# MASS SEPARATION OF RADIOLANTHANIDES FOR BIOMEDICAL R&D
# FEEDBACK FROM CERN-MEDICIS

*PRISMAP Workshop on Radiolanthanides*

*PSI*

Thierry Stora, CERN

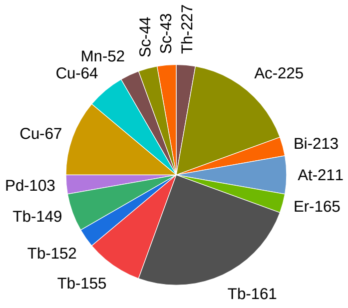
03 Sept 2024

# Radiolanthanides hold a special place in Nuclear Medicine and in PRISMAP

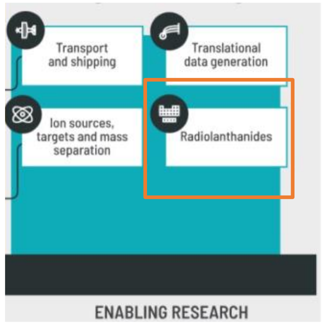
- Our web interface :

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


Industrial stakeholders interest

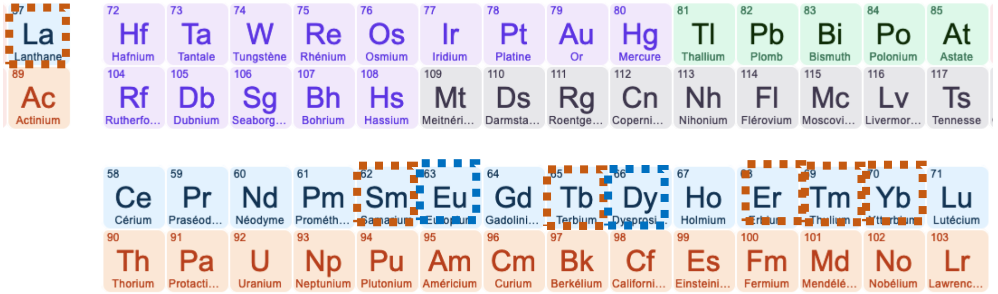



A dedicated work –package




PRISMAP

MEDICIS





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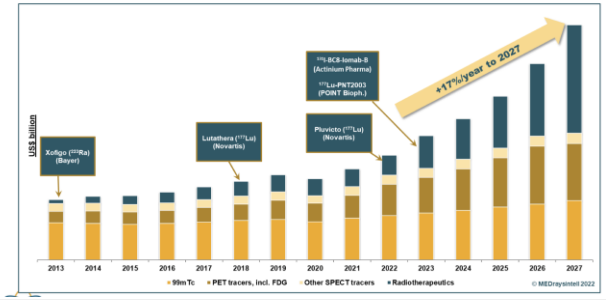
Research Article | Brief Communication

Preclinical Evaluation of Gastrin-Releasing Peptide Receptor Antagonists Labeled with $^{161}$Tb and $^{177}$Lu: A Comparative Study

Nadine Holzleitner, Tatjana Cwojdzinski, Roswitha Beck, Nicole Urtz-Urban, Colin C. Hillhouse, Pascal V. Grundler, Nicholas P. van der Meulen, Zeynep Talip, Stijn Ramaekers, Michiel Van de Voorde, Bernard Ponsard, Angela Casini and Thomas Günther

Journal of Nuclear Medicine December 2023, jnumed.123.266233; DOI: https://doi.org/10.2967/jnumed.123.266233




Lu-177 DOTATATE success story – Also key to PRISMAP approval during COVID-19
6 lanthanides already included in PRISMAP (La, Sm, Tb, Er, Tm, Yb)
While Tb-161 is clearly leading the number of projects,
other radiolanthanides may well find their way to the clinical research stage

# Historical radiolanthanides and isotope mass separation

**Table 1. PRISMAP day-1 radionuclides.**

| Radionuclide | Application | Imaging(I)/ Treatment(T)/ Generator(G) | Production reaction |
|---|---|---|---|
| Sc-44/Sc-44m | PET | I | $^{44}$Ca(p,n); $^{44}$Ca(d,2n) |
| Sc-47 | $\beta^-$ therapy, SPECT | I/T | $^{46}$Ca(n,$\gamma$)$^{47}$Ca($\beta^-$) |
| Cu-64 | PET | I | $^{64}$Ni(p,n); $^{64}$Ni(d,2n) |
| Cu-67 | $\beta^-$ therapy, SPECT | I/T | $^{68}$Zn(p,2p); $^{70}$Zn(p,$\alpha$) |
| Ag-111 | $\beta^-$ therapy, SPECT, TDPAC | I/T | $^{110}$Pd(n,$\gamma$)$^{111}$Pd(($\beta^-$); $^{110}$Pd(d,n) |
| La-135 | Auger therapy | T | $^{nat}$Ba(p,X) |
| Tb-149 | $\alpha$ therapy, PET | I/T | $^{nat}$Ta(p,spall) |
| Tb-152 | PET | I | $^{nat}$Ta(p,spall) |
| Tb-155 | Auger therapy, SPECT | I | $^{nat}$Ta(p,spall) |
| Tb-161 | $\beta^-$ therapy, SPECT | I/T | $^{160}$Gd(n, $\gamma$) |
| Dy-166 | Generator for Ho-166 ($\beta^-$ therapy, SPECT) | G | $^{164}$Dy(n, $\gamma$)(n, $\gamma$) |
| Er-165 | Auger emitter | T | $^{165}$Ho(n, $\gamma$) &(p,n) |
| Tm-165 | Generator for Er-165 (Auger therapy) | G | $^{nat}$Ta(p,spall) |
| Er-169 | $\beta^-$ therapy | T | $^{168}$Er(n, $\gamma$) |
| Yb-175 | $\beta^-$ therapy, (SPECT) | T | $^{174}$Yb(n, $\gamma$) |
| Pt-195m | Auger therapy, SPECT | I/T | $^{194}$Pt(n, $\gamma$) |
| Bi-213 | $\alpha$ therapy | T | $^{225}$Ac generator |
| At-211 | $\alpha$ therapy | T | $^{209}$Bi($\alpha$,2n) |
| Ac-225 | $\alpha$ therapy | T | $^{229}$Th generator; $^{232}$Th(p,spall) |

ISOLDE, MEDICIS,
Arronax+MEDICIS

CERN-MEDICIS
ILL+MEDICIS

High Molar Activity Sm-153 : SCK CEN + MEDICIS
Tm-167 : PSI + MEDICIS

G.J. Beyer / Radioactive ion beams for biomedical research 549

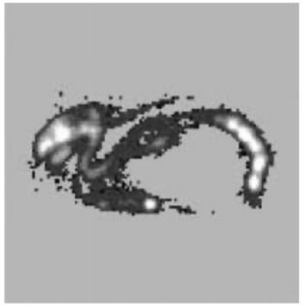


Figure 12. The picture represents a 3 mm saggital slice of a positron emission tomogram of a young rabbit 60 min after the injection of a radiopharmaceutical solution containing EDTMP as chelating ligand and 30 MBq $^{142}$Sm as the positron emitting isotope. The PET image was recorded using the rotating prototype PET scanner of the Division of Nuclear Medicine of the Geneva University Hospital [55,56]. High-density regions appear in white, illustrating high metabolic activity of bone tissue. The isotope $^{142}$Sm was produced at the CERN ISOLDE facility. The same compound (EDTMP) in combination with the $\beta^-$-emitting isotope $^{153}$Sm is used for palliative therapy of bone cancer. PET imaging using the homologue positron emitter $^{142}$Sm provides a quantitative measurement of radioactivity uptake in tissue regions of interest allowing the dose applied using $^{153}$Sm treatment to be monitored precisely in order to optimize the therapy.

G. Beyer et al,
Hyperfine Interactions 129 (2000) 529–553

Sm-142 EDTMP

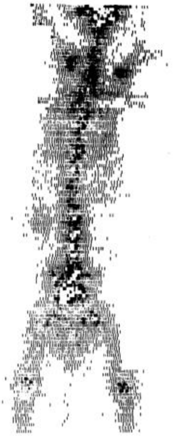


FIG. 5. Total body scan of a rabbit 6 days after i.v. injection of 300 $\mu$Ci $^{167}$Tm-citrate.
(Photo taken from a colour scan.)

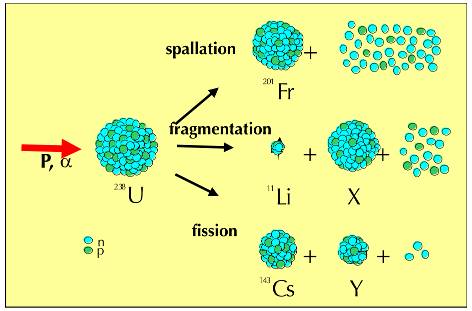
Total body scan of a rabit with Tm-167-citrate
G. Beyer et al,
https://doi.org/10.1016/0020-708X(78)90105-9.

Most of the radiolanthanides produced with the isotope mass separation technique were investigated for preclinical and imaging proof-of-concept studies

# Characteristics of the irradiation facilities in PRISMAP

- Underlying principle for CERN-MEDICIS : irradiation, transfer and mass separation for source collection

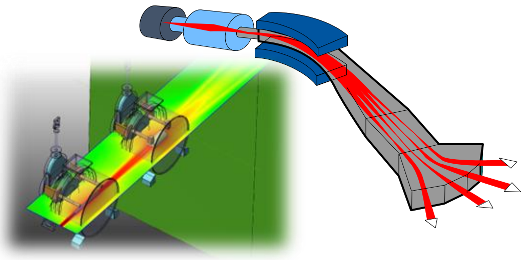
### Accelerator




$I_{[pps]} \sim F_{[pps]}\ S_{[barn]}\ N_{[g/cm2]}$ **production rate**

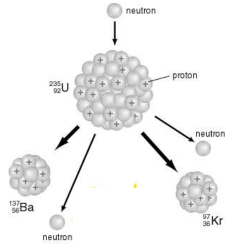
$10^{10}$pps 100∝A ($6.10^{14}$) 1mbarn 1g/cm$^2$ for $A_{target}$=30g/mol

### Isotope mass separation



$I_{[pps]} \sim F_{[pps]}\ S_{[barn]}\ N_{[g/cm2]}\ e_{[\%]}$

### Research reactor




$$\frac{dN'}{dt} = n v \sigma_{act} N_T$$

# Equation to express radionuclide production and mass separation yields

RIB intensity [$s^{-1}$ $\mu A^{-1}$]

Proton beam Intensity [$s^{-1}$ $\mu$ $A^{-1}$]

Avogadro Numb.

Diffusion+ Effusion Efficiency

$$I = \int \sigma(E)\, \Phi(E, x)\, \rho(x)\, N/A\, dx\ \varepsilon_{diff+eff}\ \varepsilon_{ion}$$

Cross section [$cm^2$]

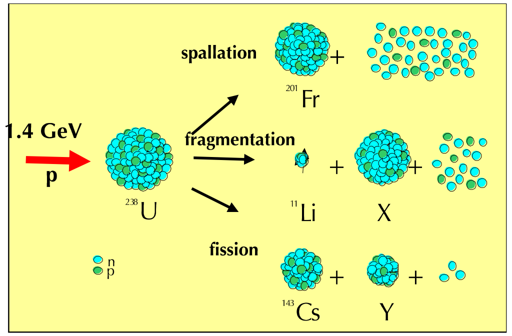
Target density [g $cm^{-3}$]

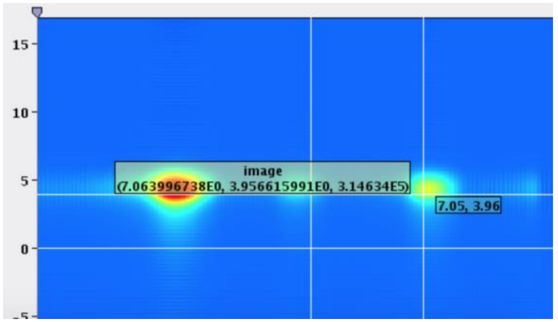
Target Atomic Mass [g]

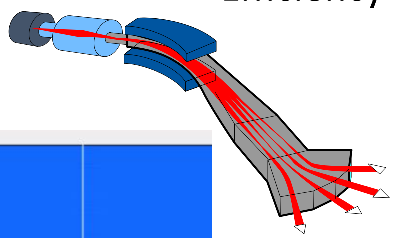
Ionization Efficiency

Ionization efficiencies

| | |
|---|---|
| $^{153}Sm$ | 12.7 |
| $^{167}Tm$ | 55 |
| $^{155}Tb$ | 1-6 |
| $^{225}Ac$ | 15.1 |
| $^{225}Ra$ | 52%* |

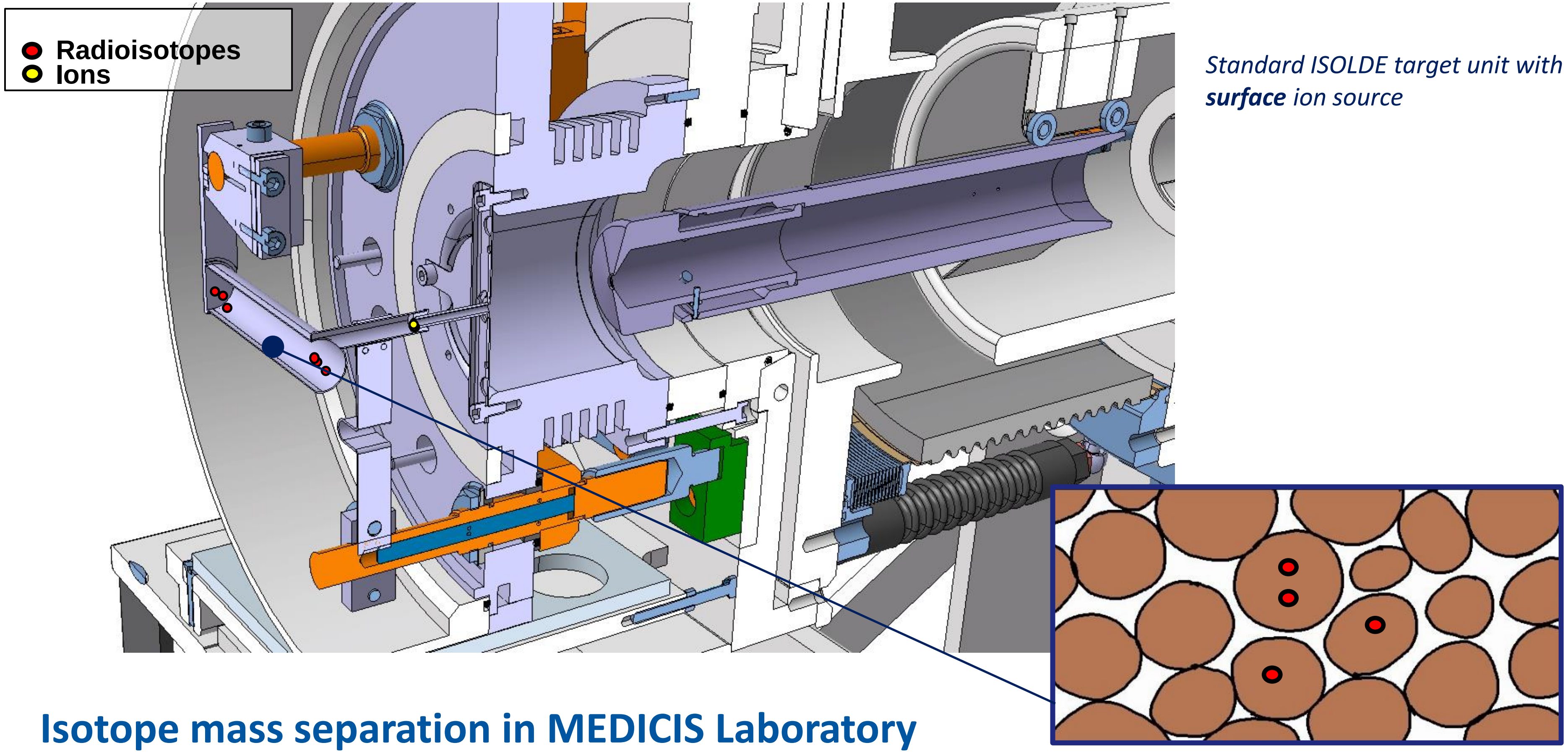


High (specific) Molar activity
And purity

# Principle of isotope production, release and acceleration

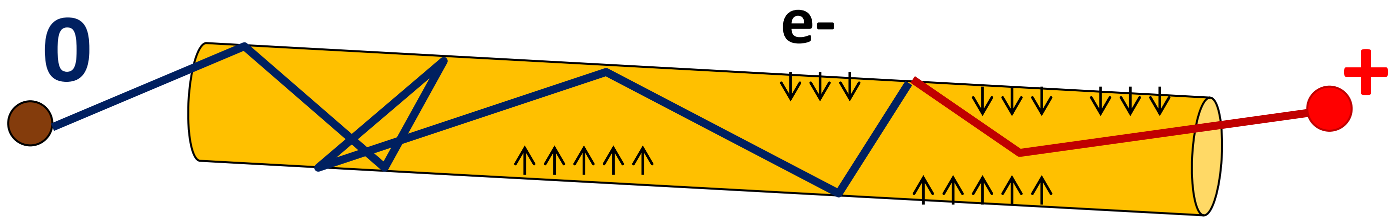



*Standard ISOLDE target unit with* ***surface*** *ion source*

## Isotope mass separation in MEDICIS Laboratory

*H. Ravn and W. Brian "On-line mass separators." Treatise on heavy ion science. Springer US, 1989. 363-439.*

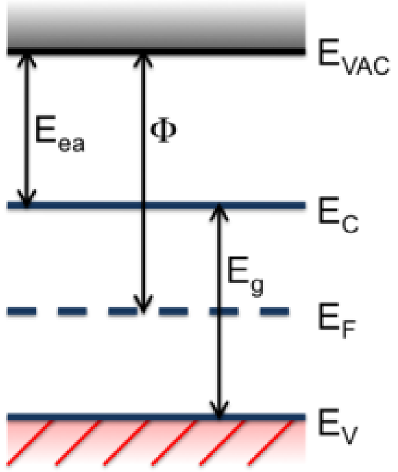
# Surface Ion Sources

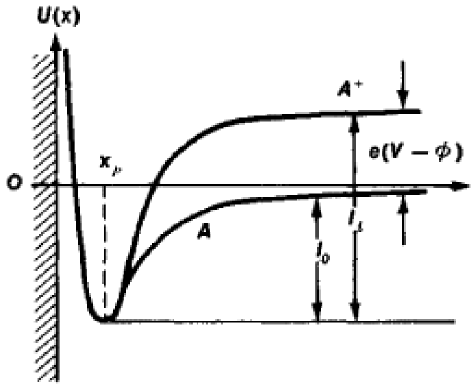



**Hot tube**

Material work function $\Phi$

Isotope 1st Ion. Pot. : Wi




## Saha-Langmuir Equation

$$\varepsilon_{\text{surface}} = \frac{1}{1 + \frac{g_0}{g_+} \exp\left(\frac{W_i - \Phi}{kT}\right)}$$

For Alkalis,

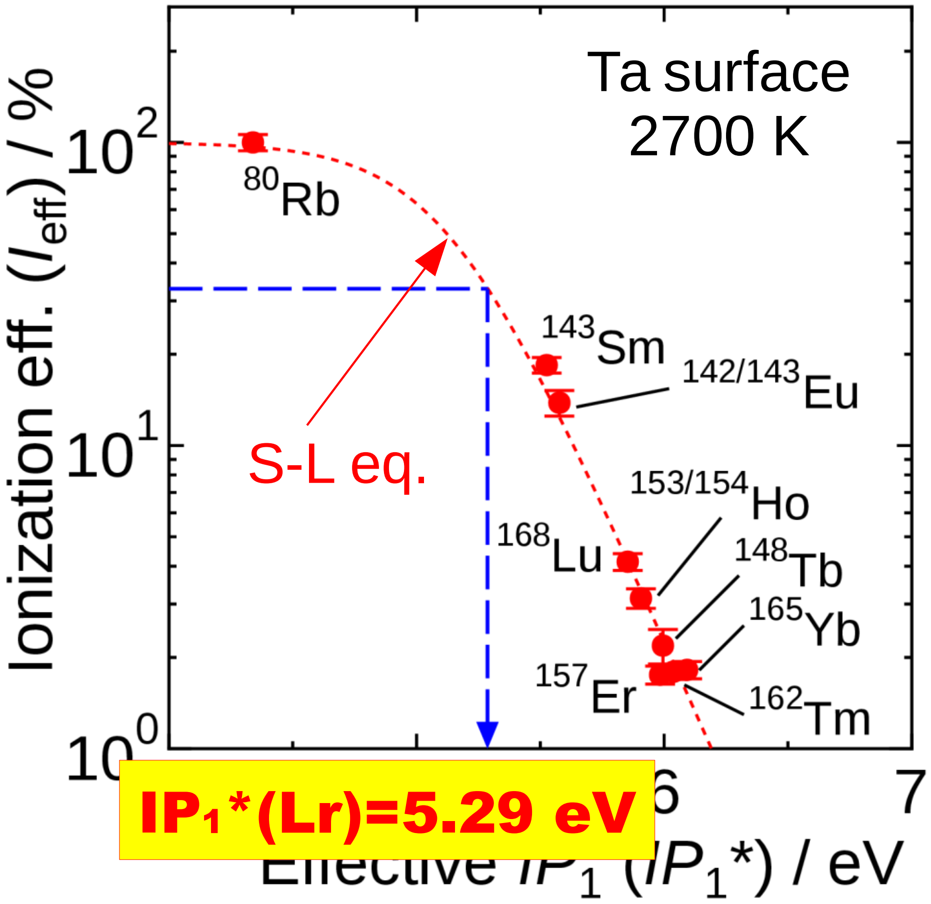
$g_0$=2 (2S1/2, degeneracy 2), g+=1

Some additional correction factors such as applied electrical potential or surface coverage

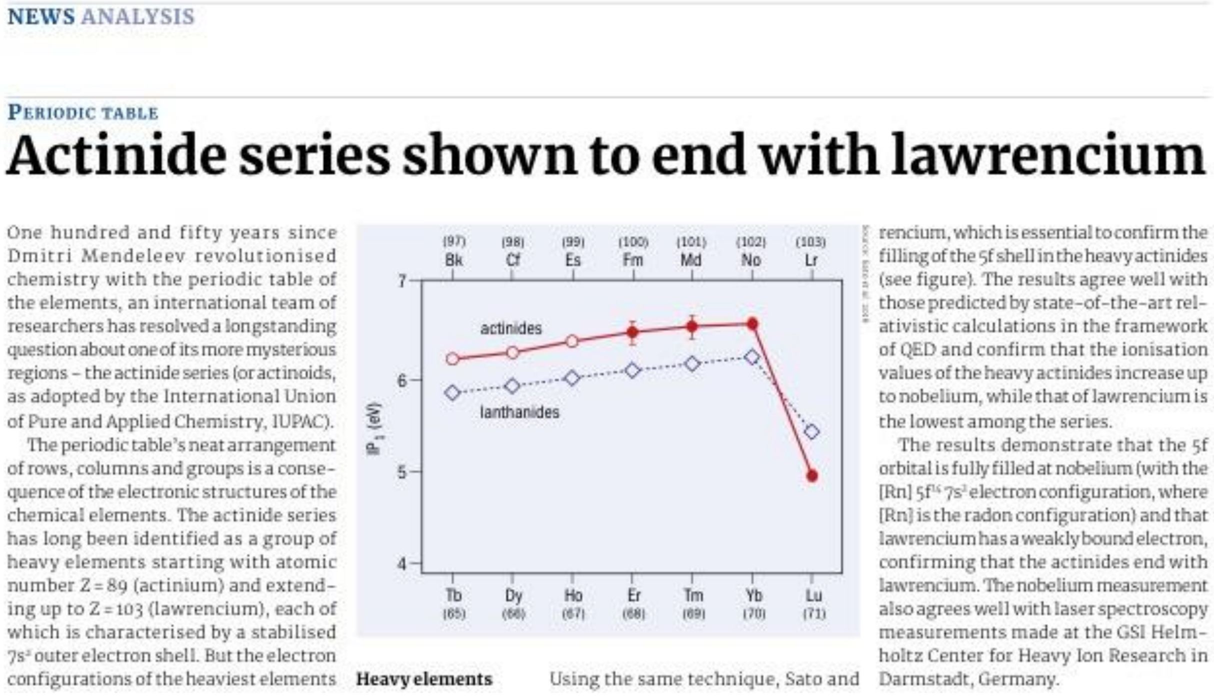
Meghnad Saha, 1920

# Eventhough we claim radiolanthanides have similar properties

## There are differences…




**$IP_1$*(Lr)=5.29 eV**

NEWS ANALYSIS

PERIODIC TABLE

# Actinide series shown to end with lawrencium

One hundred and fifty years since Dmitri Mendeleev revolutionised chemistry with the periodic table of the elements, an international team of researchers has resolved a longstanding question about one of its more mysterious regions – the actinide series (or actinoids, as adopted by the International Union of Pure and Applied Chemistry, IUPAC).

The periodic table's neat arrangement of rows, columns and groups is a consequence of the electronic structures of the chemical elements. The actinide series has long been identified as a group of heavy elements starting with atomic number Z = 89 (actinium) and extending up to Z = 103 (lawrencium), each of which is characterised by a stabilised $7s^2$ outer electron shell. But the electron configurations of the heaviest elements



**Heavy elements**

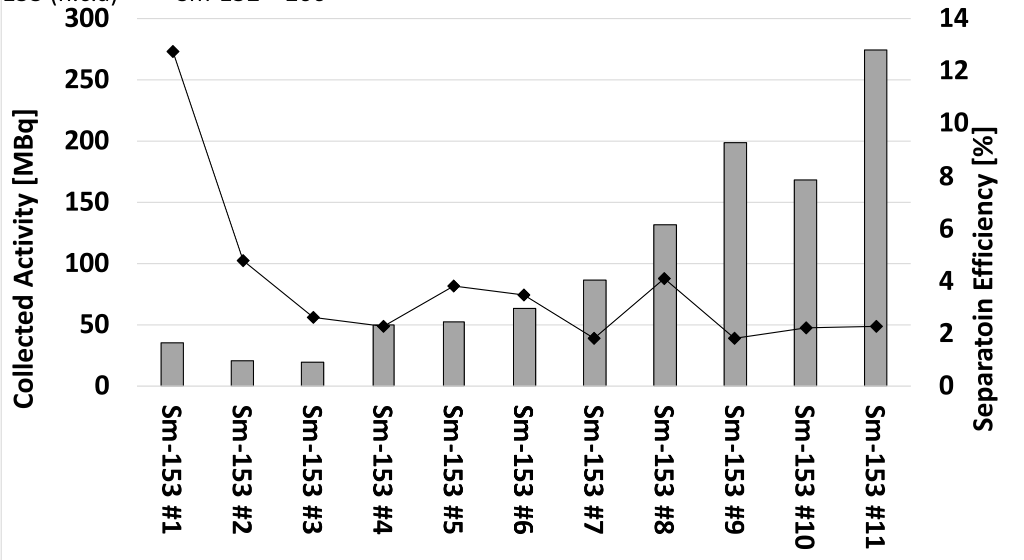
Using the same technique, Sato and

rencium, which is essential to confirm the filling of the 5f shell in the heavy actinides (see figure). The results agree well with those predicted by state-of-the-art relativistic calculations in the framework of QED and confirm that the ionisation values of the heavy actinides increase up to nobelium, while that of lawrencium is the lowest among the series.

The results demonstrate that the 5f orbital is fully filled at nobelium (with the [Rn] $5f^{14} 7s^2$ electron configuration, where [Rn] is the radon configuration) and that lawrencium has a weakly bound electron, confirming that the actinides end with lawrencium. The nobelium measurement also agrees well with laser spectroscopy measurements made at the GSI Helmholtz Center for Heavy Ion Research in Darmstadt, Germany.

# High Molar Activity Sm-153 clinical dose achieved by mass separation

| RN | Target | cross –section (barn) |
|---|---|---|
| Lu-177 (c.a) | Lu-176 | 2090, but Lu-177m (T1/2=160d) |
| Lu-177 (n.c.a) | Yb-176 | **2.85** |
| Tb-161 (n.c.a) | Gd-160 | **1.4** |
| Sm-153 (n.c.a) | Sm-152 | 206 |

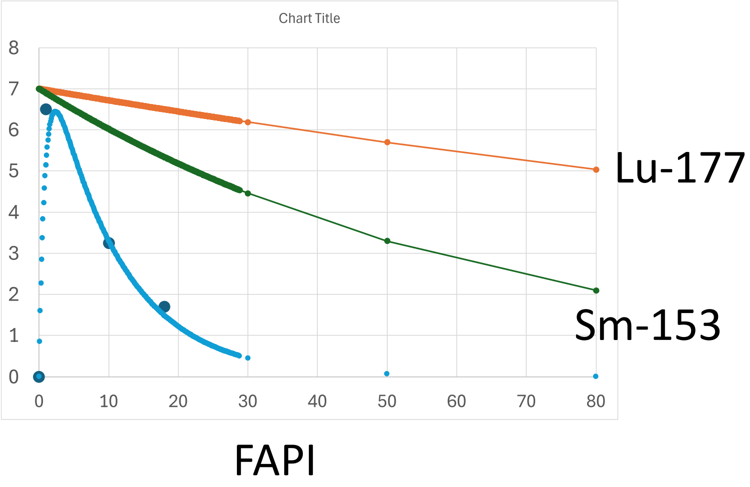



Not shown : > 1 GBq High Molar Activity Sm-153 achieved in 2023

And 6.8% collection efficiency (EOB)

*T. Stora et al. 2024 J. Phys.: Conf. Ser. 2687 082039*.

## FAPI-46 vs Isotope T1/2




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

**[153Sm]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]

One of the 4 KPI's for MEDICIS…

# Règles pour utilisation des radioisotopes dans un médicament : cas en Suisse

swissmedic

**Fabrication du radionucléide :**

Les **<u>réactions nucléaires employées</u>**…la **<u>demi-vie</u>**, le type et l'énergie du **<u>rayonnement</u>** ainsi que les **<u>effets perturbateurs engendrés par les impuretés</u>**.

**Nucléides obtenus par bombardement de cibles : matériau cible et enveloppe de la cible :**

- composition, forme chimique, pureté chimique, état physique et additifs chimiques éventuels, susceptibles d'influer sur le produit
- méthode d'irradiation, environnement physique et chimique (support de la cible)
- rendement

**Nucléides produits par fission :**

Il convient d'indiquer l'ensemble de la chaîne de nucléides, de la matière première initiale (impuretés comprises) jusqu'aux nucléides filles stables correspondants, y compris la demi-vie, le type et l'énergie du rayonnement. Les effets perturbateurs provoqués par les impuretés ou la matière première doivent être discutés.

**Traitement du radionucléide :**

- description détaillée de l'isolation (séparation de la cible) et de l'enrichissement du radionucléide souhaité ; rendement.

**Propriétés physiques du radionucléide :**

Il faut indiquer en détail la demi-vie, le type et l'énergie du rayonnement ainsi que l'évolution dans le temps à compter de la fabrication du radionucléide et jusqu'à la date d'expiration du médicament ainsi que les aspects importants pour l'élimination.

**Contrôle du produit fini :**

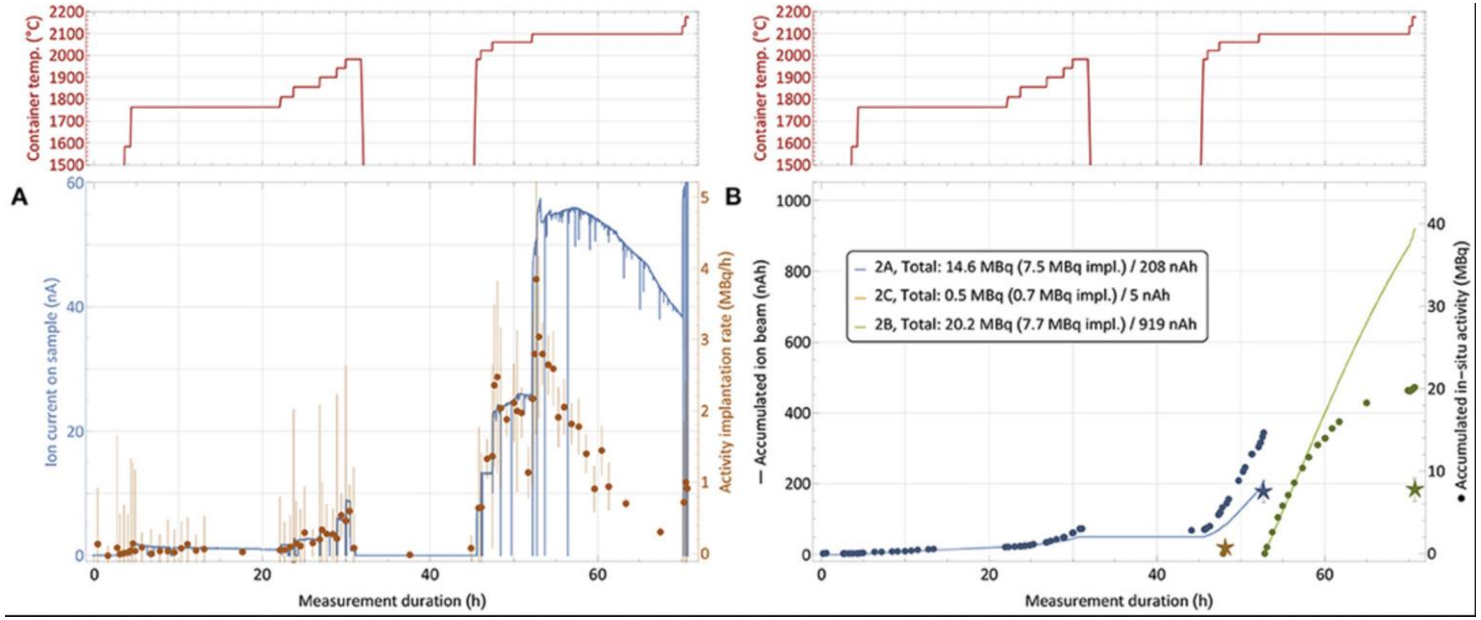
- identité des nucléides
- pureté des nucléides
- pureté radiochimique
- pureté chimique
- activité spécifique

Ident. QM : ZL000_00_003f_WL / V01 / bg, stb, cas / zro / 01.04.2015

# What about other radiolanthanides : Tm-167

## Separation from a cyclotron target (Er2O3) irradiated at PSI

| | | | Separated $^{167}$Tm | | | Collected $^{167}$Tm | | | |
|---|---|---|---|---|---|---|---|---|---|
| No. | $^{167}$Tm content[a] (MBq) | Foil | Activity per foil[b] (MBq) | Total run activity[c] (MBq) | Dec.-corr.[d] (%) | Activity per foil[b] (MBq) | Total run activity[c] (MBq) | Dec.-corr.[d] (%) | Ion load[e] (nAh) |
| 1 | 83.0 (80) | 1A | 33.6 | 33.8 → 41% | 51 | 8.7 | **8.9(15) → 11(2)%** | 13 | 938 |
| | | 1B | 0.2 | | | 0.2 | | | 1 |
| 2 | 76.9 (73) | 2A | 14.6 | 34.4 → 45% | 55 | 7.5 | **15.4(19) → 20(3)%** | 24 | 208 |
| | | 2B | 20.2 | | | 7.7 | | | 919 |
| | | 2C | 0.5 | | | 0.7 | | | 5 |
| 3 | 122.9 (118) | 3A | 28.8 | 33.1 → 27% | 32 | 15.4 | **19.2(25) → 16(3)%** | 19 | 496 |
| | | 3B | 2.9 | | | 2.9 | | | 45 |
| | | 3C | 4.0 | | | 2.4 | | | 504 |




R. Heinke et al, Front. In Medicine, https://doi.org/10.3389/fmed.2021.712374

# Also ongoing in PRISMAP – the Terbium quadruplet

scientific reports

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Article | Open access | Published: 26 July 2019

**Chemical Purification of Terbium-155 from Pseudo-Isobaric Impurities in a Mass Separated Source Produced at CERN**

Ben Webster, Peter Ivanov, Ben Russell, Sean Collins, Thierry Stora, Joao Pedro Ramos, Ulli Köster, Andrew Paul Robinson & David Read

*Scientific Reports* 9, Article number: 10884 (2019) | Cite this article

ELSEVIER
Applied Radiation and Isotopes
Volume 190, December 2022, 110480

**Half-life determination of $^{155}$Tb from mass-separated samples produced at CERN-MEDICIS**

S.M. Collins [a b], A.P. Robinson [a c d], P. Ivanov [a], U. Köster [e], T.E. Cocolios [f], B. Russell [a], B. Webster [a b], A.J. Fenwick [a], C. Duchemin [f g], J.P. Ramos [f g h], E. Chevallay [g], U. Jakobsson [i j], S. Stegemann [f], P.H. Regan [a b], T. Stora [g]

ELSEVIER
Applied Radiation and Isotopes
Volume 202, December 2023, 111044

**Determination of the Terbium-152 half-life from mass-separated samples from CERN-ISOLDE and assessment of the radionuclide purity**

S.M. Collins [a b], U. Köster [c], A.P. Robinson [a d e], P. Ivanov [a], T.E. Cocolios [f], B. Russell [a], A.J. Fenwick [a], C. Bernerd [f g], S. Stegemann [f], K. Johnston [g], A.M. Gerami [g], K. Chrysalidis [g], H. Mohamud [a], N. Ramirez [a], A. Bhaisare [a], J. Mewburn-Crook [a], D.M. Cullen [e], B. Pietras [e], S. Pells [e], K. Dockx [f]...P.H. Regan [a b]

Cicone *et al. EJNMMI Research* (2019) 9:53
https://doi.org/10.1186/s13550-019-0524-7
EJNMMI Research

ORIGINAL RESEARCH · Open Access

**Internal radiation dosimetry of a $^{152}$Tb-labeled antibody in tumor-bearing mice**

Francesco Cicone[1*], Silvano Gnesin[2], Thibaut Denoël[1], Thierry Stora[3], Nicholas P. van der Meulen[4,5], Cristina Müller[4], Christiaan Vermeulen[4], Martina Benešová[4], Ulli Köster[6], Karl Johnston[3], Ernesto Amato[7], Lucrezia Auditore[7], George Coukos[8], Michael Stabin[9], Niklaus Schaefer[1], David Viertl[1] and John O. Prior[1]

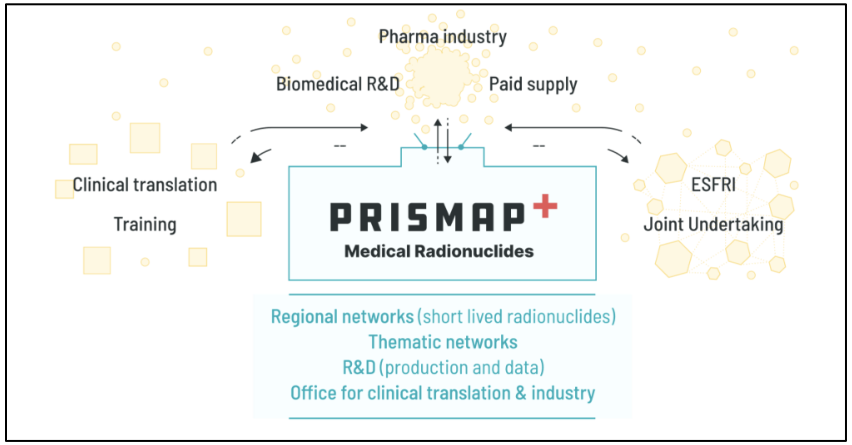
UNIL | Université de Lausanne
Faculté de biologie et de médecine

CHUV

# Thank you !

*Need isotopes ?*

*call 5 is open !*



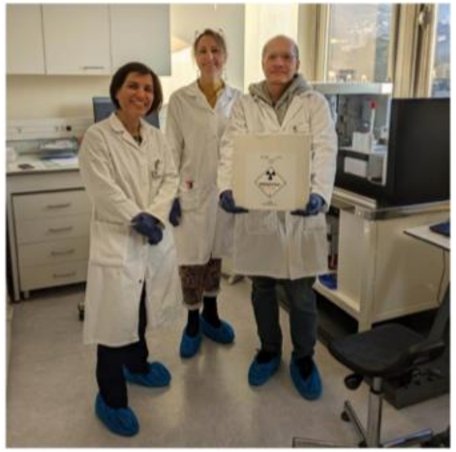

**PRISMAP + MEETING IN NANTES**
**https://indico.cern.ch/event/1438450/**


Acknowledgement* :

Happy MEDICIS Team*

Happy PRISMAP Team*

Happy biomedical Researchers*




Frontiers in Medicine : Advances in Radioactive Ion Beams for Nuclear Medicine (J. Prior, C. Decristoforo, T. Stora eds) ISBN 978-2-83250-522-9

https://prismap.eu, https://medicis.cern/publications-articles, https://zenodo.org (search for PRISMAP)


This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008571 (PRISMAP).

WWW.PRISMAP.EU (CALL 5 OPEN !)

PRISMAP+ 19 SEPT : HTTPS://INDICO.CERN.CH/EVENT/1438450/

WWW.PRISMAP.EU

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PRISMAP PROJECT

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008571 (PRISMAP).