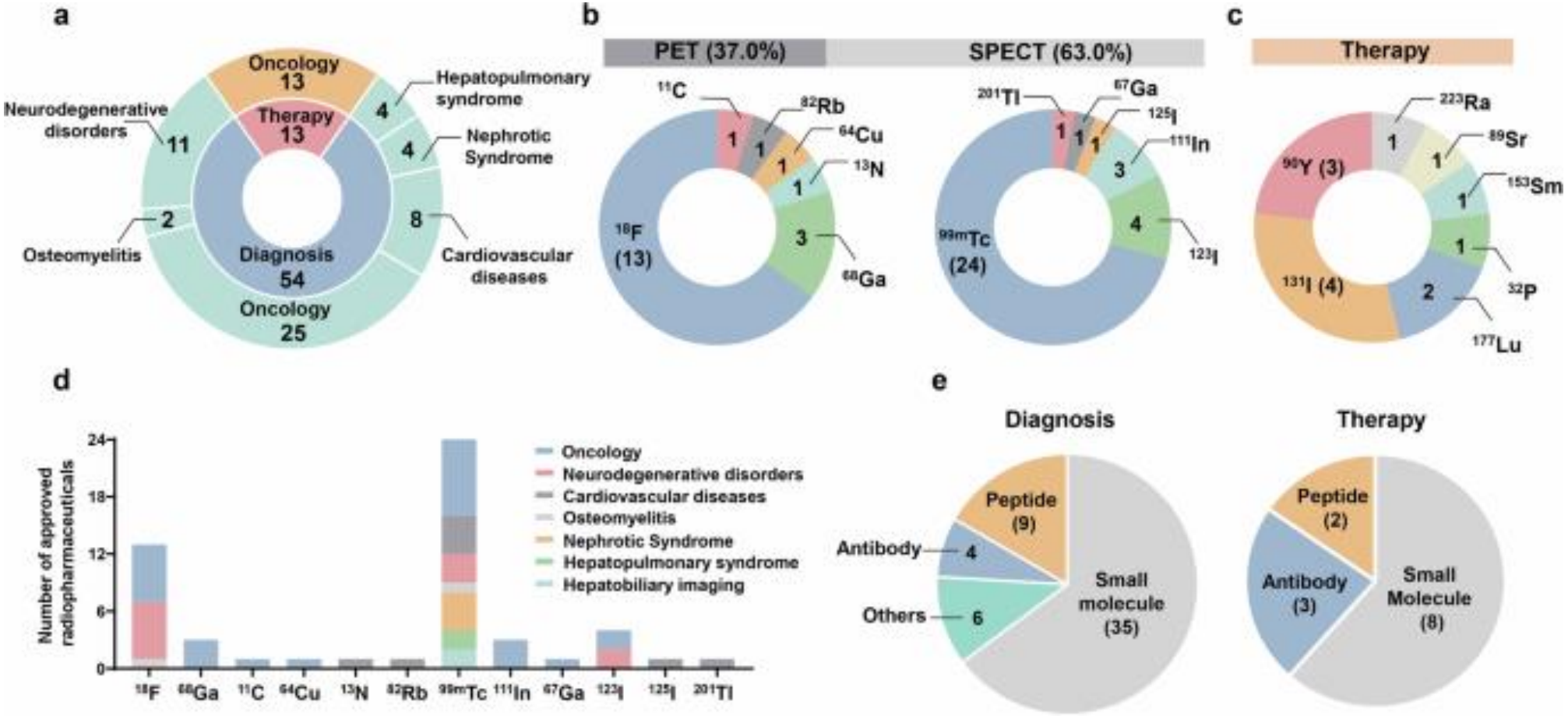
If a single radioisotope decays by both γ-ray or β^+ emission and α or β^- emission, then that single radioisotope can be used to **treat** and at the same time **monitor the patient dose** and the treatment's efficacy.

Important to match biodistribution to half-life!

Final aim: personalized medicine where the treatment is tailored to the needs of the patient

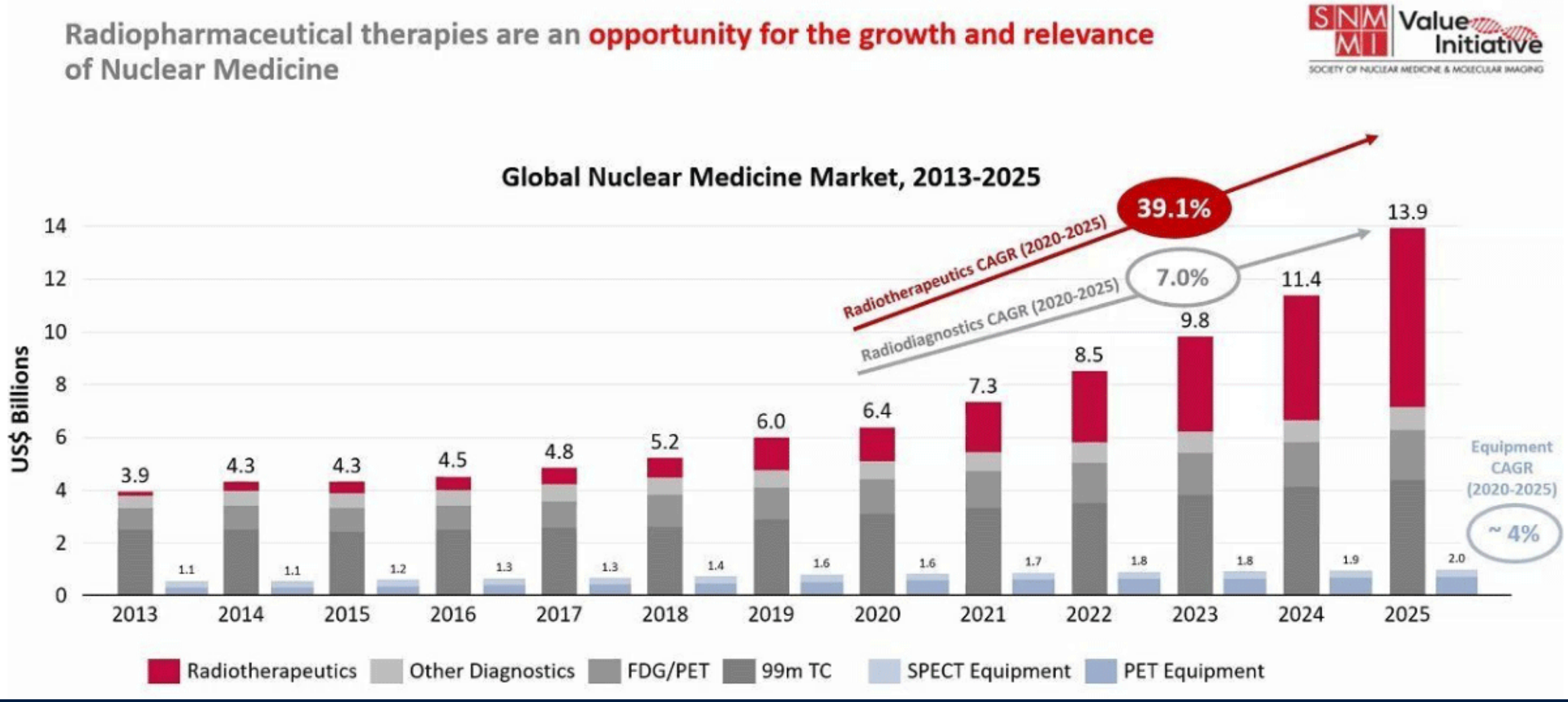
KU LEUVEN

Medical radionuclide landscape



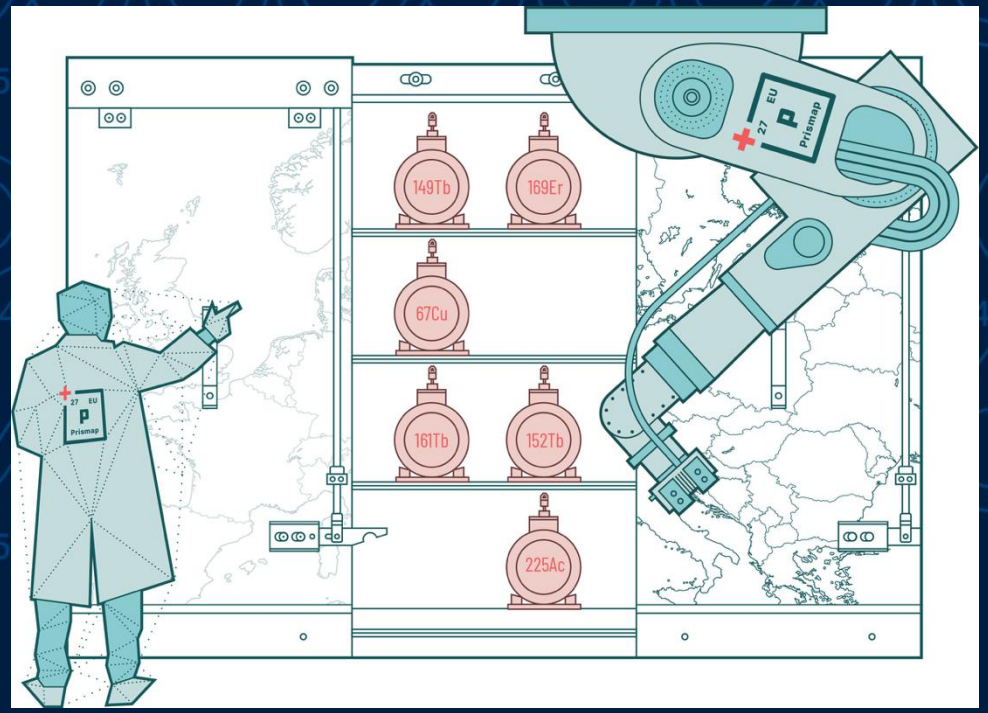
*S. Zhang et al., Radiopharmaceuticals and their applications in medicine, Signal Transduction and Targeted Therapy **10** (2025) 1.*

Medical radionuclide market



MEDraysintell, as presented at the SNMMI ivrtual meeting 2021 and retrieved from https://www.oncidiumfoundation.org/2021/06/17/global-nuclear-medicine-market-2013-2025/#

Radionuclide shopping:
How we choose the best radionuclide



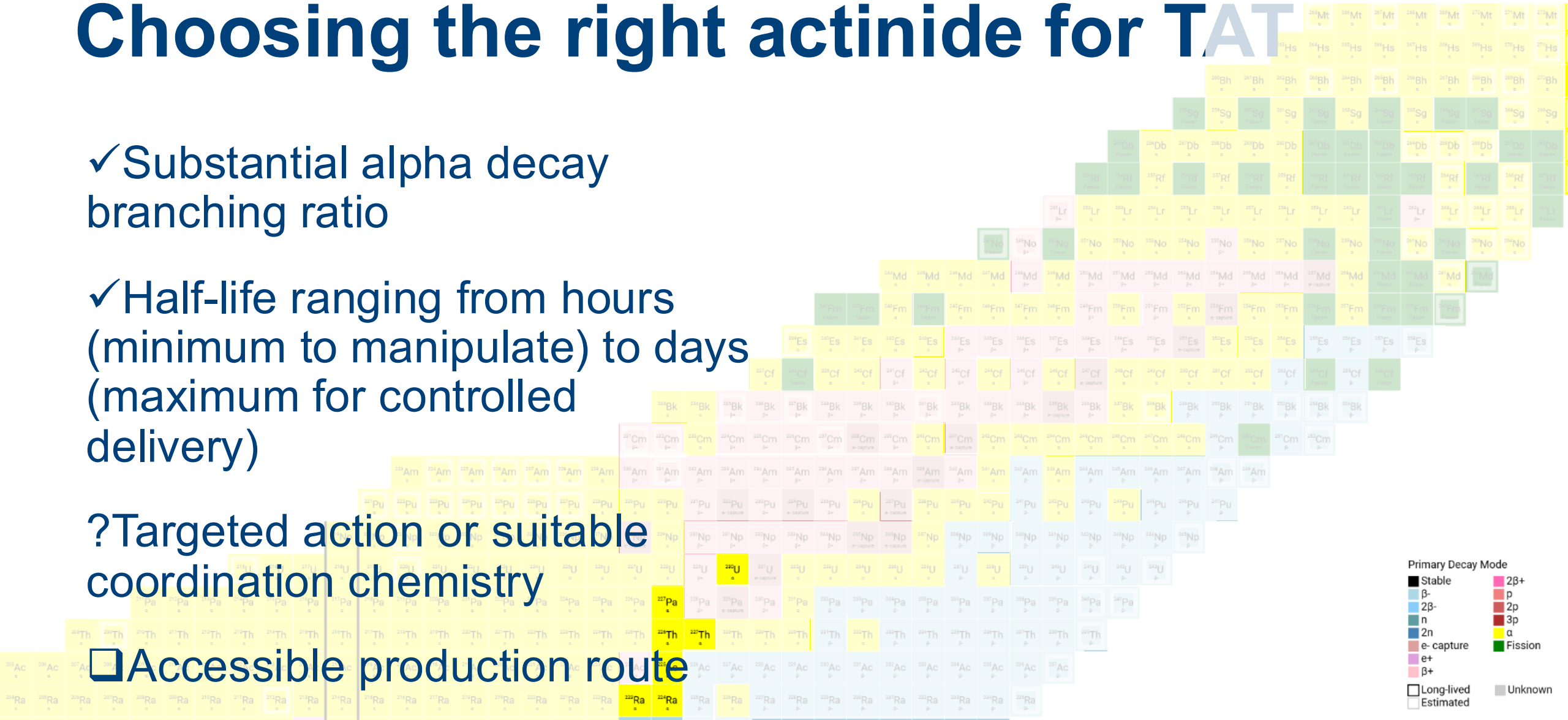
Choosing the right actinide for TAT

✓Substantial alpha decay branching ratio

✓Half-life ranging from hours (minimum to manipulate) to days (maximum for controlled delivery)

?Targeted action or suitable coordination chemistry

❑Accessible production route



 The Colourful Nuclear Chart: https://people.physics.anu.edu.au/~ecs103/chart/

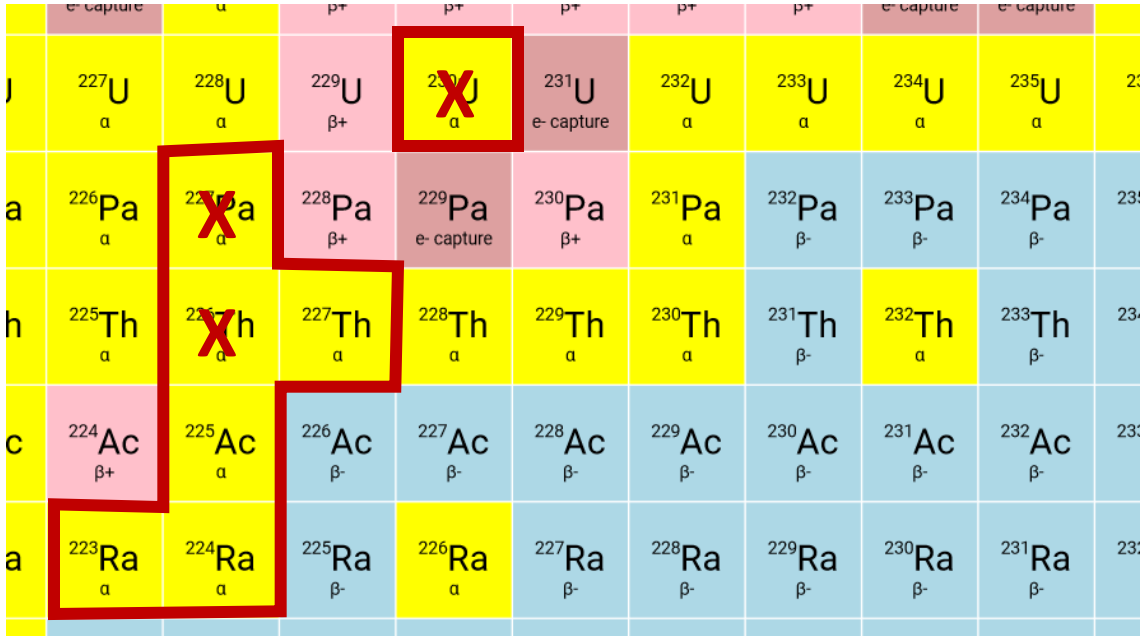
Isotopes effectively used

149 Tb Terbium

211 At Astatine

212 Pb Lead

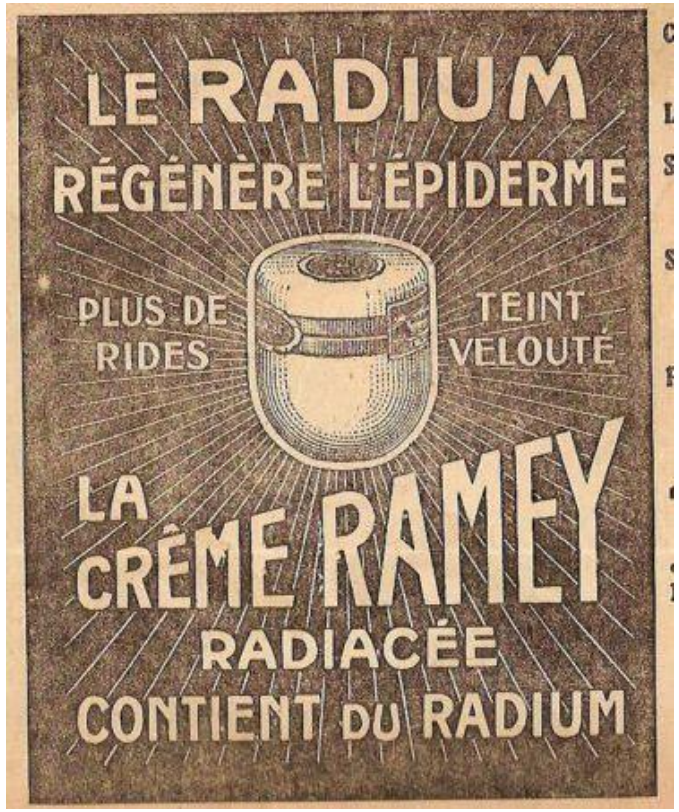
- ✓^{211}At
  - 6 clinical trials
- ✓^{223,224}Ra
  - ✓Xofigo® for the treatment of bone metastasis in castration resistant prostate cancer
  - ~200 clinical trials
- ✓^{225}Ac
  - 13 ongoing clinical trials
  - Mostly about prostate cancer
- ✓^{227}Th, ^{213}Bi, ^{212}Pb
  - <5 trials



https://clinicaltrials.gov

Radium: a long tradition

Cutaneous application



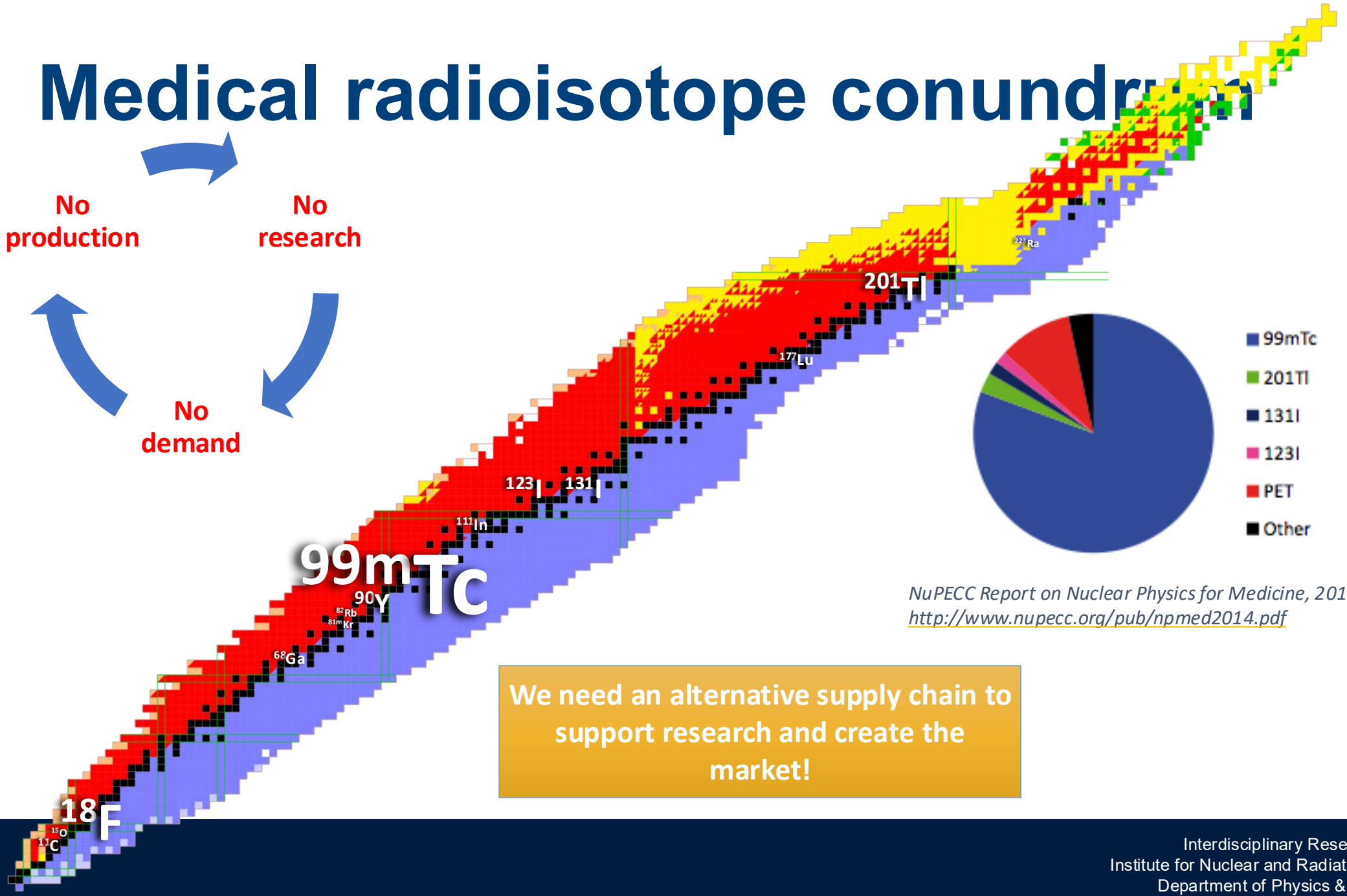
Radium salts

Medical radioisotope conundrum

No production

No research

No demand



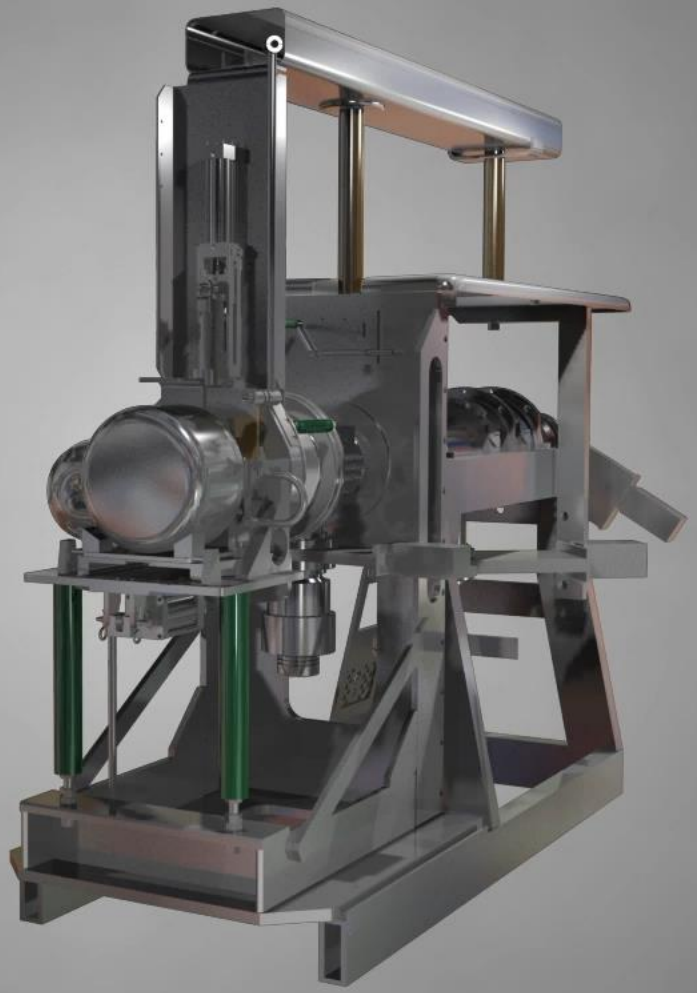
NuPECC Report on Nuclear Physics for Medicine, 2014
http://www.nupecc.org/pub/npmed2014.pdf

We need an alternative supply chain to support research and create the market!

Interdisciplinary Research Group
Institute for Nuclear and Radiation Physics
Department of Physics & Astronomy
KU LEUVEN

From CERN ISOLDE to CERN MEDICIS

KU LEUVEN

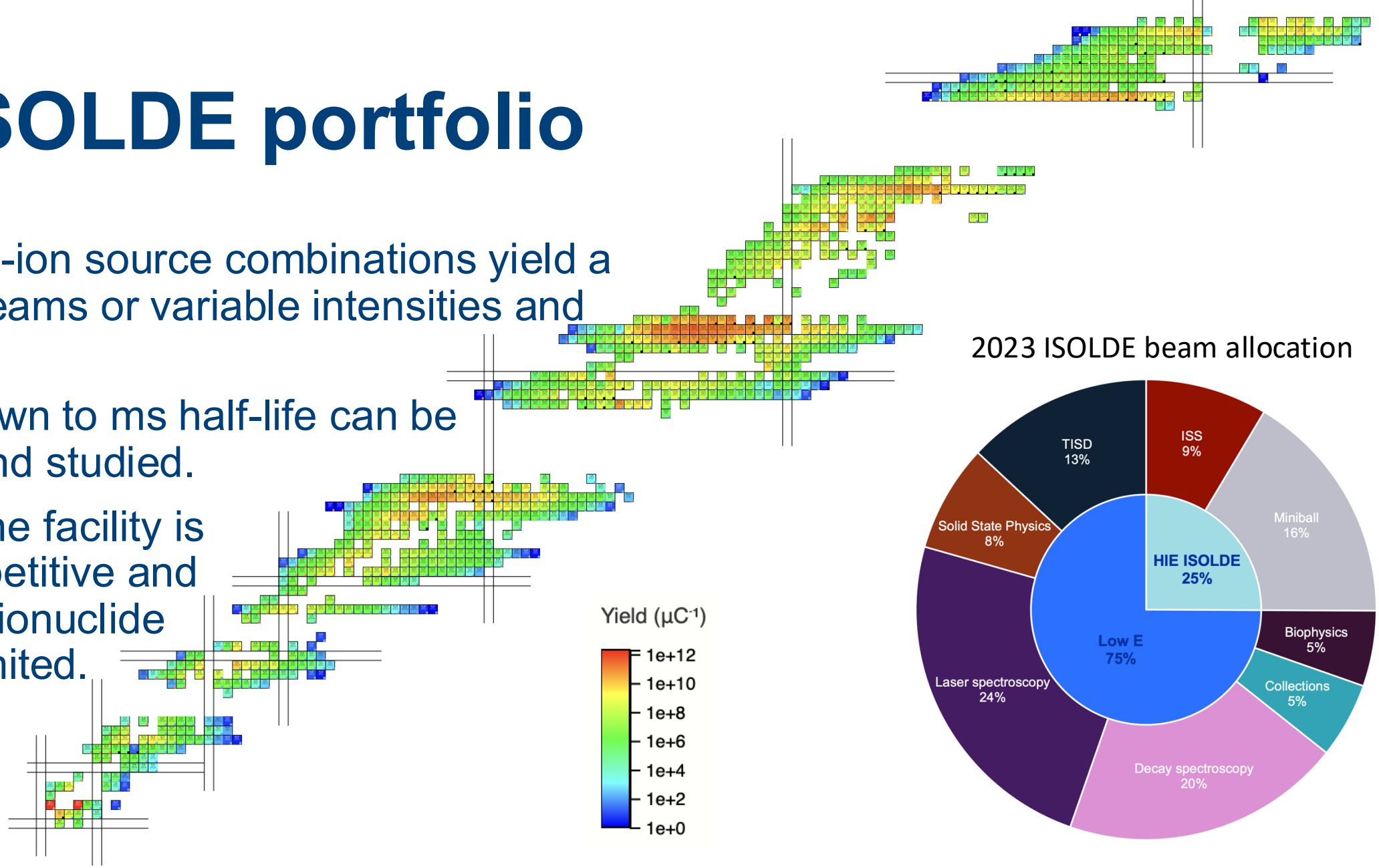


The ISOLDE portfolio

Many target-ion source combinations yield a variety of beams or variable intensities and purity.

Isotopes down to ms half-life can be extracted and studied.

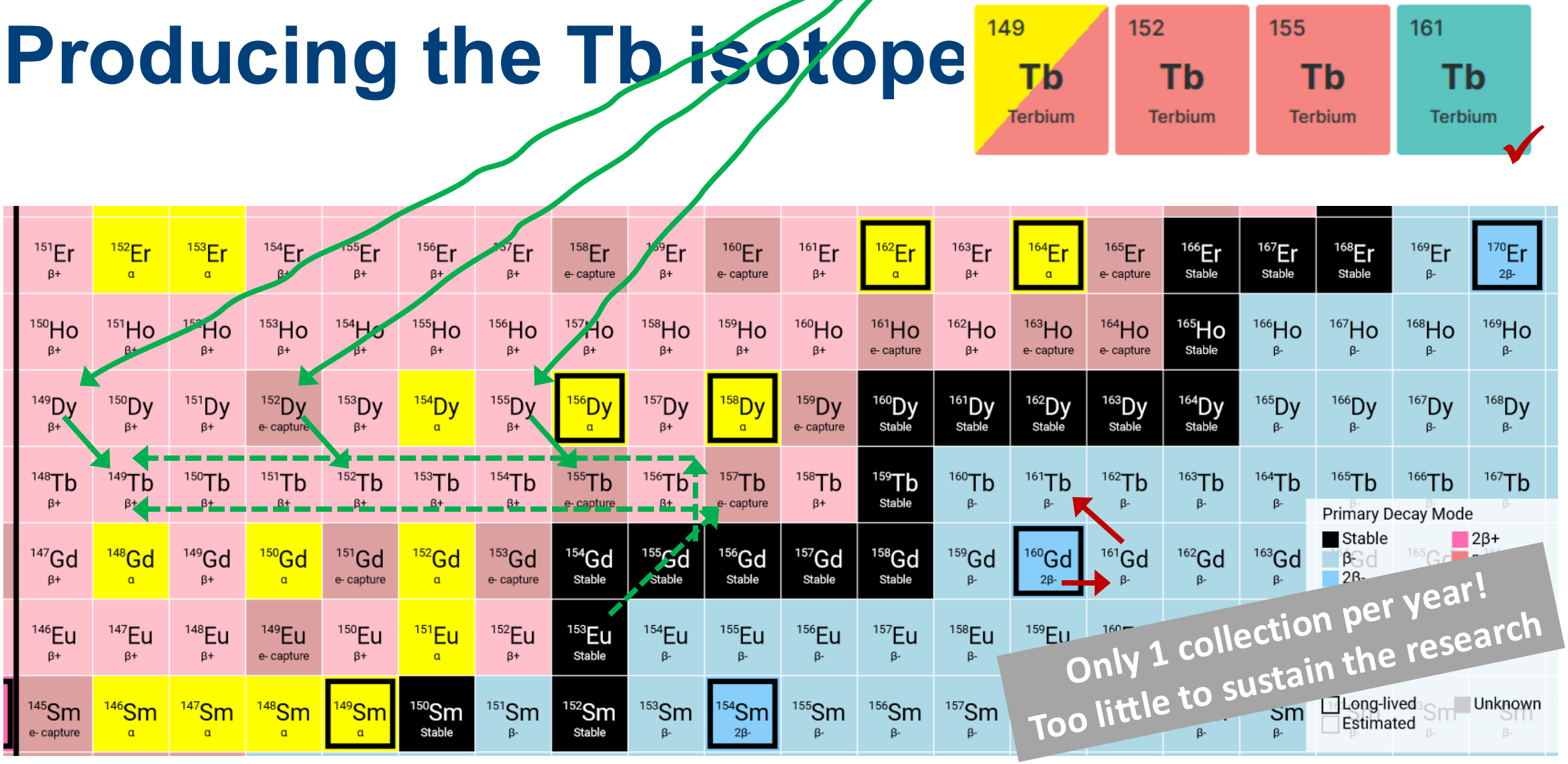
Access to the facility is highly competitive and medical radionuclide supply is limited.

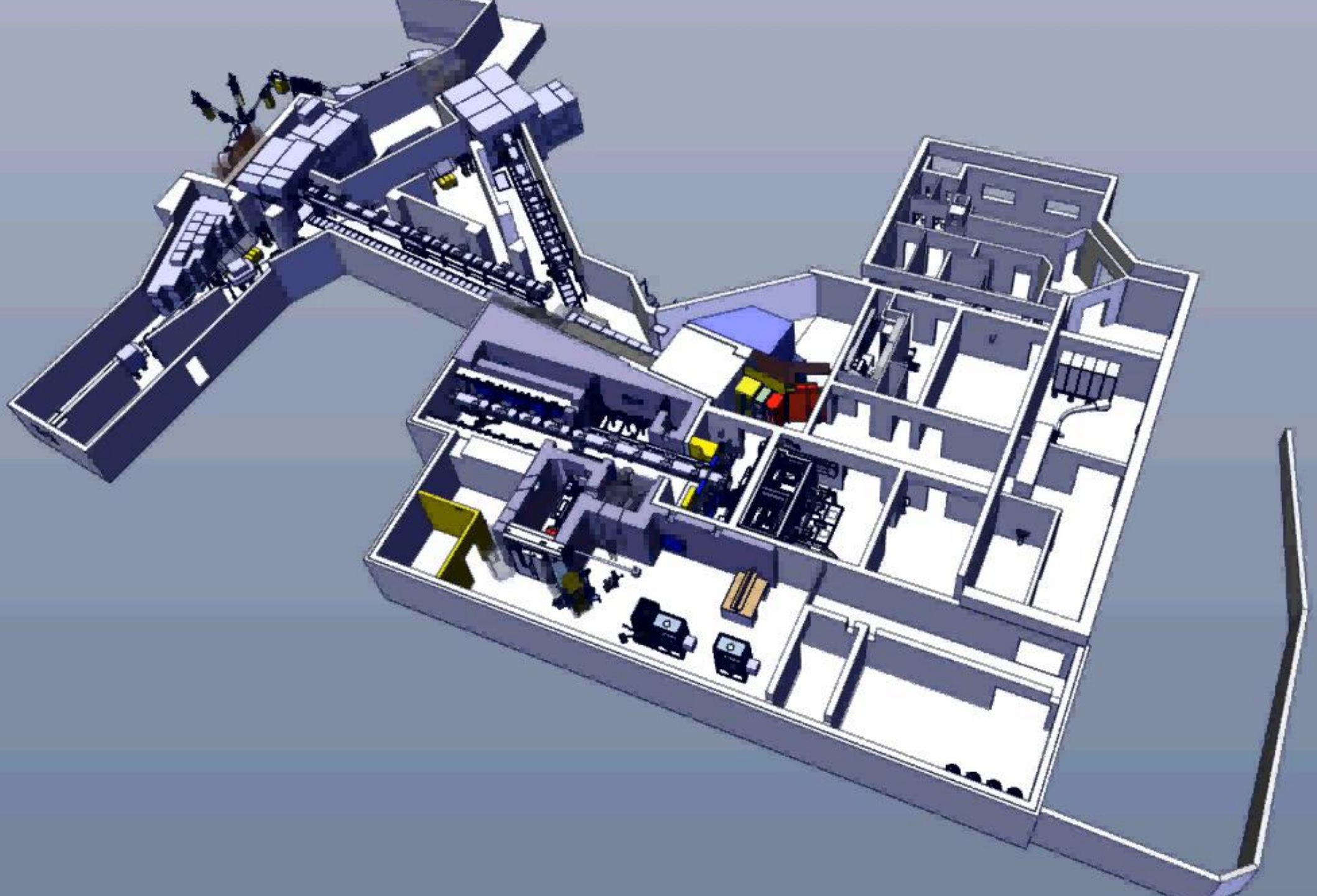


2023 ISOLDE beam allocation

https://isoyields2.web.cern.ch/IsoldeYieldChart.aspx

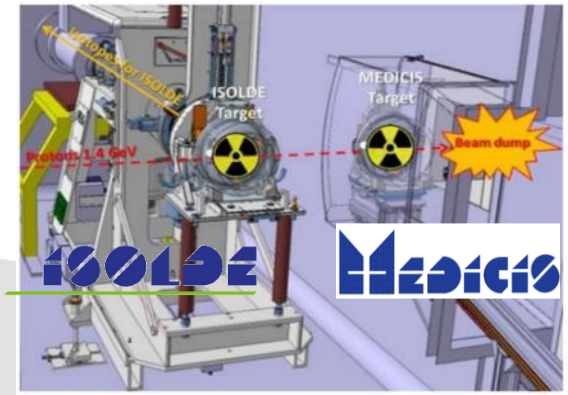
Producing the Tb isotope

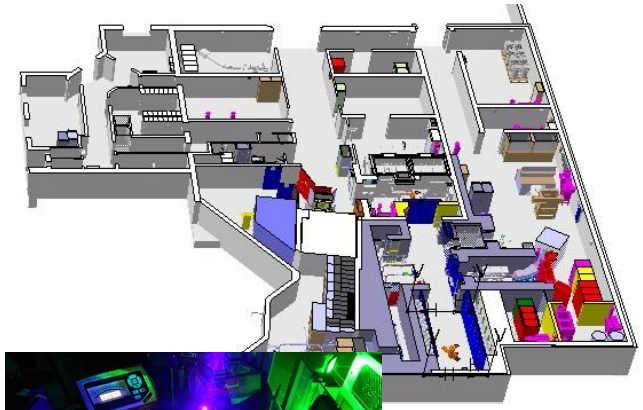




CERN MEDICIS

KUKA® handling arm





JG|U

MELISSA laser lab

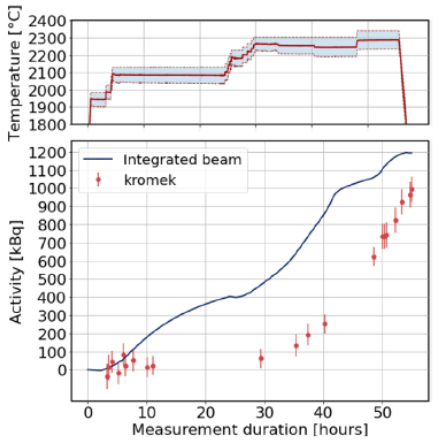
Collection point

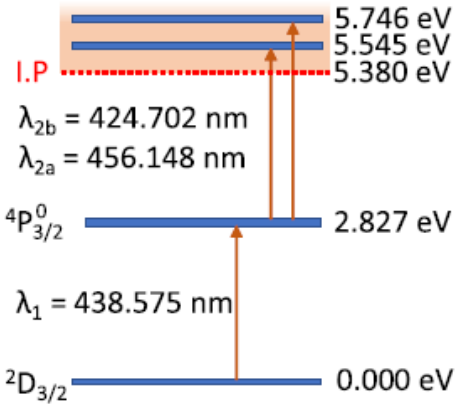
he collection of
edical research
s from CERN or
d sources

KU LEUVEN

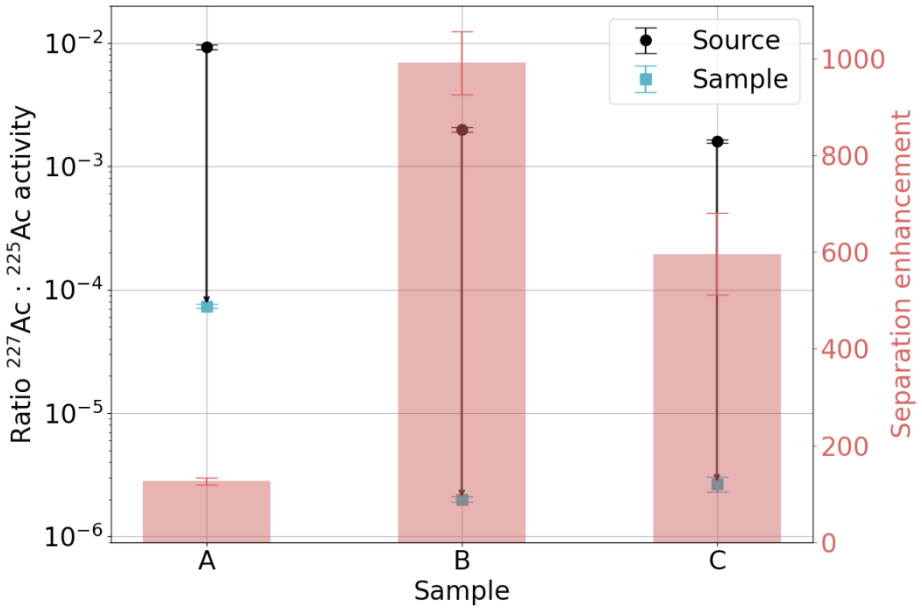
^{225}Ac production

- High-energy proton-induced spallation of ^{232}Th produces large amounts of ^{227}Ac.
- TRIUMF: ^{225}Ra generator by radiochemistry, limited production yields.
- MEDICIS: (laser +) mass separation.
- Highest achieved efficiencies are 75% on ^{225}Ra vs 1% on ^{225}Ac.
- Routine delivery of clinically relevant activities of ^{224,225}Ra (e.g., >100 MBq).





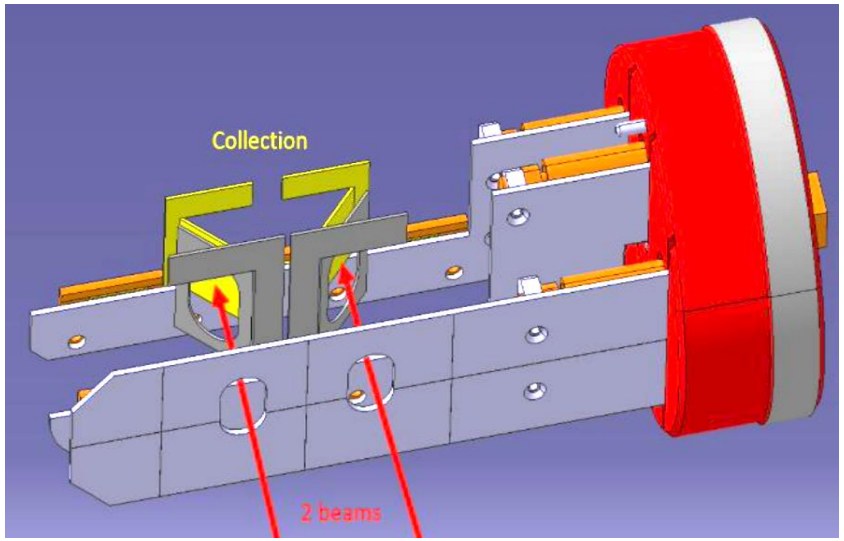
225
Ac
Actinium

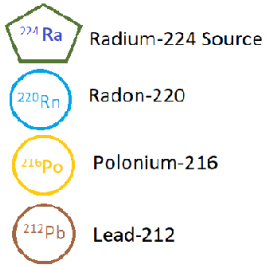


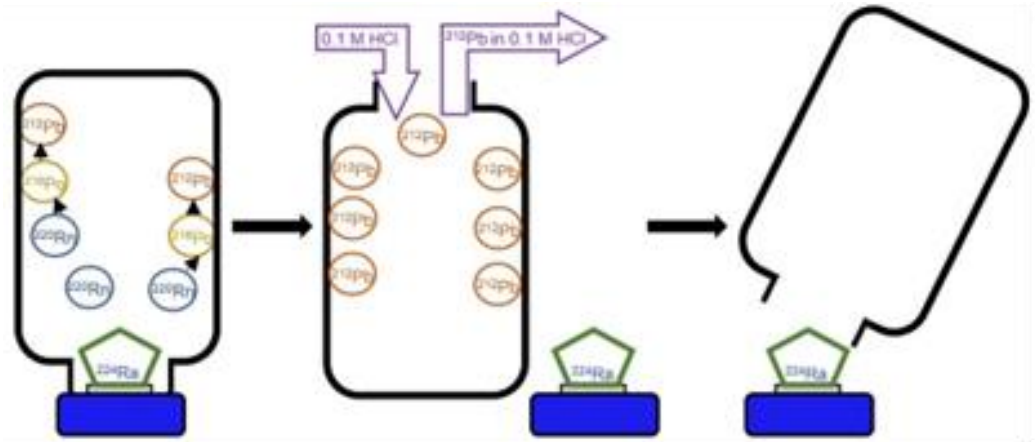
*J.D. Johnson et al, Resonant laser ionization and mass separation of ^{225}Ac, Scientific Reports **13** (2023) 1347.*
J.D. Johnson, PhD Thesis, KU Leuven (2024).

^{224}Ra: ^{212}Pb generator

- Collections of ^{224}Ra next to ^{225}Ra with high purity.
- 100s MBq can be collected, making these relevant clinical quantities.
- ^{224}Ra is a generator for ^{212}Pb







Next step: clinical trial?

PRISMAP
The European Medical Radionuclide Programme

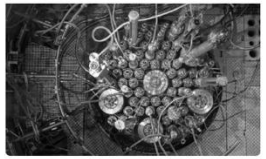
The PRISMAP infrastructure

MEDICIS
European organization for nuclear research - CERN

PSI
Paul Scherrer Institut – PSI

Hevesy Laboratory
Danmarks Tekniske Universitet – DTU

BR2
Belgian Nuclear Research Centre — SCK CEN



ARRONAX
Groupement interet public ARRONAX — ARRONAX

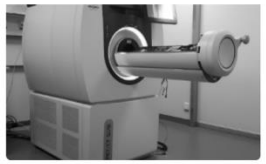
RHF
Institut Max von Laue - Paul Langevin – ILL

JRC Karlsruhe
Joint Research Centre - European Commission – JRC

NCBJ
Narodowe Centrum Badań Jądrowych — NCBJ

Hevesy Laboratory
Danmarks Tekniske Universitet – DTU

AGORA
Centre hospitalier universitaire vaudois — CHUV



NURA
Studiecentrum voor Kernenergie / Centre d'étude de l'énergie nucleaire — SCK CEN

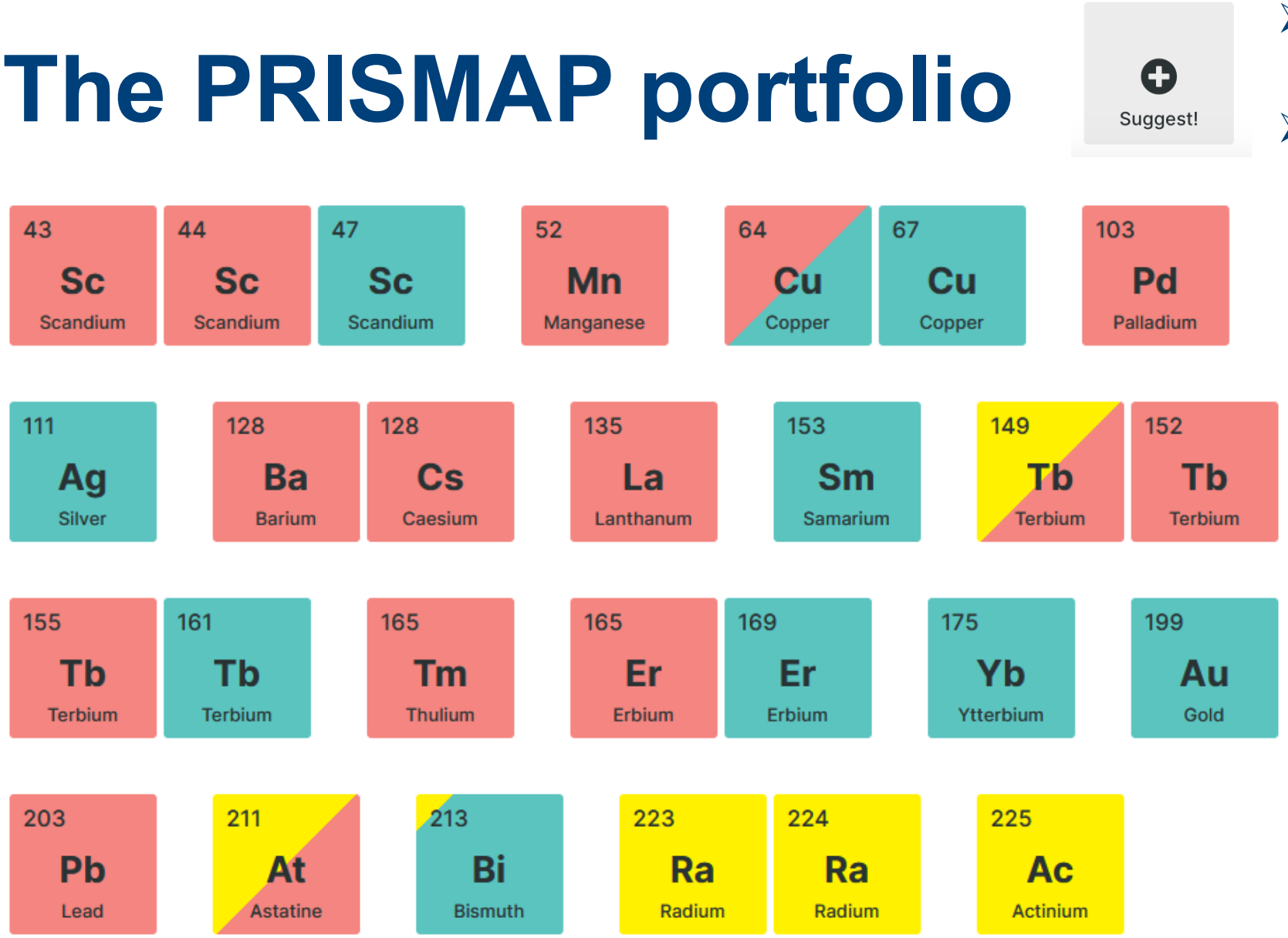
Nuklearmedizin
Klinikum rechts der Isar der Technischen Universität München — TUM

POLATOM
Narodowe Centrum Badań Jądrowych – NCBJ

- 4 **neutron irradiation facilities**, including 3 research reactors and a spallation source.
- 5 **accelerators** delivering protons with energy ranging from 18 MeV to 1.4 GeV.
- 2 accelerators delivering other particles (**deuteron**, **alpha**) at medium energy (K30 & K70).
- **1 mass separator.**
- Access to the **^{229}Th generator** for ^{225}Ac/^{213}Bi supply from JRC Karlsruhe.
- 5 **biomedical research facilities** bound to production centers (x3) or embedded within university hospitals (x2).
- **Regional clusters** for access to short-lived radionuclides.

https://www.prismap.eu/radionuclides/production-facilities/
https://www.prismap.eu/radionuclides/medical-facilities/

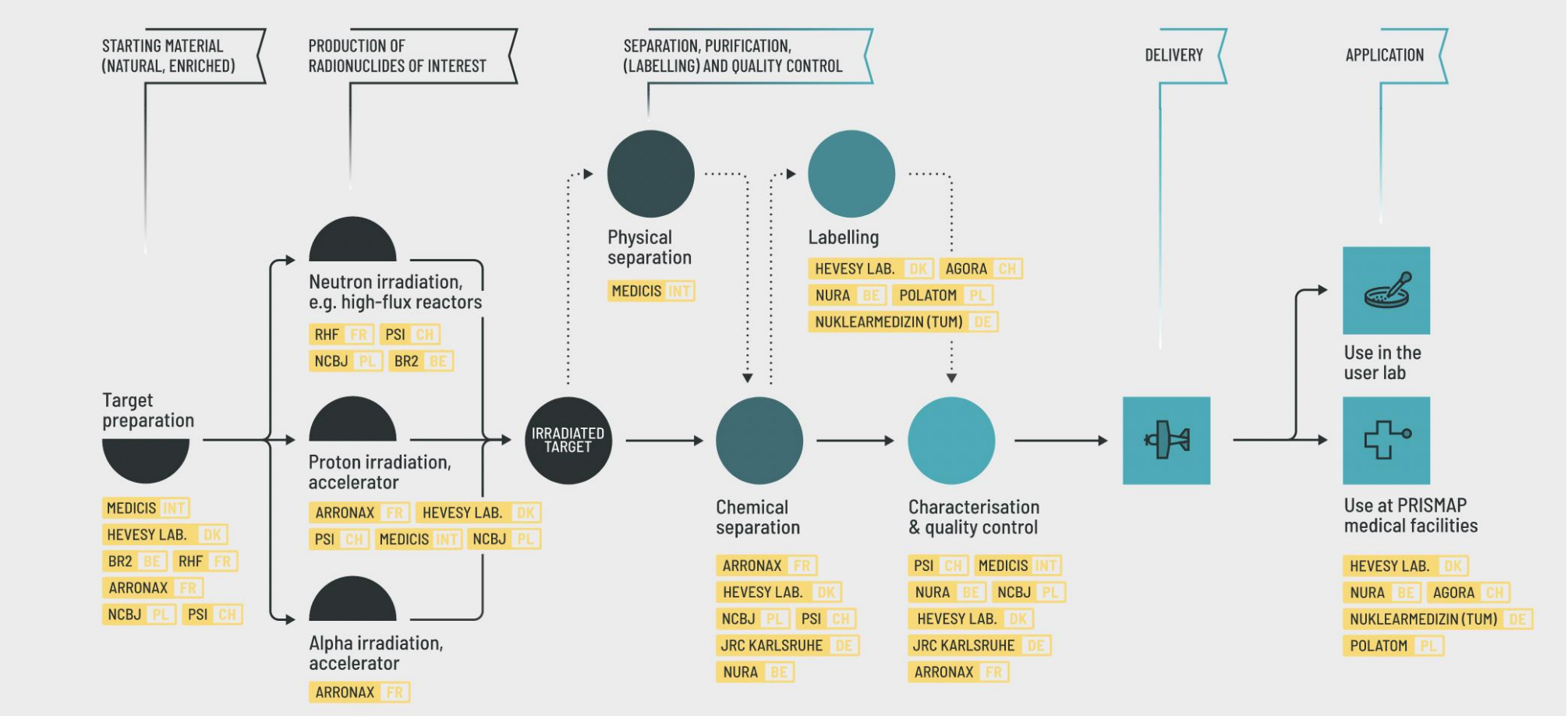
The PRISMAP portfolio



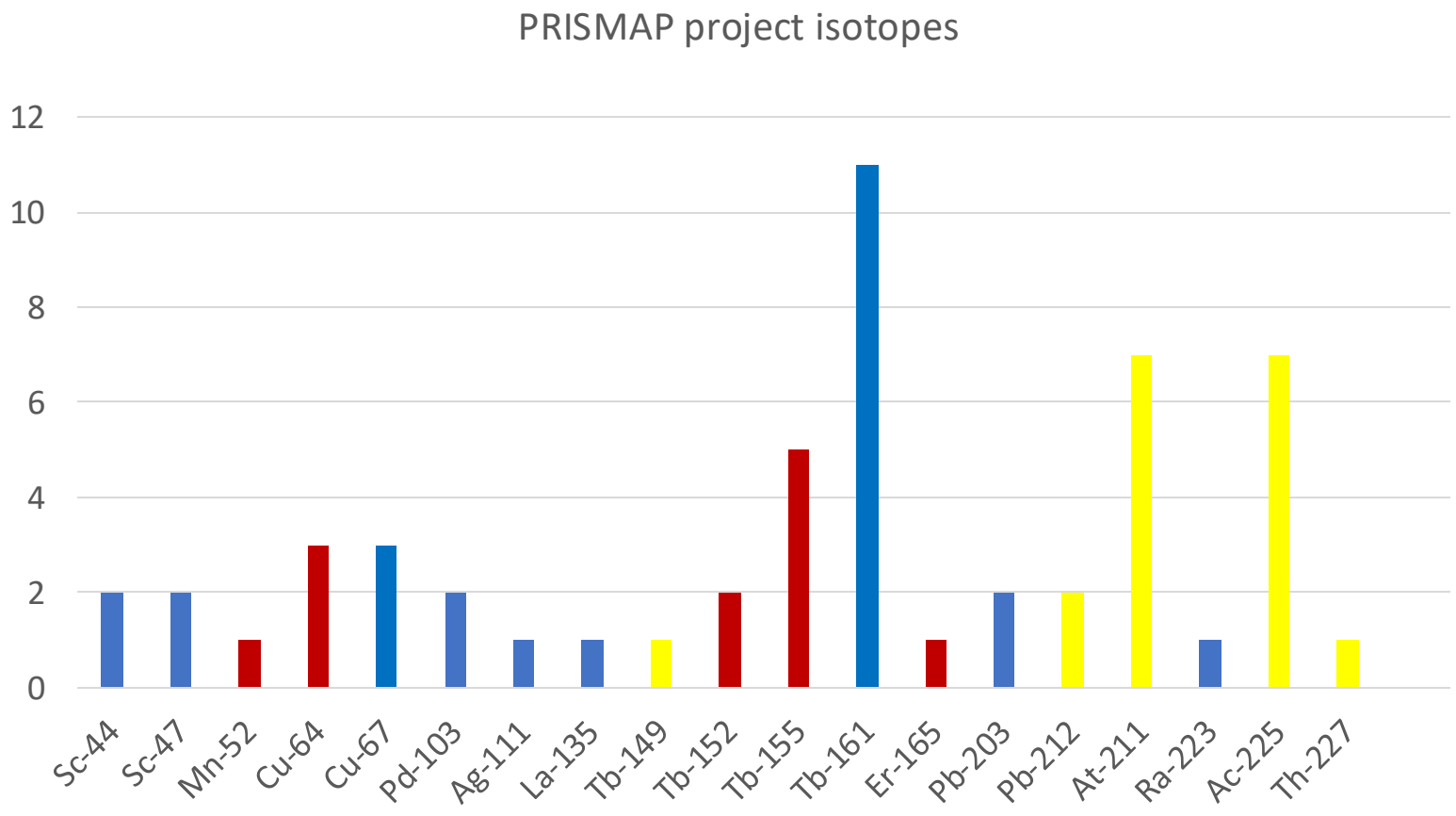
- 28 radionuclides offered on our portfolio.
- Covering SPECT and PET imaging, and beta, alpha, and Auger therapy radionuclides.
  - Many offer theranostic sets while others may be combined for novel theranostics approach (e.g., ^{135}La/^{225}Ac).
  - Some are uniquely available through our infrastructure, in particular those requiring mass separation of the radionuclides (^{128}Ba, ^{149,152,155}Tb, ^{165}Tm, ^{169}Er, ^{175}Yb).
  - We are open to your suggestion. Let us know!

https://www.prismap.eu/radionuclides/portfolio/

PRISMAP: the supply chain



Est. 2021



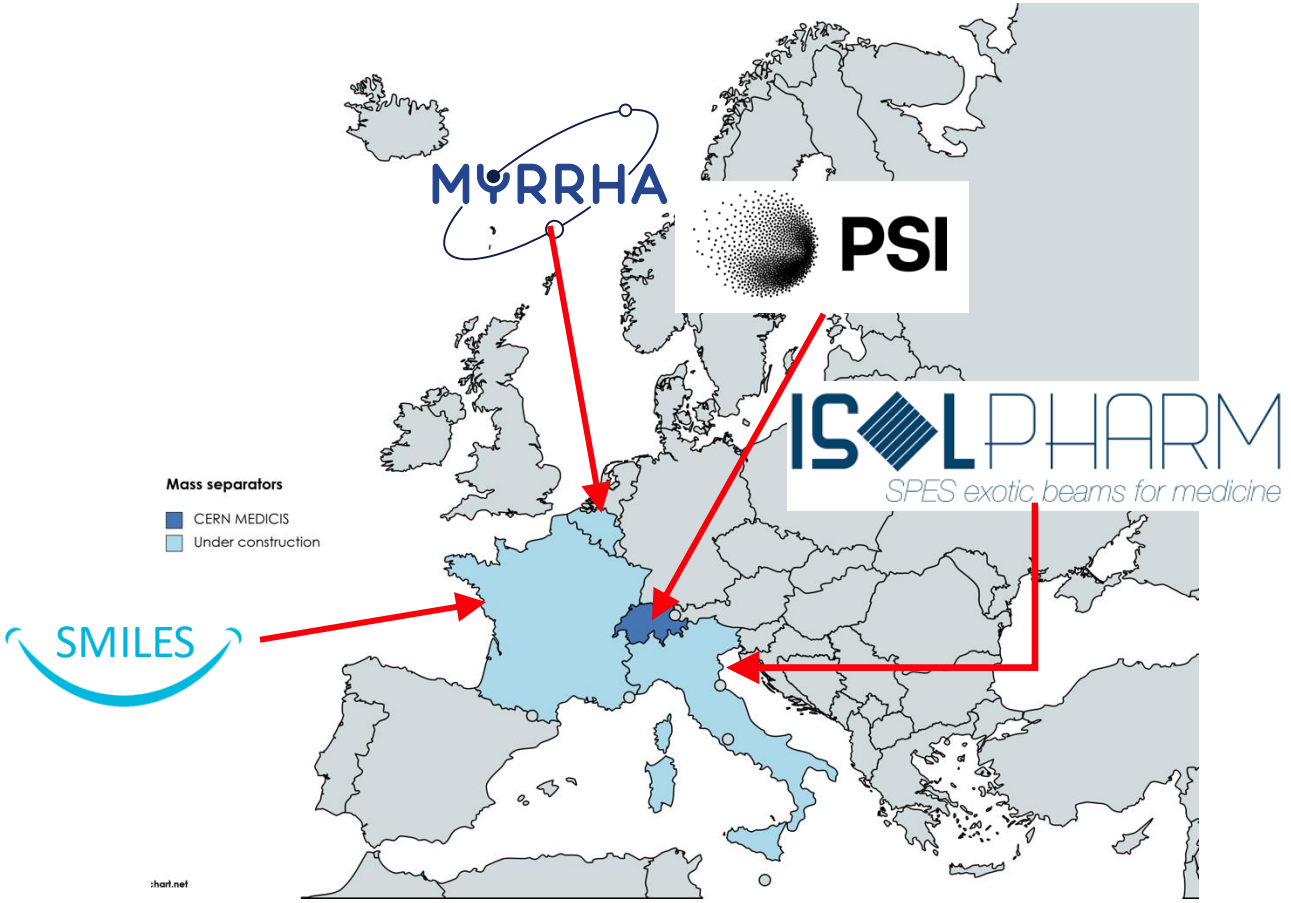
- 5 calls
- 45 projects approved
  5 projects completed
- > 60 deliveries
- 21 radionuclides from our portfolio
- Covering all stages of development:
  - new generator concepts
  - radiochemical investigations
  - radiopharmaceutical synthesis
  - radiobiology
  - in vitro & in vivo pre-clinical
- 2 projects already published and 10 having reported at international conferences.
- 2 returning users.
- 2 projects moving for clinical proof of concept.

PRISMAP Emerging Infrastructure

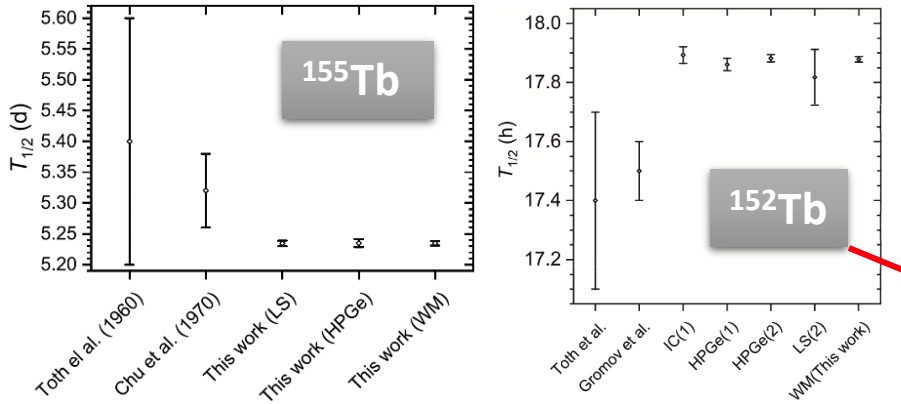
MEDICIS is the only mass separator dedicated to medical radionuclides in Europe.

4 projects are at different stages of development:

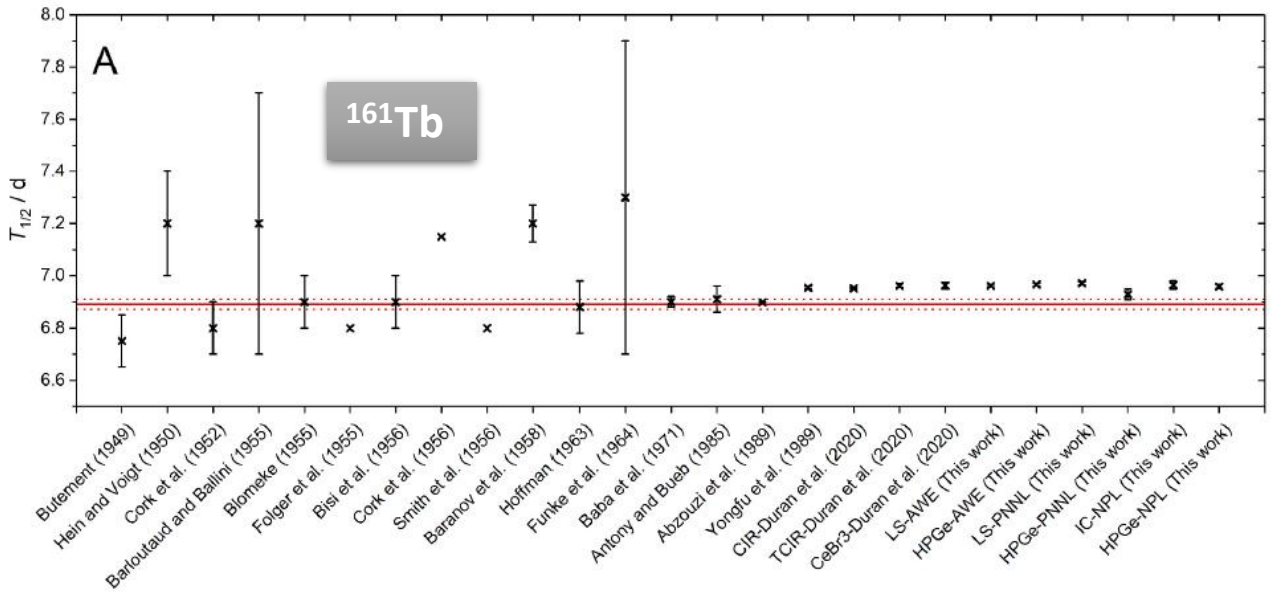
- ISOLPHARM at SPES
- ISOL@MYRRHA at SCK CEN
- TATTOOS at PSI
- SMILES at ARRONAX

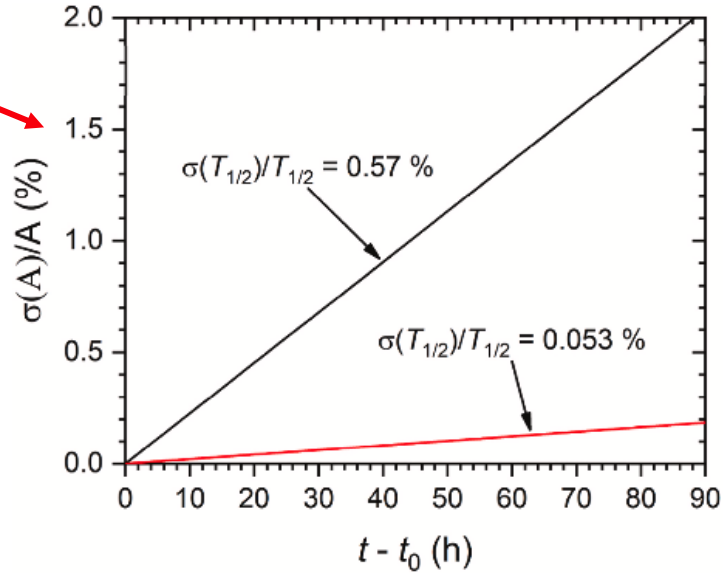


Beyond supply: nuclear data



- Many of those isotopes were studied in the early days of radioisotopes synthesis (1950-1970) and the accuracy on their nuclear data is questionable.





*S.M. Collins et al., Applied Radiation and Isotopes **182** (2022) 110140.*
*S.M. Collins et al., Applied Radiation and Isotopes **190** (2022) 110480.*
*S.M. Collins et al., Applied Radiation and Isotopes **202** (2023) 111044.*

- Nuclear medicine has a lot to offer for improved patient care in Europe and worldwide, and is undergoing a rapid growth – especially in therapy.
- Targeted alpha therapy offers additional therapy potency but also increased challenges to research and supply.
- Radionuclide mass separation provides access to a wide portfolio of radionuclides to sustain the research while other avenues are being developed for scaling up the production.
- PRISMAP has federated this effort at the European level, creating a one-stop portal for medical researchers and generating synergies at the European level.
- New mass separators are on the horizon across Europe to bring hope to the field.


NPL
National Physical Laboratory
KU LEUVEN
NUCLEAR AND RADIATION PHYSICS
CHUV
TÉCNICO LISBOA
NEUTRONS FOR SOCIETY
ARRONAX
fabis
Fundación Andaluza Beturia para la Investigación en Salud
CERN
HUG
Hôpitaux Universitaires Genève
L'ESSENTIEL, C'EST VOUS.
PSI
European Commission
Joint Research Centre
RĪGAS STRADIŅA UNIVERSITĀTE
JG|U
JOHANNES GUTENBERG UNIVERSITÄT MAINZ