PSI

Radiochemistry step for the production of medical radionuclides

Dr. Zeynep Talip
KU Leuven, 31 May 2024

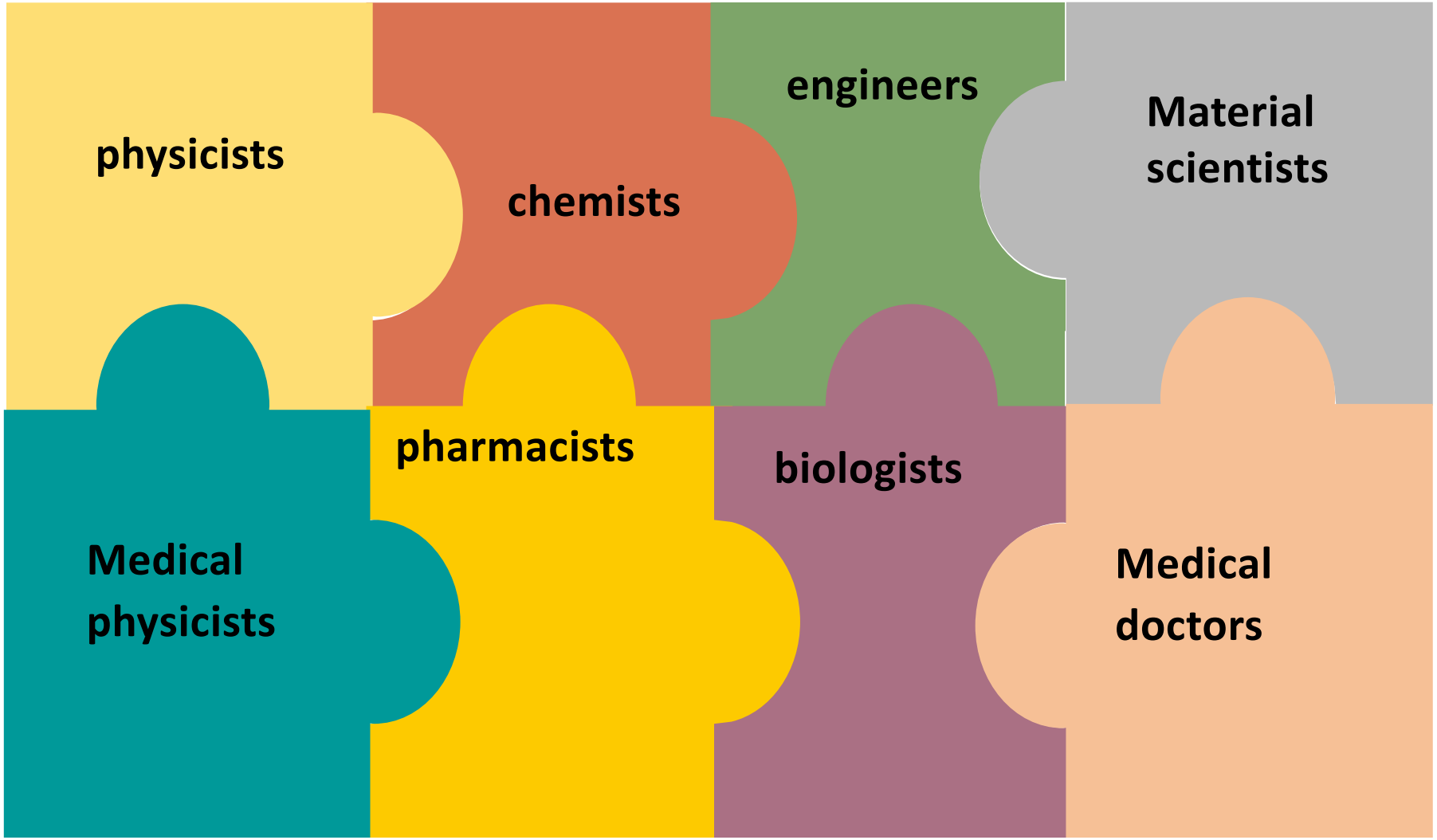
Paul Scherrer Institute

Participants

	Name	Occupation
1	Flora Mansour	Radiochemist - lab manager
2	Laurine Puren	PhD student in production of radionuclides of medical interest with alpha beam
3	Santiago Andrés Brühlmann	PhD Student Accelerator-based production of radiometals
4	Magda Silva	Nuclear physicist
5	Busani Bhengu	MSc. Project: iThemba LABS
6	ChristiAnna Brantley	PostDoc in delivery systems for alpha-emmiting radionuclides
7	Stijn De Schepper	Medical Physics expert and PhD Candidate: research in quantitative SPECT/CT
8	Max Conroy	PhD on radioisotope production
9	Davide Serafini	PhD student in experimental physics
10	Edward O'Sullivan	PhD Student in Nuclear Physics on complete decay spectroscopy of 152Tb
11	Mamad Eslami	PhD Student in production of the 64Cu/67Cu
12	Jonathan Walg	PostDoc in radionuclide production
13	Vanessa RHODEN	PhD student in fabrication and characterization of Gd targets
14	Edoardo Renaldin	PhD Student in producing medically relevant radiolanthanides
15	VARUN VIJAY SAVADI	PostDoc optimization of tritium losses
16	Aurora Leso	PhD Student evaluation of radiopharmaceuticals containing 111Ag
17	Letizia Canziani	PhD Student utilizing a TRIGA Mark II reactor to produce radioisotopes for radiolabeling
18	Pavithra Kankanamalage	R&D radiochemist
19	Lisa Gubbels	PhD Student Development of a thorium based target for the production and release of Ac225 at the ISOL facility of MYRRHA
20	James Hill	Perform, manage and consult on radiochemistry research projects primarily concerning therapeutic nuclides
21	Ho Sze Chan	R&D manager. Mission: produce GMP grade 225Ac using a cyclotron in the future
22	Julia Raitanen	PhD Student assessment of new radiopharmaceuticals radiotherapies by using of 2D and 3D cell culture models

	Name	Occupation
23	Gauri Gauri	PhD Student in synthesizing Mo-based nanomaterials
24	Pirmettis Nektarios-Nikolaos	PhD Student on Radiopharmaceutical Chemistry
25	Valeria Narykina	PhD Student developing 225AC and 212 Pb
26	Kristoffer August Poulsen	Master´s degree in Nuclear Science
27	Om prakash Dash	Researcher in experimental nuclear physics
28	Ghazal Yazdanpanah	Master´s student in Nuclear Applications
29	Mohamed Nawar	Radiochemist
30	Aicha Nour Laouameria	PhD Student in production of radionuclides for Targeted Auger Electron-Emitter Therapy
31	Anna Krzyczmonik	PostDoc on production of novel prosthetic groups for radiohalogenation
32	Ihab shokair	PhD Student in radiolabeling various prosthetic groups
33	Adriano Biolognani	PhD Student on radiochemistry
34	Karolina Zajdel	PostDoc in development of next-generation lanthanide-doped up-converting nanoparticles for theranostic applications
35	Hasanul Banna	PhD student in radionuclide production and molecular mechanism of radioactive molecules in cellular signaling, diagnosis and therapeutics developments
36	Nosihle Msabala	Bc. in Physics. Investigating in finding a material that will shield healthy cells when the cancerous ones are being irradiated
37	Alexandra Fonseca	PhD Student in a new generation of copper-based radiopharmaceuticals at ICNAS Pharma
38	Danai Bili	(Implementation and leading of AI projects within the medical technology sector of Johnson & Johnson
39	Ralitsa Mancheva	PhD Student on improving radionuclide production at MEDICIS
40	Konstantina Botsiou	Master´s degree student in Nuclear Physics and Astrophysics
41	Nik Muhammad Fitri	Radiopharmaceutical Production Pharmacist
42	Busisiwe Mbatha	BSc Hydrology & physics student

Radiopharmaceutical Development Pipeline



What have you learned so far?

PRISMAP School on Radionuclide Production

Day 1	Methods to measure cross sections	The medical practice perspective				
Day 2	The ISOL technique	Target materials for ISOL	Ion Sources for ISOL	Mass separators	Importance of beam diagnostics	Ion implantation, ion range, sputtering affect
Day 3	Cyclotrons for medical radionuclides	Exotic cyclotrons for innovative radionuclides				
Day 4	Radionuclides from nuclear reactors	Stable isotope enrichment				
Day 5	Radiochemistry	QC in nuclear medicine	Medical radionuclide transport			

Learning objectives: Separation of Lanthanides

After attending this lecture, you will be able to:

- name the required **steps for the radiopharmaceutical development pipeline**

- understand the importance of each step of **medical radionuclide production**

- understand the selection criteria for **medical radionuclide**

- understand the working principle of **column chromatography**

- understand the working principle of **ion exchange and extraction resins**

- understand the **method development for separation chemistry**

- describe the **challenges for the production of novel medical radionuclides from bench to bedside**

Production of Medical Radionuclides

Radiopharmaceutical Development Pipeline

PSI

Targetry

Irradiation

Separation

Nuclear Data

Quality control

Radionuclide Production

Ligand design

Dosimetry studies

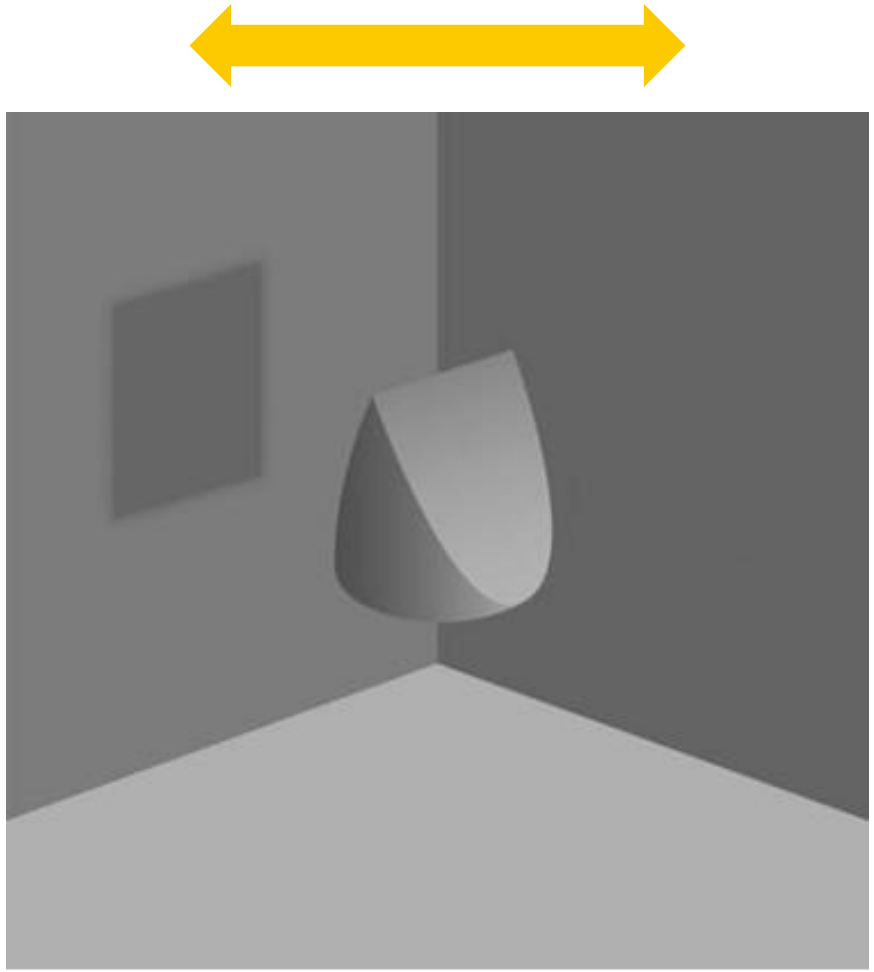
Preclinical Studies

GMP Process

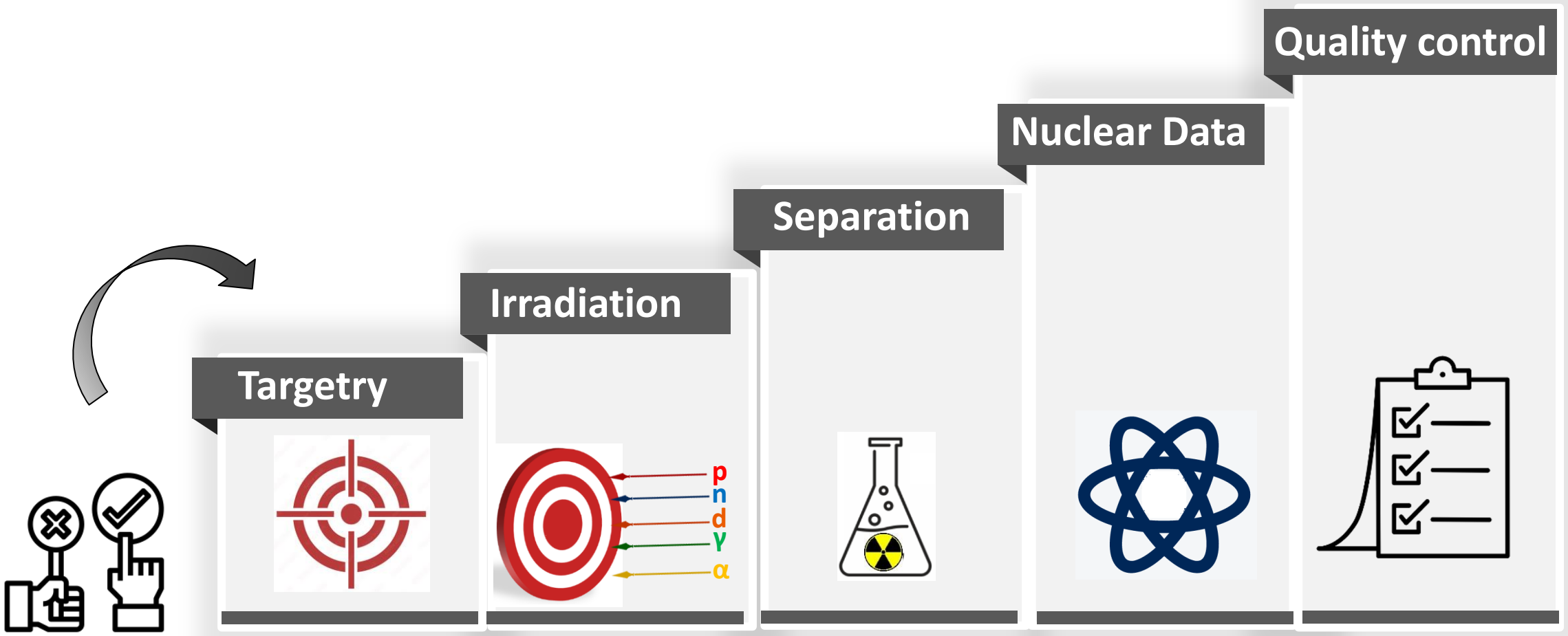
Authorities

Clinical Trials

View from a producer side



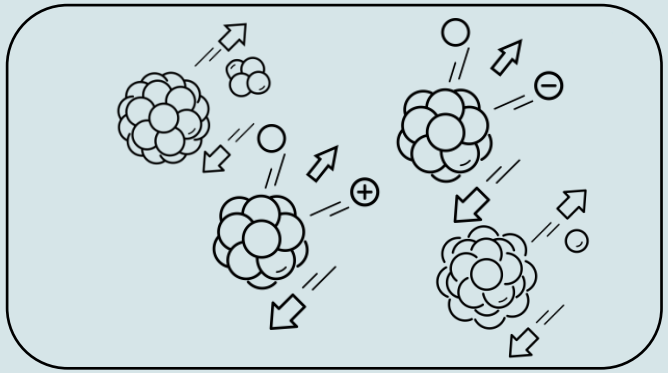
Production of Medical Radionuclides



Z. Talip et al., Molecules, 25 (2020) 966.

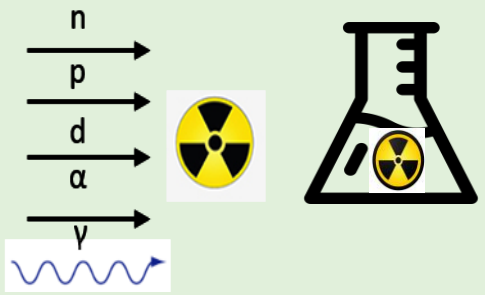
Selection of Medical Radionuclides

Decay properties



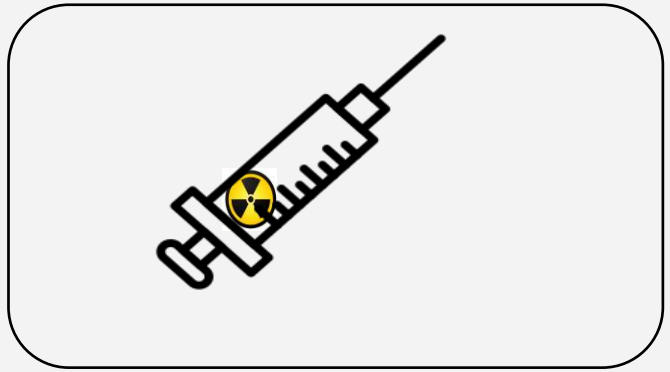
- Decay emission
- Half-life
- Energy of emission
- Associated emission

Production



- Cross sections
- Production routes
- Targetry
- Availability of target
- Cost of production
- Separation chemistry
- Specific activity

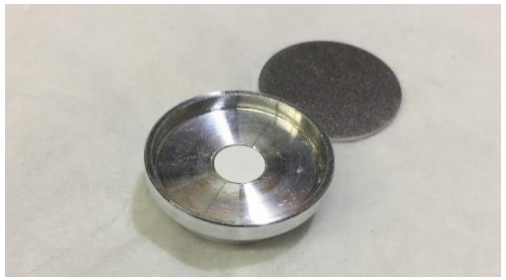
Radiopharmaceutical

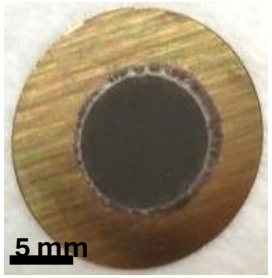


- Synthesis of labeling precursor
- Labeling of the precursor
- Chemical purification of the labelled compound
- Chemical properties
- Stability

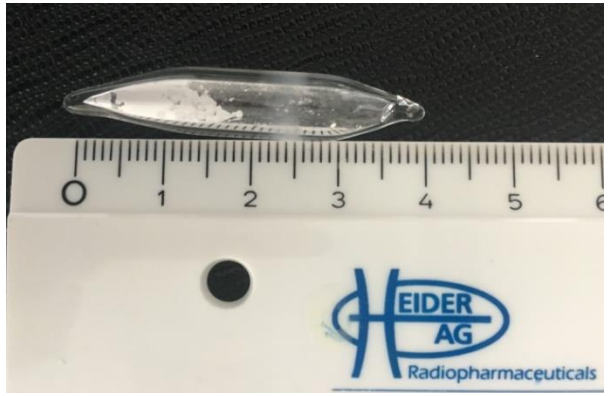
N. van der Meulen and Z. Talip, 2021, Nuclear Medicine and Molecular Imaging

Targetry for cyclotron produced radionuclides





Targetry for reactor produced radionuclides



The target material effects

- Production yields
- Side products
- Separation chemistry

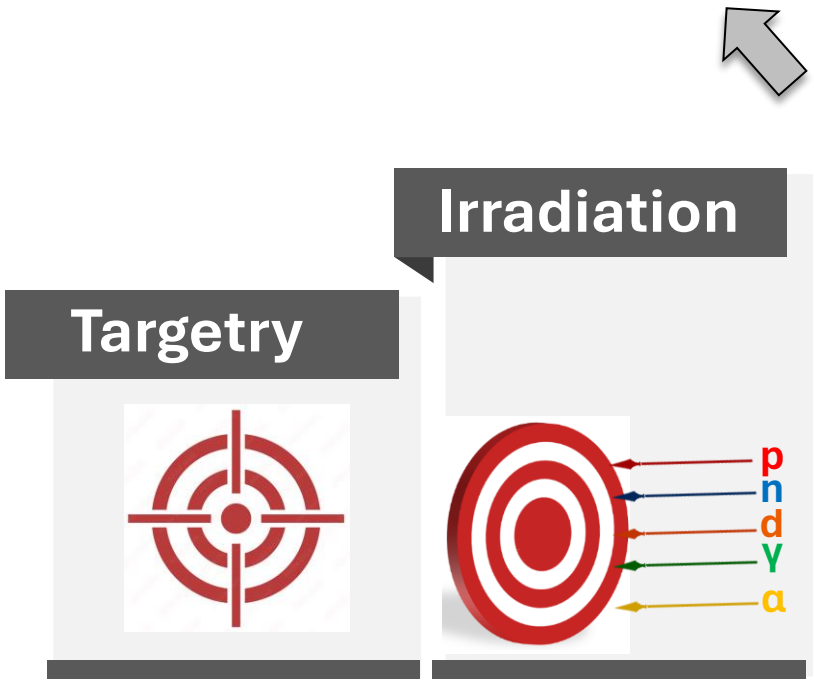
Nuclear Data

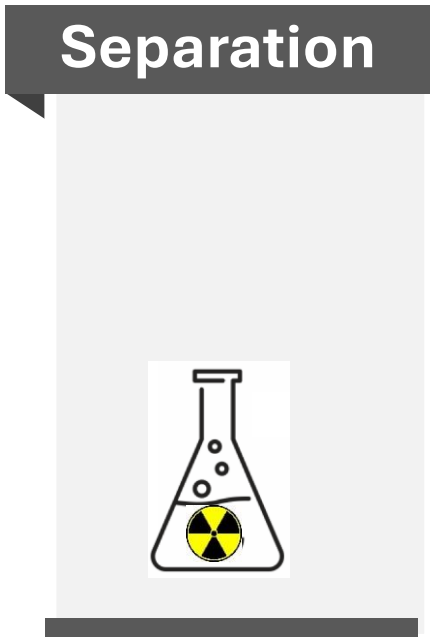
Production yields

Precise activity measurements

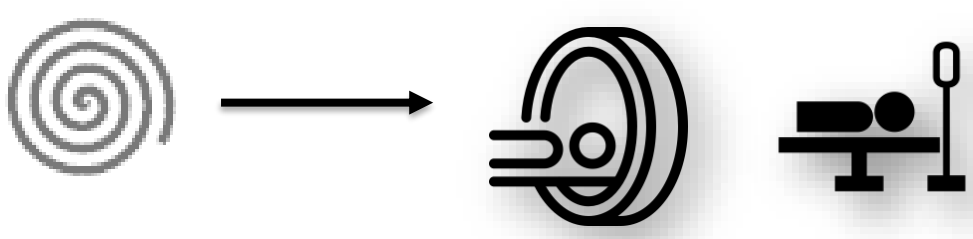
Production cross section data

Half-life, emission intensity





Irradiation



Cylotrons

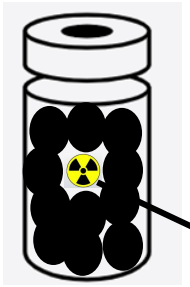
Reseach reactors

Separation of Medically Relevant Radionuclides

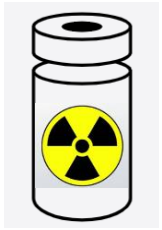
Separation Chemistry for Medical Radionuclides

mg

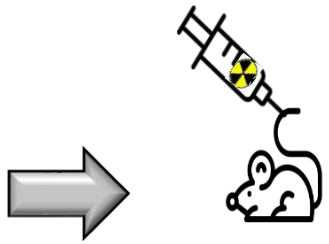
Chemical separation

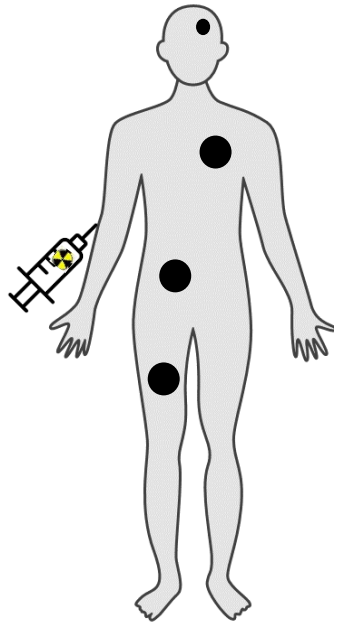


µg or ng

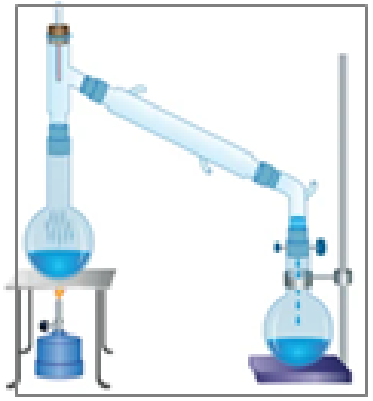


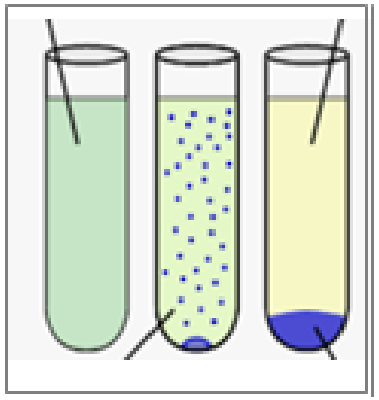
Radiopharmaceutical

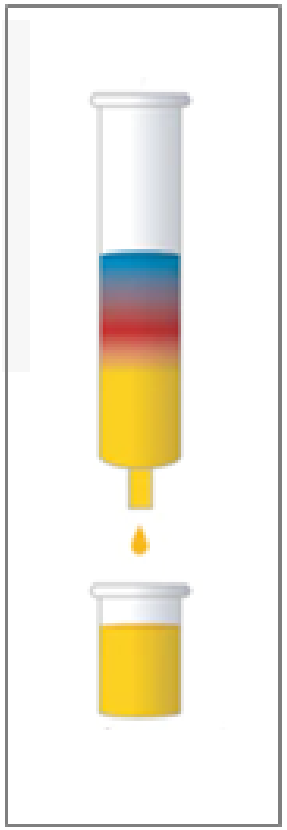


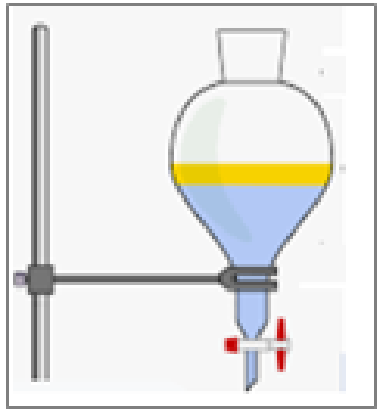


Chemical Separation





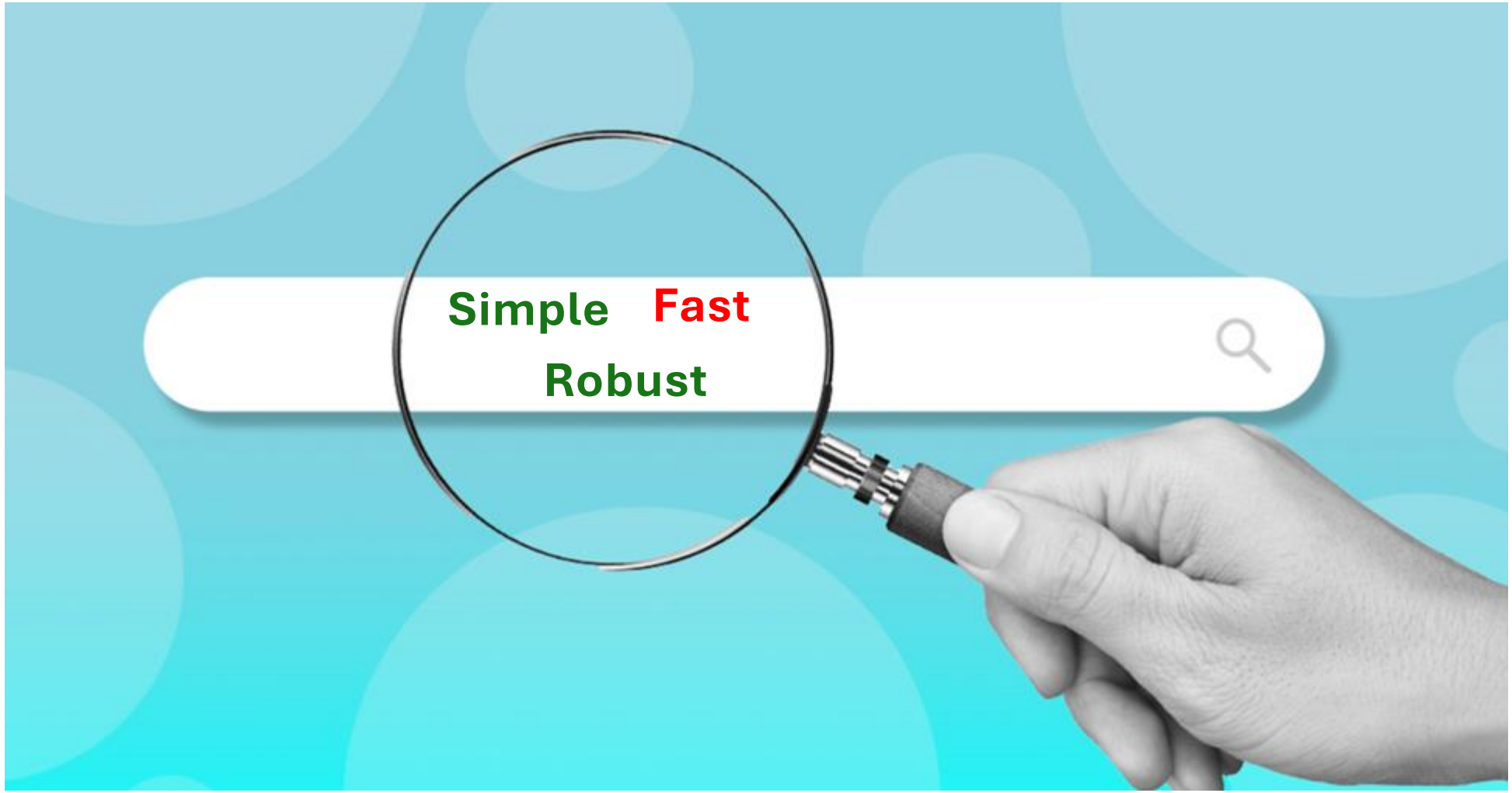




Separation Chemistry for Medical Radionuclides

Separation Modules

Separation Chemistry for Medical Radionuclides



Separation Chemistry for Medical Radionuclides

PSI

Target

Product

< 1 µg

Simple

Robust

Fast

→ **Development of chemical separation method** →

Low acidity 

Low volume (high specific activity) 

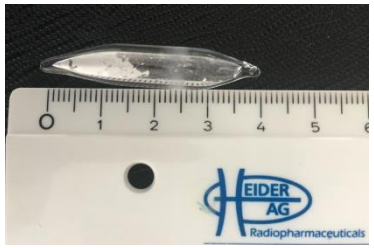
High chemical and radionuclidic purity 

Method development

Separation Chemistry for Medical Radionuclides

X → **Y**
target product

Characterization of the target (X) material



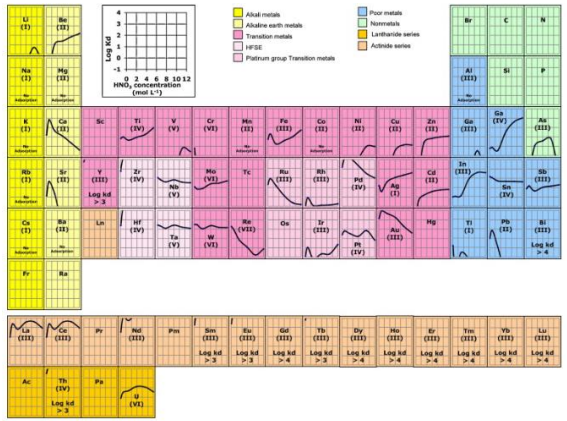
Production yields of **Y**
Radionuclidic impurities (**A, B**)
Chemical impurities (**D, E**)

Dissolution of the target material

S Solution

Distribution coefficient data

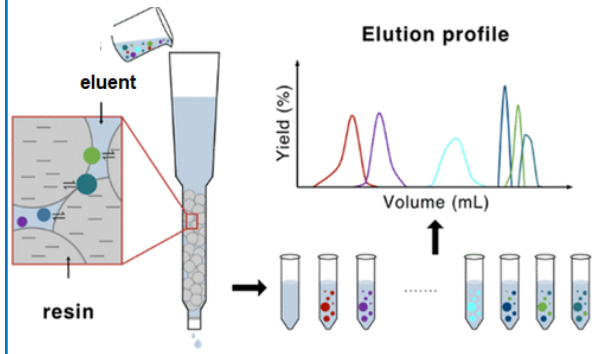
Literature/experimental data



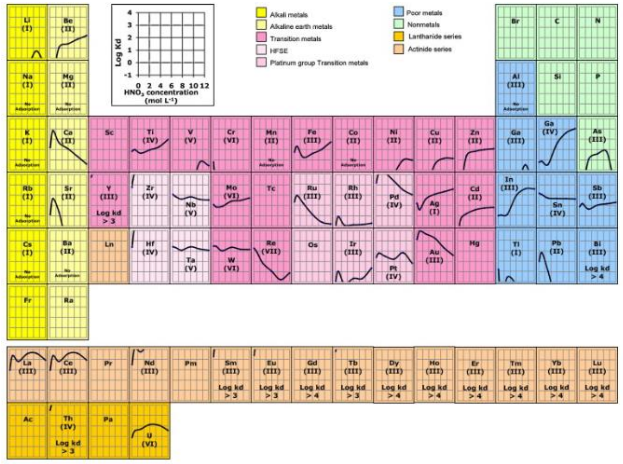
Selection of the separation system

Separation of **Y from X, A, B, D, E**
Loading solution: S

Column Chromatography



Distribution coefficient

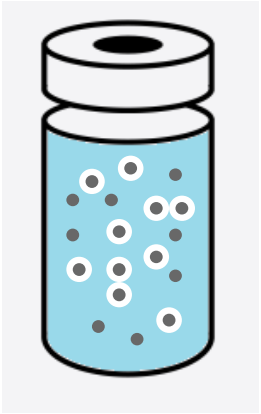


Distribution coefficient, K_D

$$K_D = \frac{[M]_{stat}}{[M]_{mob}}$$

$[M]_{stat}$ the quantity of analyte in the stationary phase

$[M]_{mob}$ the quantity of analyte in the mobile phase



$$K_D = \frac{(Co - Cs)\,V}{Cs\ x\ w}$$

High Kd values: Loading concentration

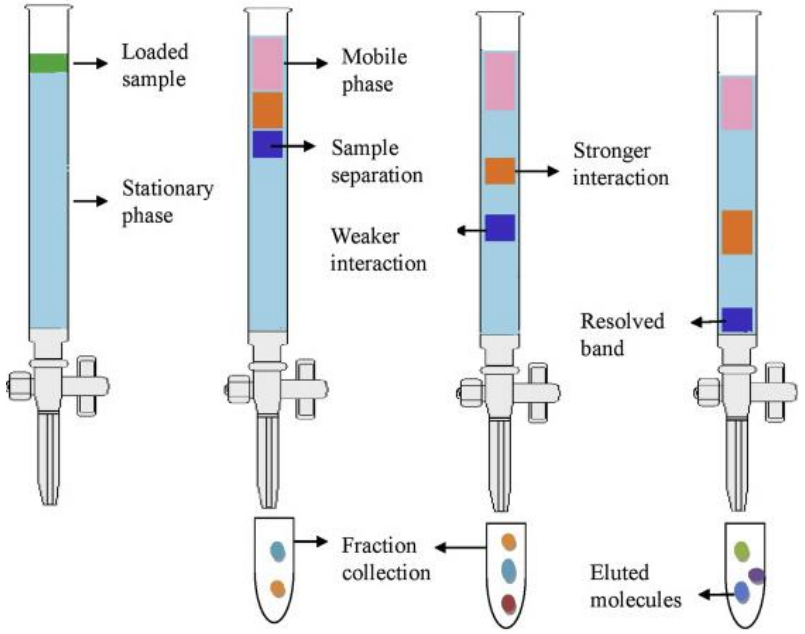
Low Kd values: Elution concentration

Separation factor, S_F

$$S_F = \frac{K_D\,(A)}{K_D\,(B)}$$

Definition:

"The term «chromatography» is the general name for a wide range of physicochemical separation processes in which the components to be separated are distributed between a stationary and a mobile phase."



- **Ion Exchange Chromatography**
- **Extraction Chromatography**

Natural bioactive compounds, Technological advancements, 2020

Classification of Ion Exchange Chromatography

It is divided in two groups:

- **Cation** exchange chromatography

$$R{-}X^{-}C^{+} + M^{+}B^{-} \rightleftharpoons R{-}X^{-}M^{+} + C^{+} + B^{-}$$

- **Anion** exchange chromatography

$$R{-}X^{+}A^{-} + M^{+}B^{-} \rightleftharpoons R{-}X^{+}B^{-} + M^{+} + A^{-}$$

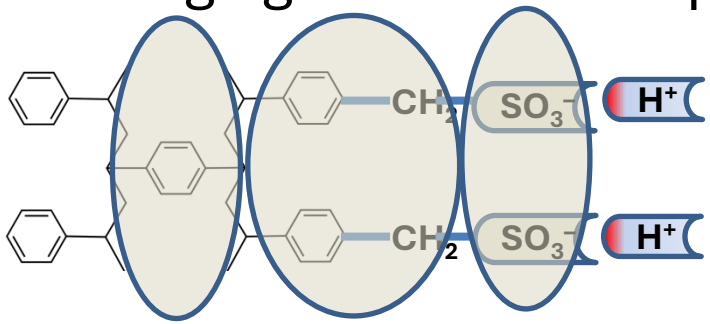
Strongly acidic cation exchanger:
sulphonic acid groups attached
to a co-polymer styrene (sites for exchangeable functional groups)
and divinyl benzene (cross linking agent).
It can exchange cations in all pH range

Weakly acidic cation exchanger:
carboxylic acid group attached to acrylic and divinyl benzene co-polymer

Cation exchange chromatography

cross linking agent

sulphonic acid groups



co-polymer styrene

$$R{-}SO_3^-H^+ \rightleftharpoons R{-}SO_3^- + H^+$$

Principe of Strong Cation Exchanger

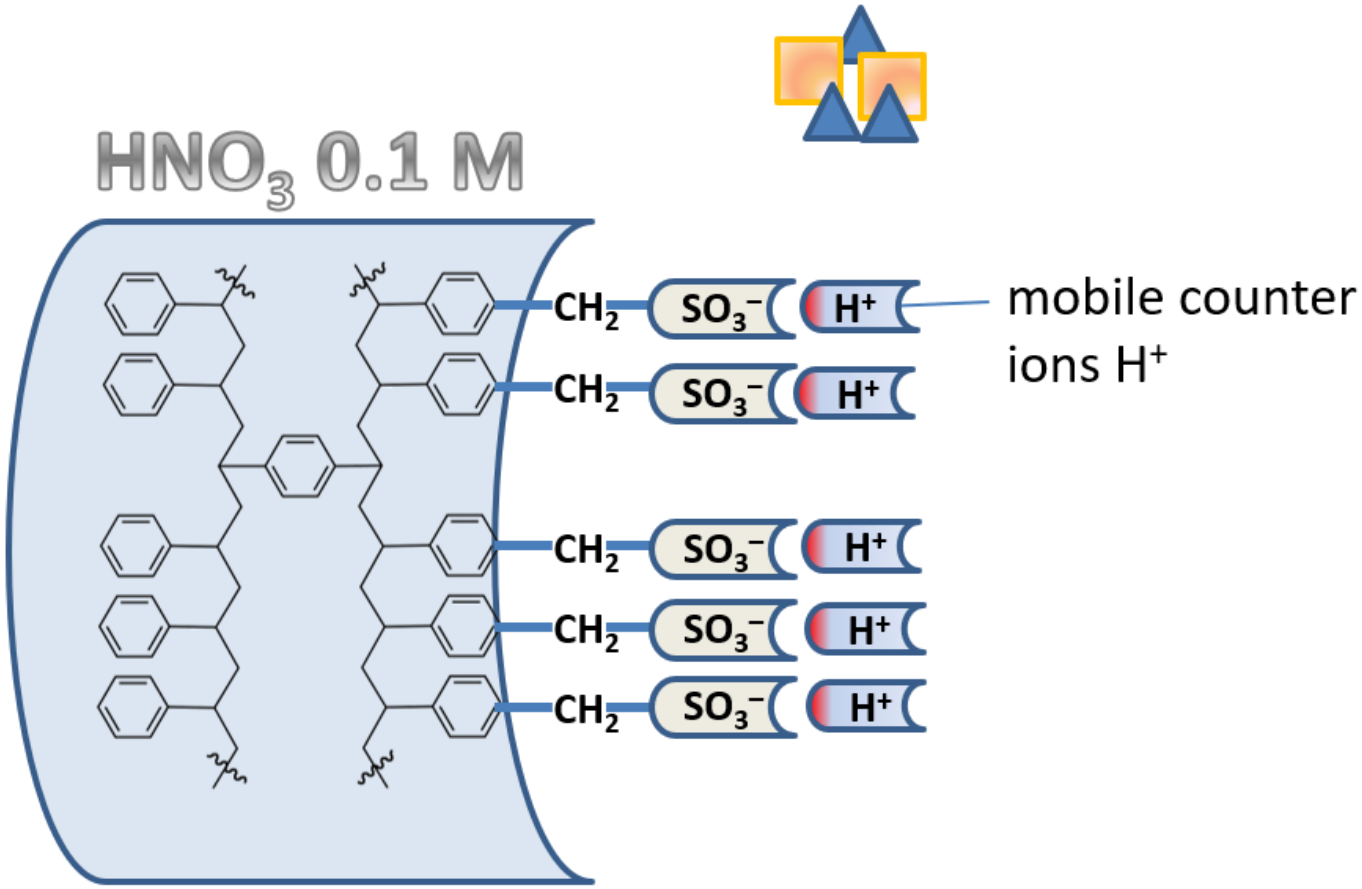
- The process is **reversible.**

- The exchange reactions take place on the basis of equivalency in accordance with the principle of **electro neutrality**. The number of milimoles of an ion sorbed by an exchange should correspond to the number of milimoles of an **equally charged ion** that has been released from the ion exchange.

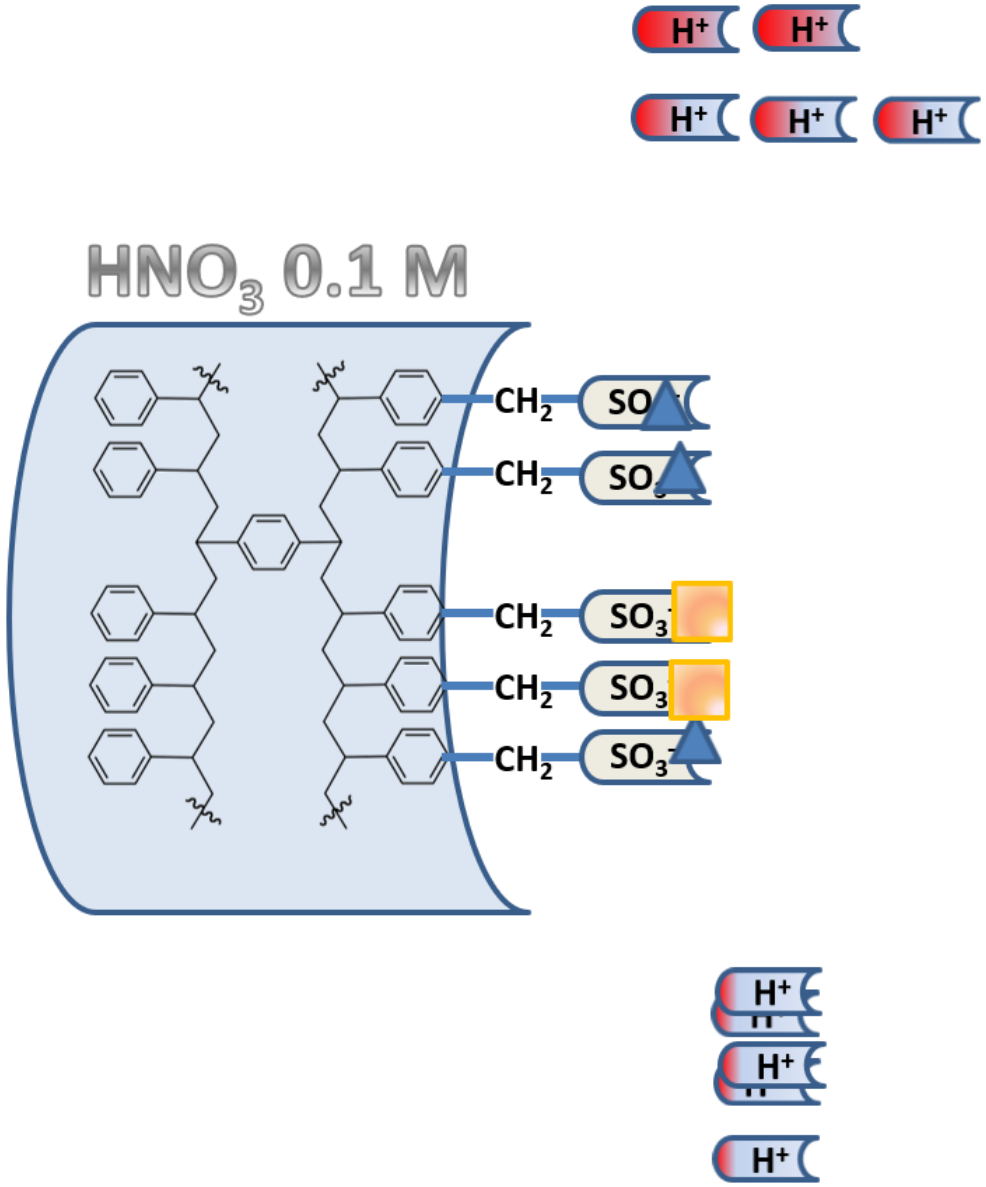
- The selectivity is proportional to the valence.
  (For example, **$Na^+ < Ca^{2+} < Al^{3+} < Th^{4+}$**).

- When the valence is same, the selectivity become higher in order of increasing atomic number
  (**$Li^+ < Na^+ < K^+ < Rb^+ < Cs^+$, $Mg^{2+} < Ca^{2+} < Sr^{2+} < Ba^{2+}$**)

1. Starting conditions



2. Adsorption of sample substance



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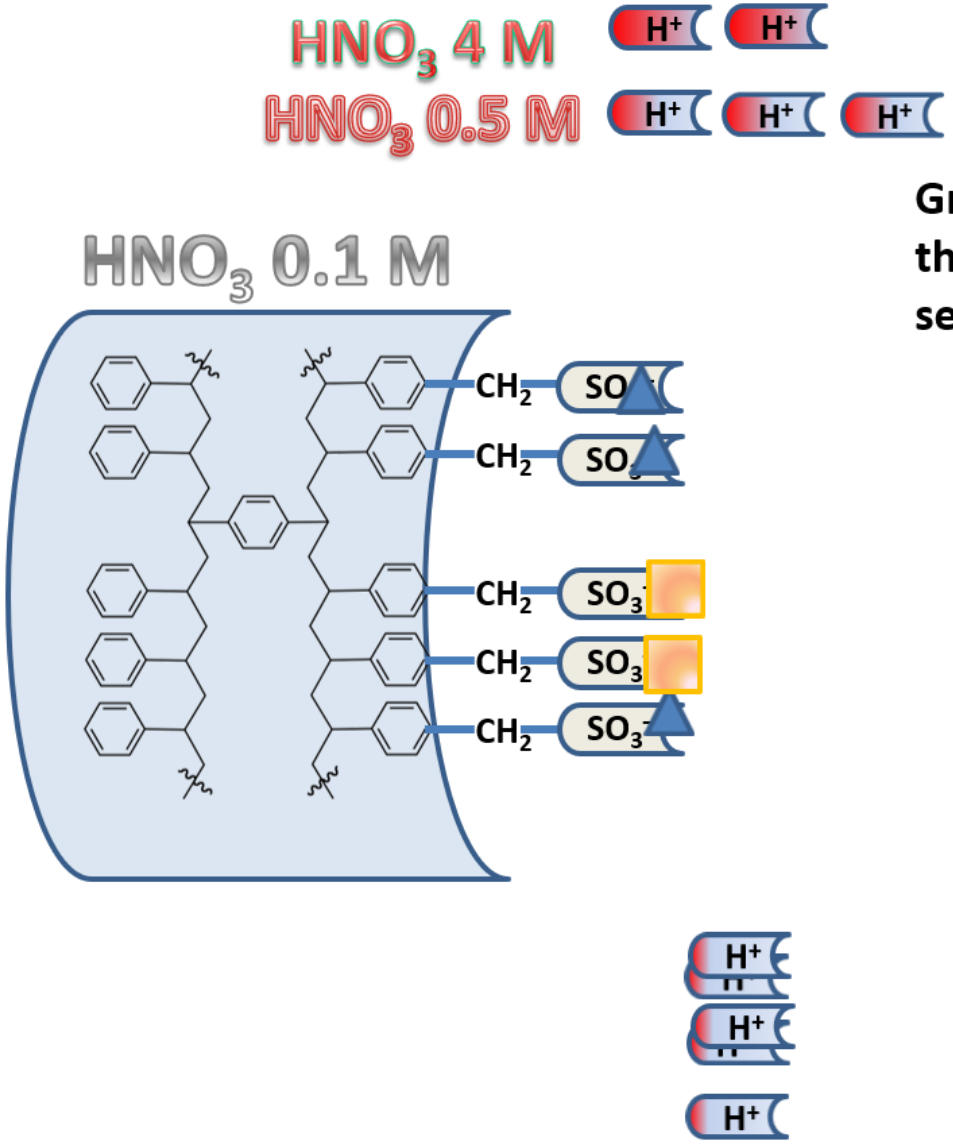


Gradient elution is accomplished by increasing the concentration of the eluent during the separation

3. Start of desorpion

HNO_3 4 M

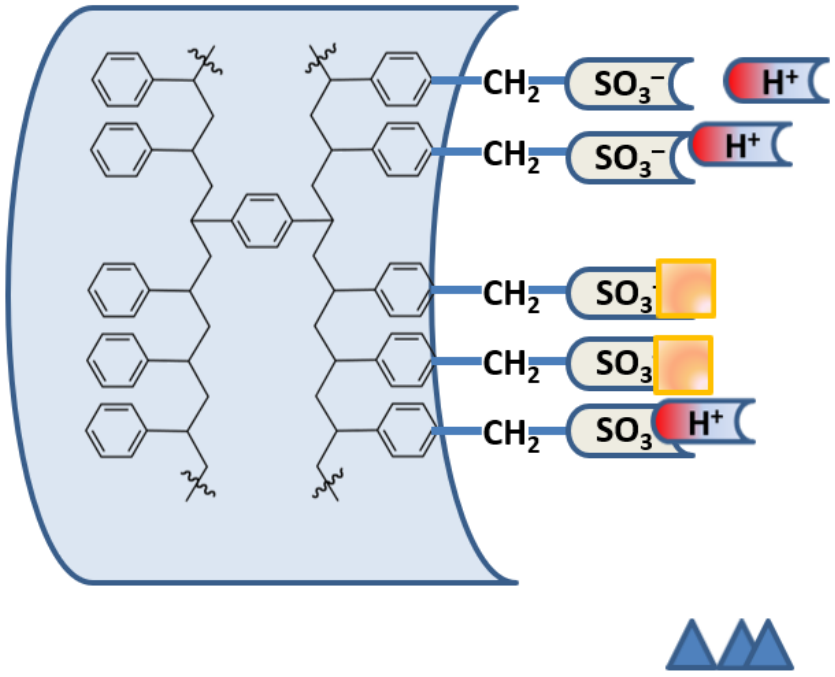
HNO_3 0.5 M

H^+ H^+

M_1^+

M_2^{++}

HNO_3 0.1 M



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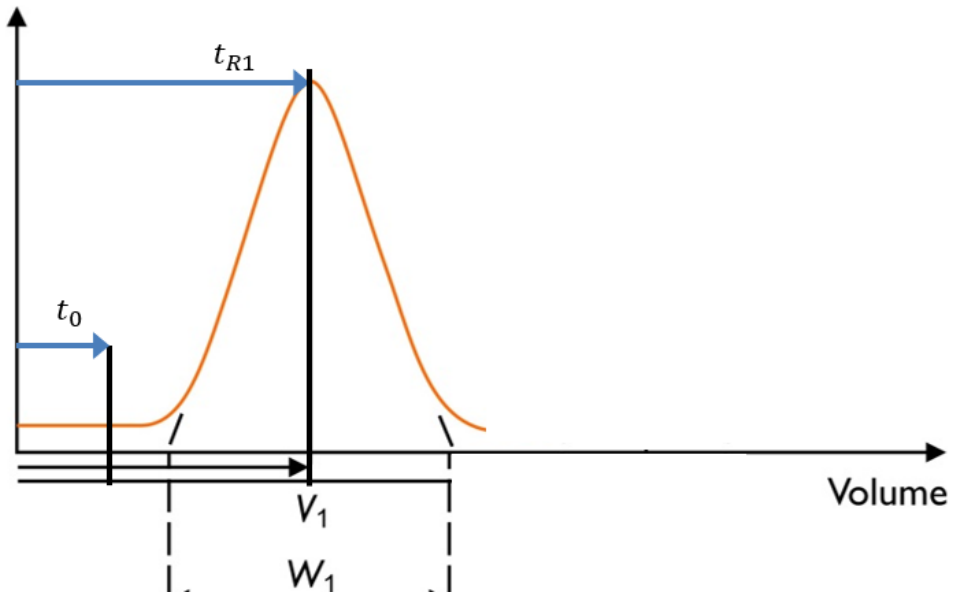
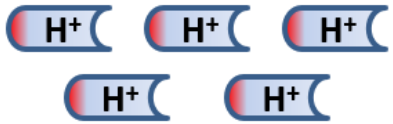
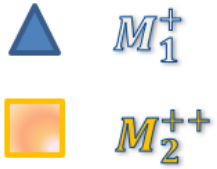


4. End of desorpion





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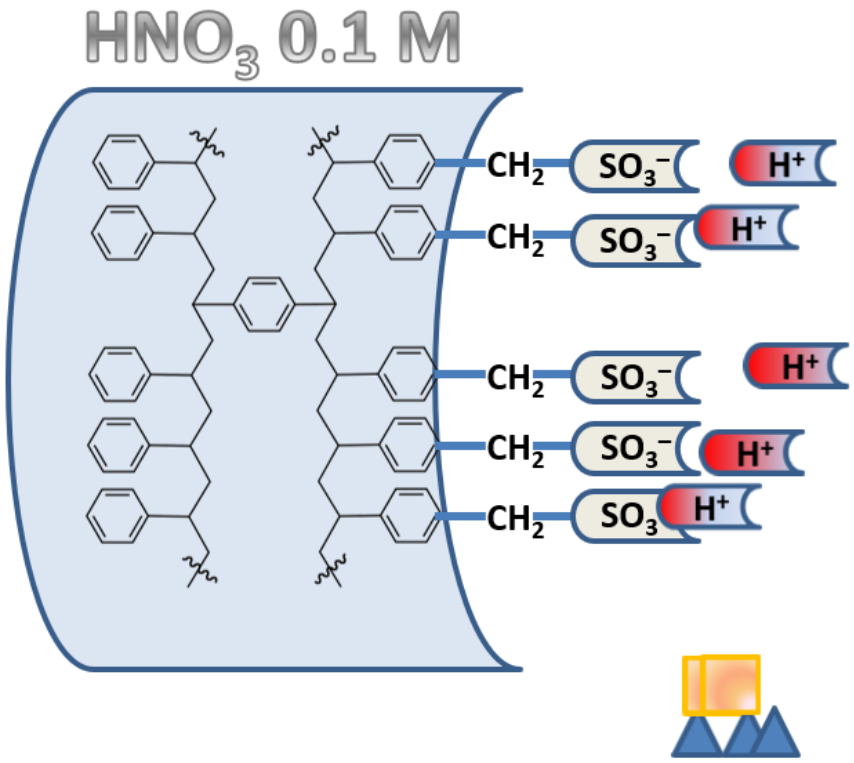
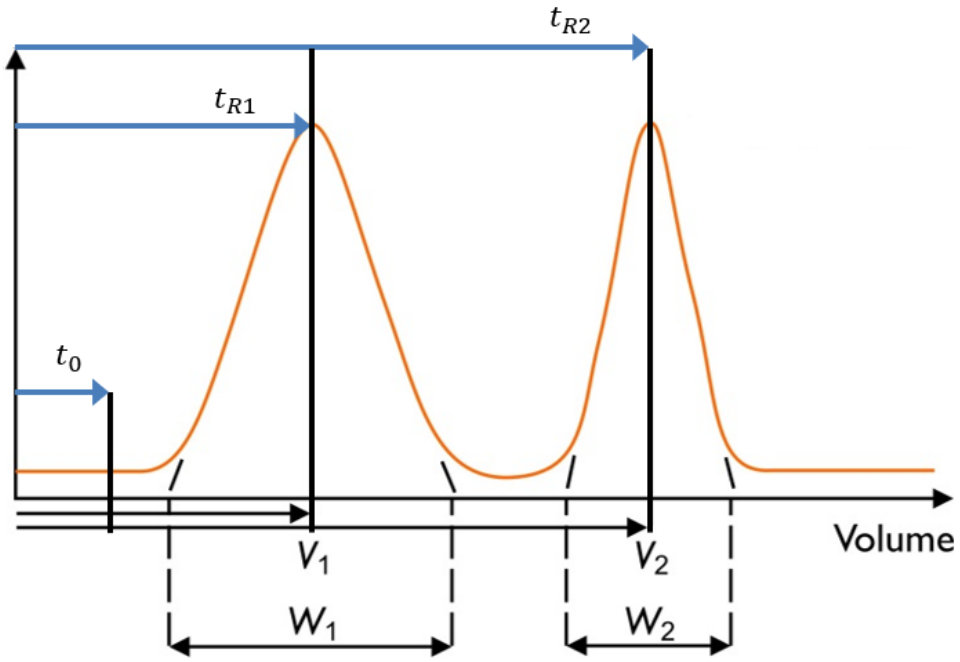




Strong Acid Cation Exchange Resins

DOWEX 50W: hydrogen form

AG MP-50: hydrogen form, macroporous

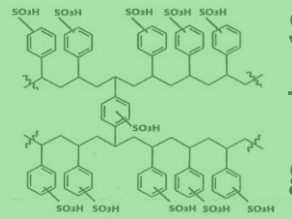
AMINEX RESIN: hydrogen form, macroporous

SYKAM RESIN: hydrogen form, macroporous

Comparison of Cation Exchange Resins

What are the differences?

Functional group



Sulfonic acid functional group

Supporting material

styrene divinylbenzene copolymer

Level of cross-link

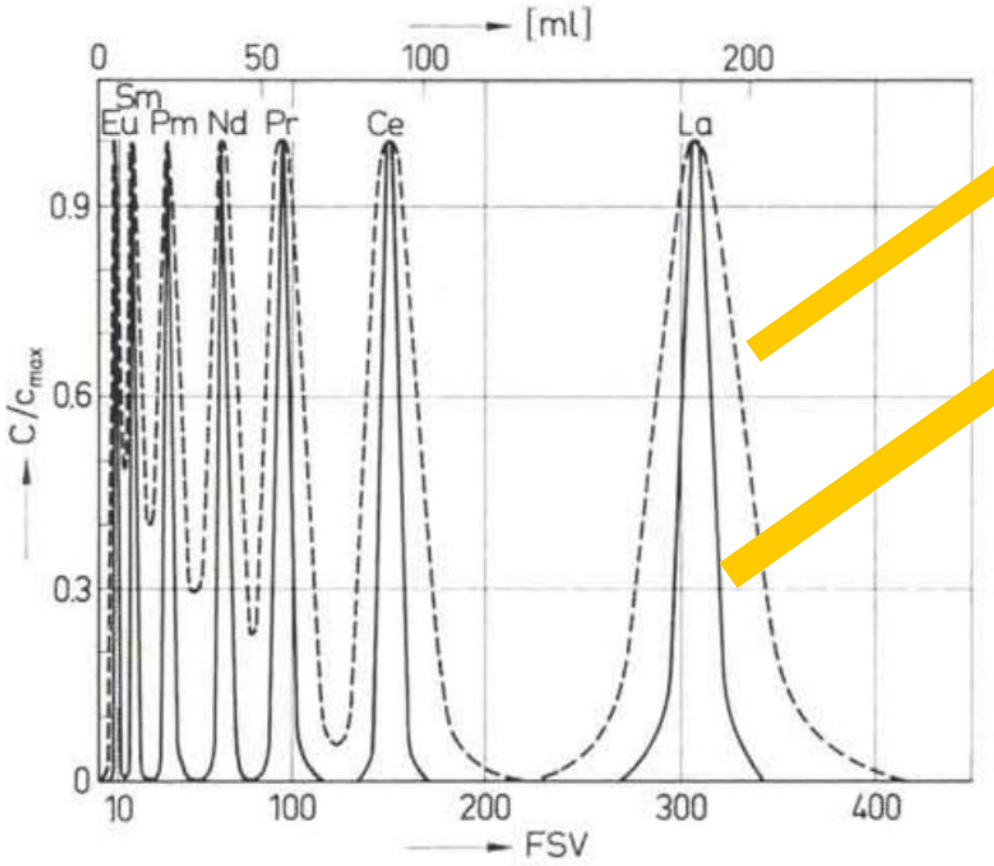
Particle size

Particle size distribution

Price

Resolution increases with decreasing particle size and narrower size distribution ranges.

DOWEX versus AMINEX Resin



Vergleich von Lanthanidentrennungen an Aminex A 5 (ausgezogene Kurve) und Dowex AG 50 X 8 (70 μ strömungsklassiert, gestrichelte Kurve). Elutionsmittel ist 0,5 m α-Hydroxyisobuttersäure, p_H = const.

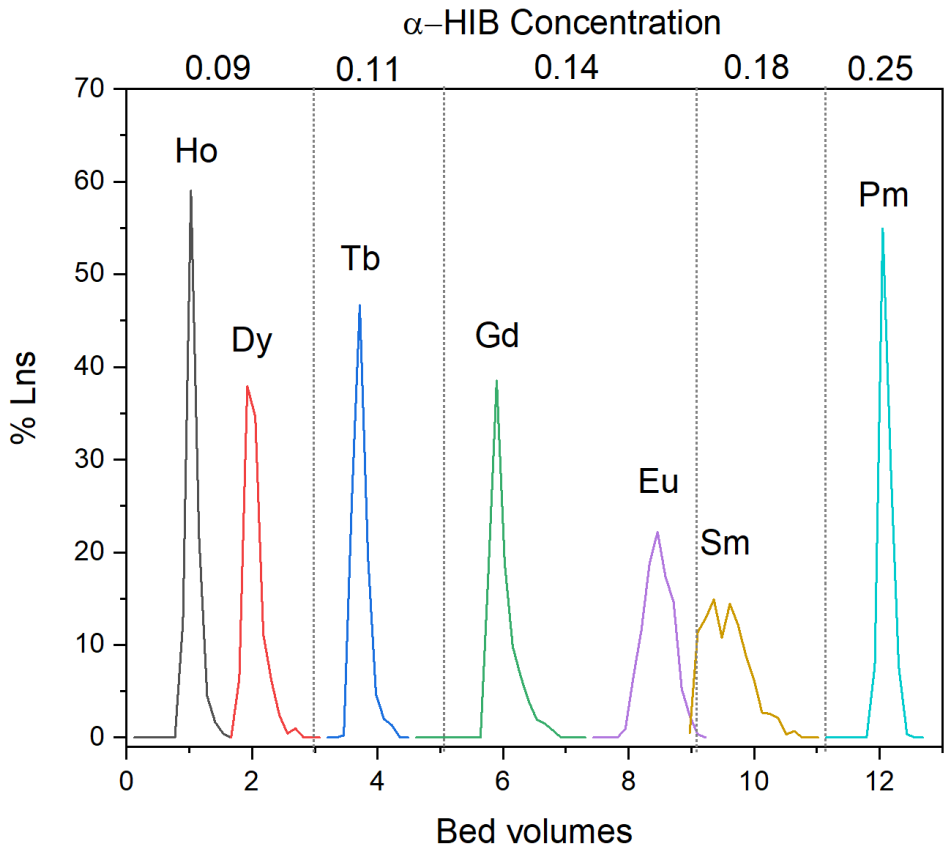
DOWEX 50W resin: 70 µm

Aminex resin: 15 µm

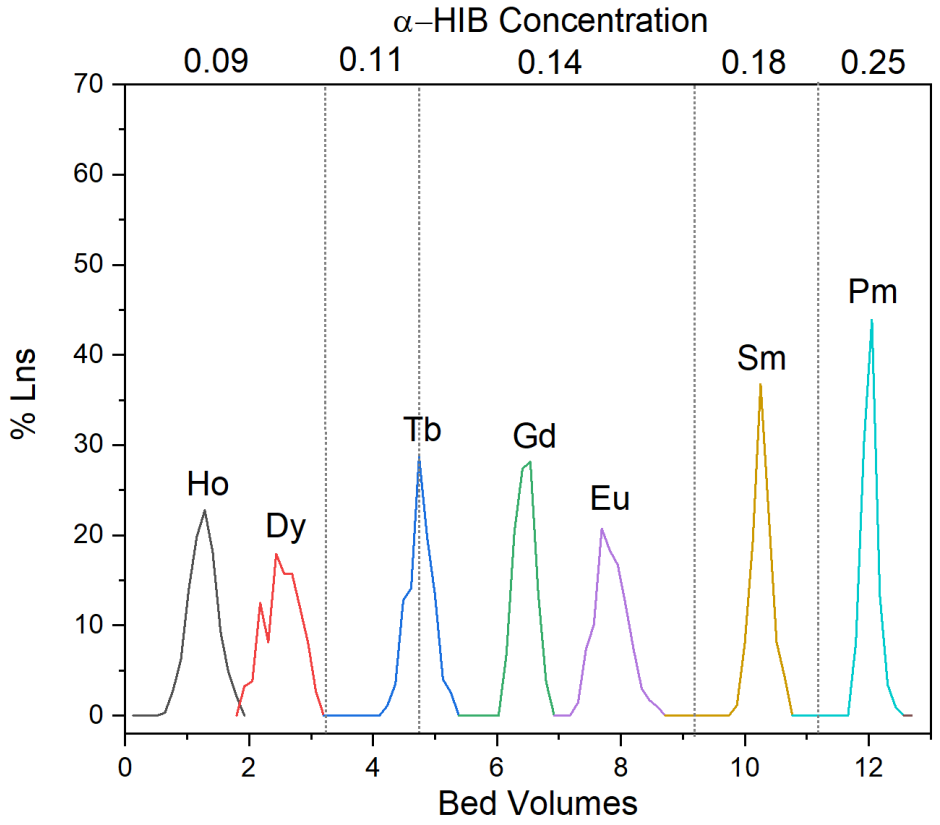
Hohlein et al. 1969

AMINEX Resin versus SYKAM Resin

Aminex Resin (7-11 µm)



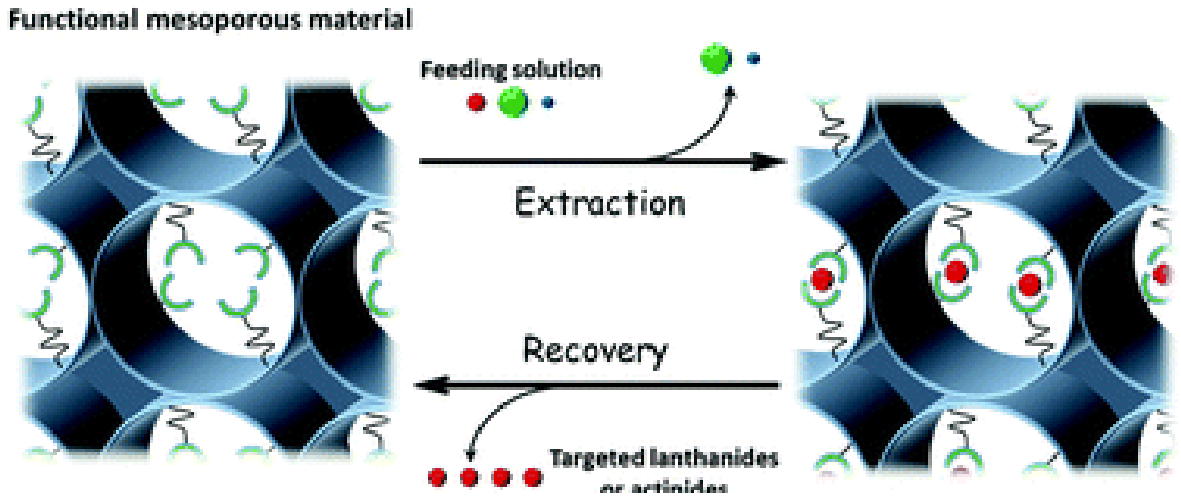
Sykam Resin (12-22 µm)



Talip et al., Anal. Chem. 2021, 93, 10798−10806.

Extraction Chromatography

Extraction chromatography is the application of conventional **solvent extraction chemistry in a chromatographic mode**.



Traditional polymeric resin material employed as the backbone for EXC material or ordered mesoporous silica and carbon nanoparticles are used due to their high surface areas, tunable pore sizes, large pore volumes, and uniform morphology.

Dalton Trans., 2016, 45, 14832–14854.

Extraction Chromatography

SOLVENT EXTRACTION AND ION EXCHANGE
2020, VOL. 38, NO. 3, 251–289
https://doi.org/10.1080/07366299.2020.1720958

Taylor & Francis
Taylor & Francis Group

A Survey of Extraction Chromatographic *f*-Element Separations Developed by E. P. Horwitz

Erin R. Bertelsen [a], Jessica A. Jackson[a], and Jenifer C. Shafer [a,b]

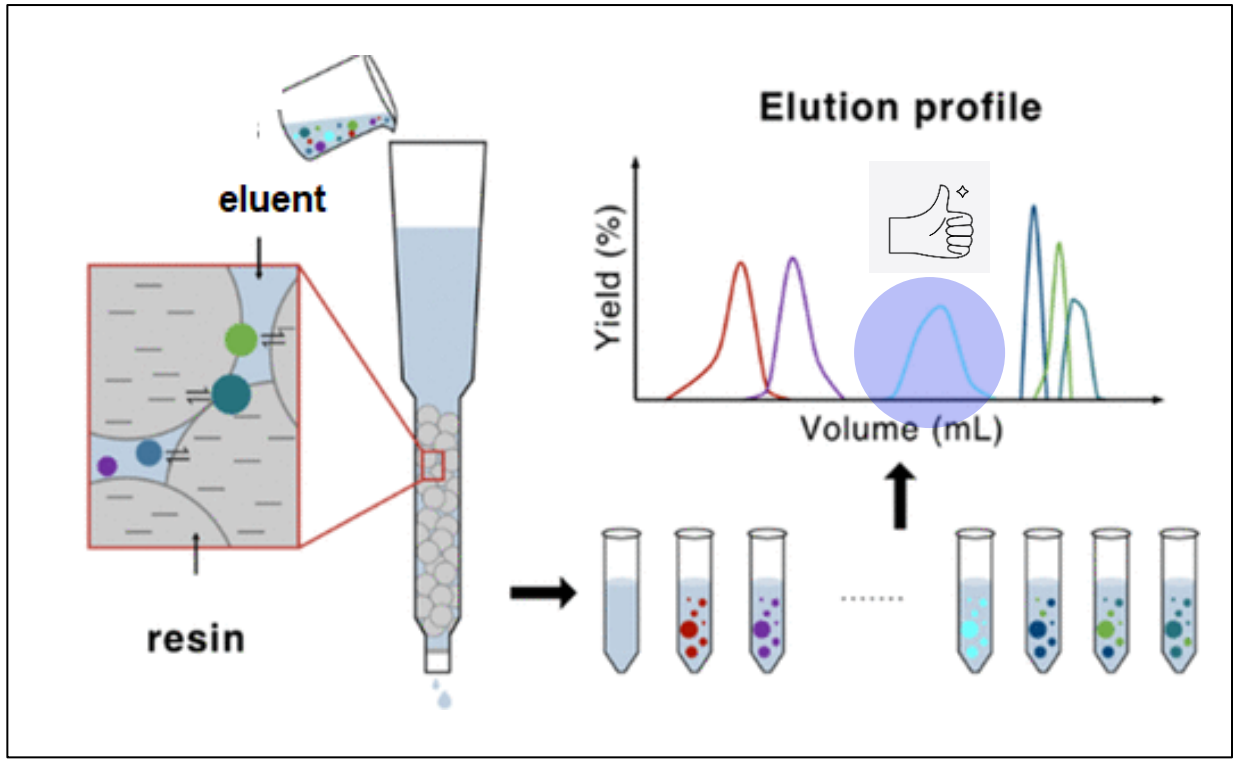
[a]Department of Chemistry, Colorado School of Mines, Golden, CO, USA; [b]Nuclear Science and Engineering Program, Colorado School of Mines, Golden, CO, USA

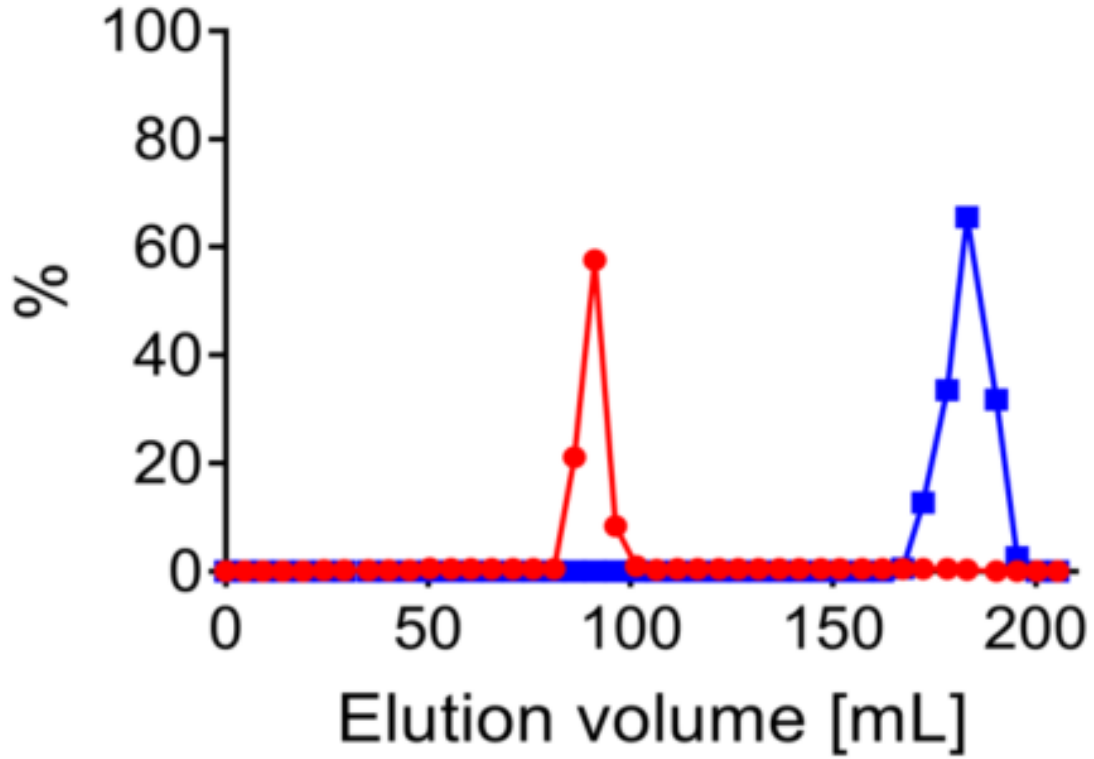
Key separations and extractants used for EXC resins developed by Horwitz.

EXC resin	Key separations	Extractant
TEVA	An(IV)/An(III,V,VI)	Aliquat-336
LN	Trivalent *f*-elements:	HDEHP
LN2	Ln/Ln′, An/Ln, An/An′	HEH[EHP]
LN3		H[DTMPP]
Actinide	An(III, VI, IV)/matrix	Dipex
UTEVA	An(IV,VI)/An(III,V)	DAAP
UTEVA-2	An(IV,VI)[a]/An(III)	DAAP/Cyanex 923
TRU	An(IV,VI)[b]/An(III)	CMPO in TBP
DGA	An(III)[c]/An(IV)/An(VI)	TODGA or TEHDGA

Elution Profiles

What good separation means?



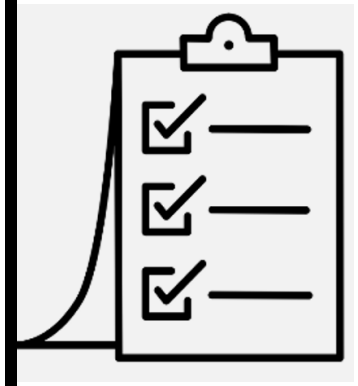


L. Houyu et al., ACS Earth Space Chem., 5 (2021) 55–65

Quality Control

Quality Control

For novel radionuclides



driven by research

- ✓ **Target material** (impurities)
- ✓ **Irradiated target** (long-lived impurities)
- ✓ **Purified solution** (radionuclidic purity, chemical purity)
- ✓ **Labelled molecule** (radiochemical purity)

For GMP

driven by EU Pharmacopia

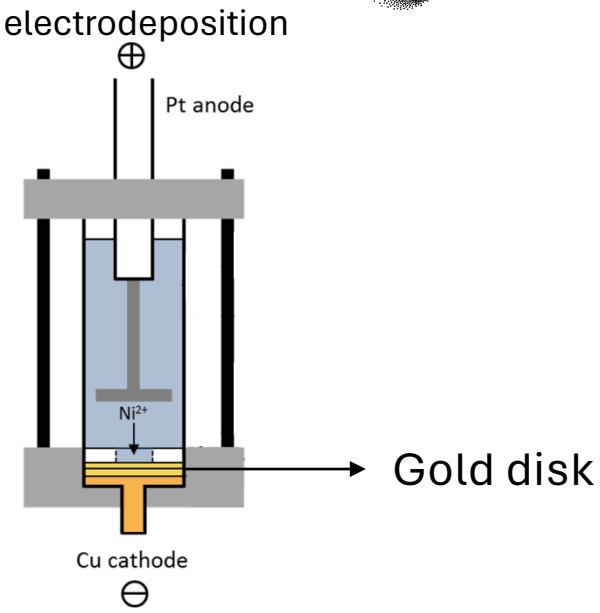
- ✓ **Radioactive precursor** 
- ✓ **Chemical precursor** 
- ✓ **Radiopharmaceutical** 

See Kristof's lecture

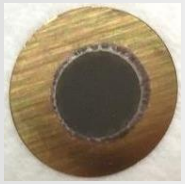
Examples

Production of Cupper-64

Zn 60	Zn 61	Zn 62	Zn 63	Zn 64	Zn 65	Zn 66
2.38 m	89.1 s	9.193 h	38.1 m	49.17	243.93 d	27.73
β+ 2.5, 3.1... γ 670, 61, 273 334...	β+ 4.6... γ 475, 1660 970...	ε β+ 0.6 γ 597, 41, 548 508...	β+ 2.3... γ 670, 962 1412...	σ 0.731 $\sigma_{n,\alpha}$ 1.1E-5 $\sigma_{n,p}$ < 1.2E-5	ε, β+ 0.3 γ 1115... σ 66, $\sigma_{n,\alpha}$ 2.0	σ 0.62, $\sigma_{n,\alpha}$ < 2E-5
Cu 59	**Cu 60**	**Cu 61**	**Cu 62**	**Cu 63**	**Cu 64**	**Cu 65**
81.5 s	23.7 m	3.339 h	9.67 m	69.15	12.7004 h	30.85
β+ 3.8... γ 1302, 878 339, 465...	β+ 2.9, 3.8... γ 1332, 1792 826...	β+ 1.2... γ 283, 656, 67 1185...	β+ 2.9... γ (1173...)	σ 4.50	ε γ (1346) β− 0.6, β+ 0.7 σ ~270	σ 2.17
Ni 58	**Ni 59**	**Ni 60**	**Ni 61**	**Ni 62**	**Ni 63**	**Ni 64**
68.0769	$7.6 \cdot 10^4$ a	26.2231	1.1399	3.6345	100 a	0.9256
σ 4.39 $\sigma_{n,\alpha}$ < 0.000030	ε, β+... no γ σ 73, $\sigma_{n,\alpha}$ 12.3 $\sigma_{n,p}$ 2.0, σ_{abs} 88	σ 2.45	σ 2.1 $\sigma_{n,\alpha}$ < 0.000030	σ 14.9	β− 0.07 no γ σ 24.4	σ 1.63

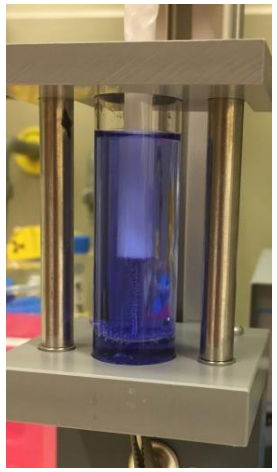


$^{64}Ni(p,n)^{64}Cu$



60 mg ^{64}Ni target (99.1 % enriched)

11 MeV, 50 µA, 4 h irradiation EOB 8 GBq **^{64}Cu**



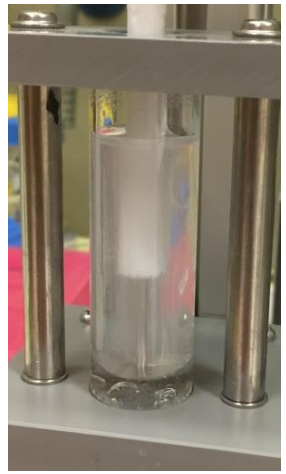
dark blue

Time

(16 h)

2.6 V

30mA



Clear/colorless

N. van der Meulen et al., J. Label. Compd. Radiopharm, 2020, 62, 460.

Questions to be asked

- What should be separated? **Characterization of the target**
- Separation time? **Half-life of the desired radionuclide**
- Dissolution of the target? **Loading solution**
- **Available Kd data?** **Selection of the resins**
- Aimed decontamination factors? **Radiolabeling efficiency**
- Aimed separation yields? **EOB and EOS activities**
- Acidity and volume of the final solution? **Usage: preclinical/clinical**

To take into account: minimizing the radioactive waste volume & recycling the target material

Separation of Cupper-64

Separation of Ni, Co and Cu

Commonly used method in the past

Anion exchange resin: AG1-X8 resin

Elution order: Ni – Co – **Cu**

Cation exchange resin: AG-MP 50 resin

Elution order: **Cu** – Co – Ni

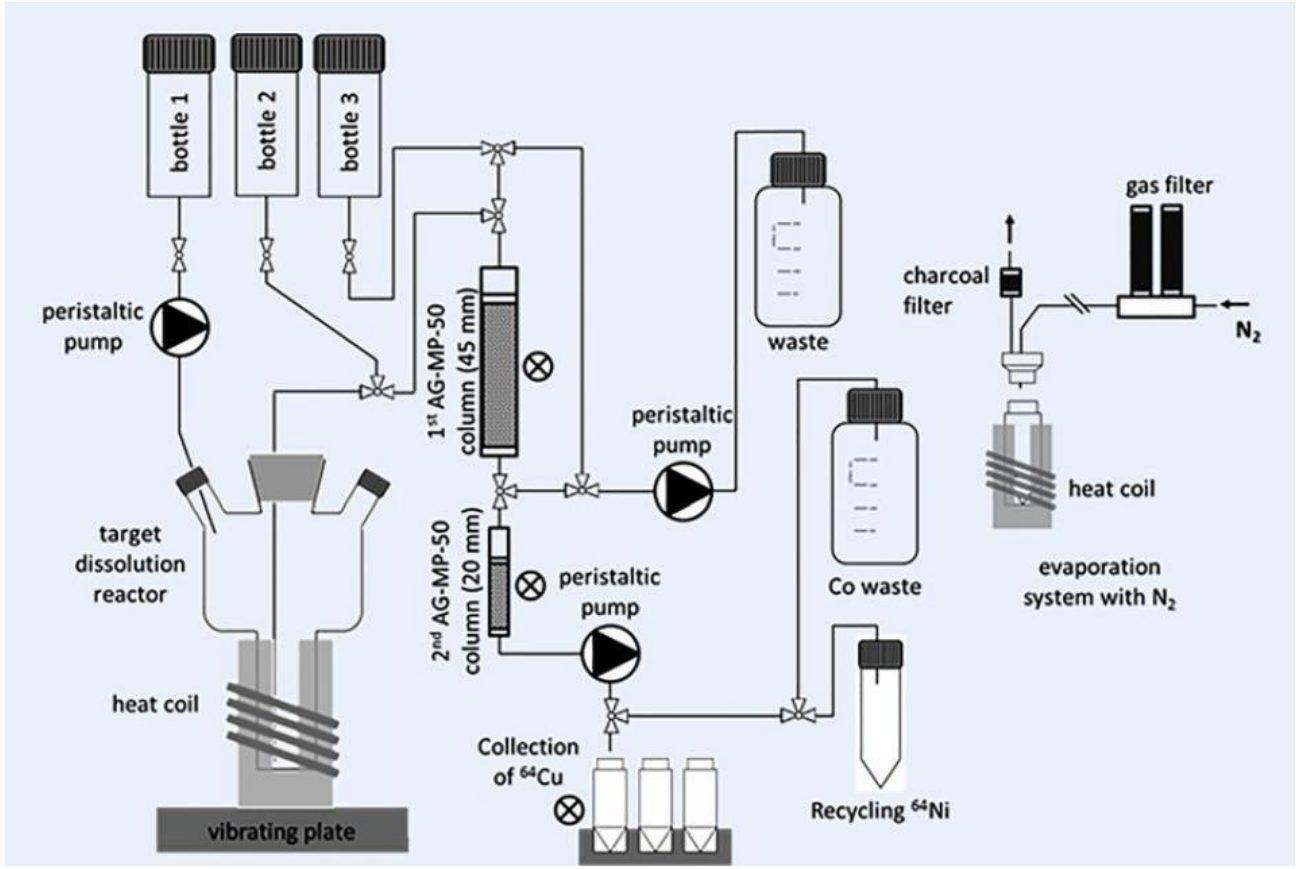
0.1 M HCl/60% Acetone ^{64}Cu

0.2 M HCl/95% Acetone ^{55,57,61}Co

2 M HCl ^{64}Ni

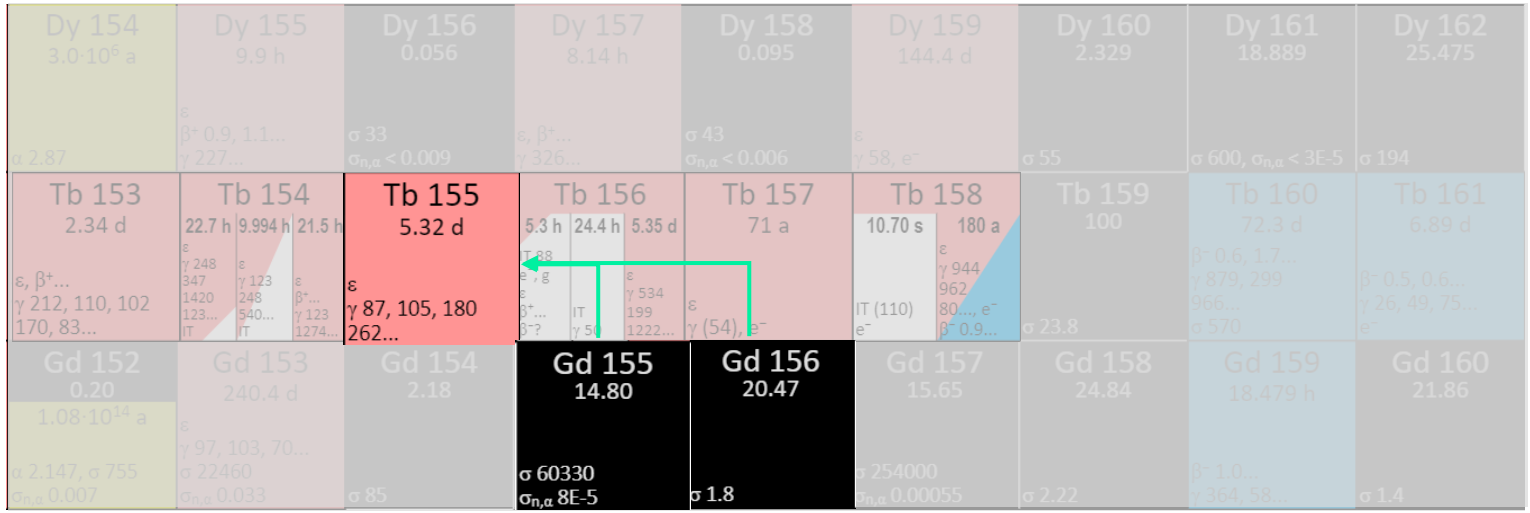
Final product in 0.05 M HCl

F. Strelow, Talanta, 1988, 35, 385.



N. van der Meulen et al., J. Label. Compd. Radiopharm, 2020, 62, 460.

Production of Terbium-155



$^{155}Gd(p,n)^{155}Tb$

100 mg $^{155}Gd_2O_3$ target (91.9 %)

25 µA, 8 h irradiation EOB: **200 MBq ^{155}Tb**

$^{156}Gd(p,2n)^{155}Tb$

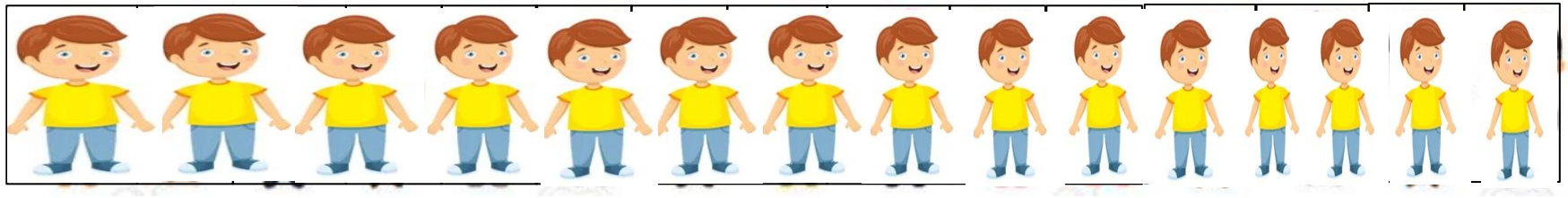
100 mg $^{156}Gd_2O_3$ target (93.3%)

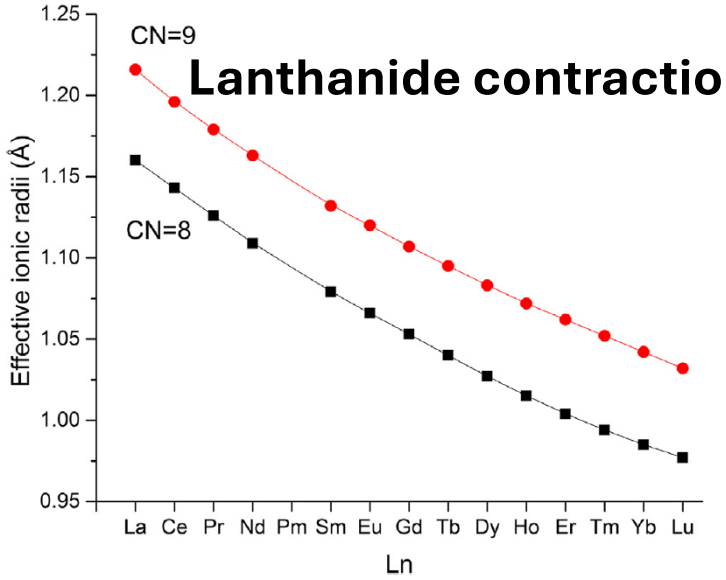
25 µA, 8 h irradiation EOB: **4.4 GBq ^{155}Tb**

Favaretto et al., EJNMMI Radiopharmacy and Chemistry, 6 (2021) 37.

How we separate lanthanides?/ Why it is difficult?

57	58	59	60	61	62	63	64	65	66	67	68	69	70	71
La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Lanthanum 138.905	Cerium 140.116	Praseodymium 140.908	Neodymium 144.242	Promethium 144.913	Samarium 150.36	Europium 151.964	Gadolinium 157.25	Terbium 158.925	Dysprosium 162.500	Holmium 164.930	Erbium 167.259	Thulium 168.934	Ytterbium 173.055	Lutetium 174.967

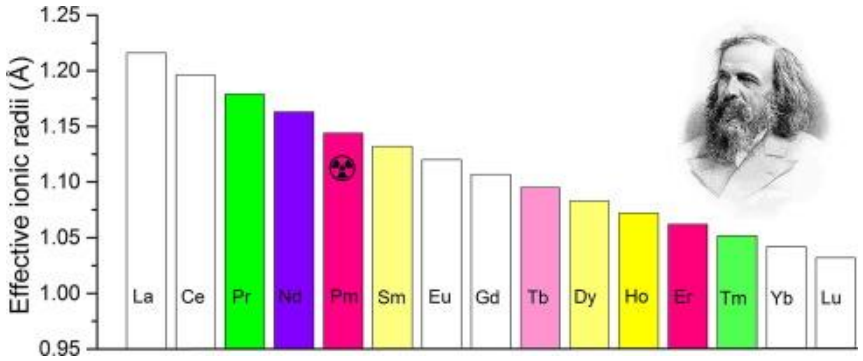




Lanthanide contraction

Effective ionic radii of 8- and 9-coordinated Ln^{3+}-ions

electronic configuration: [Xe]4fn (n = 0–14)

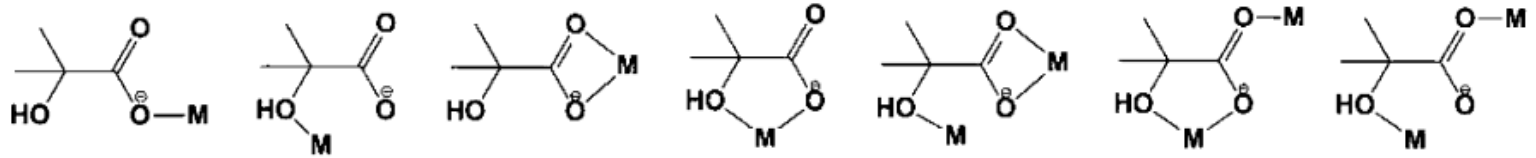


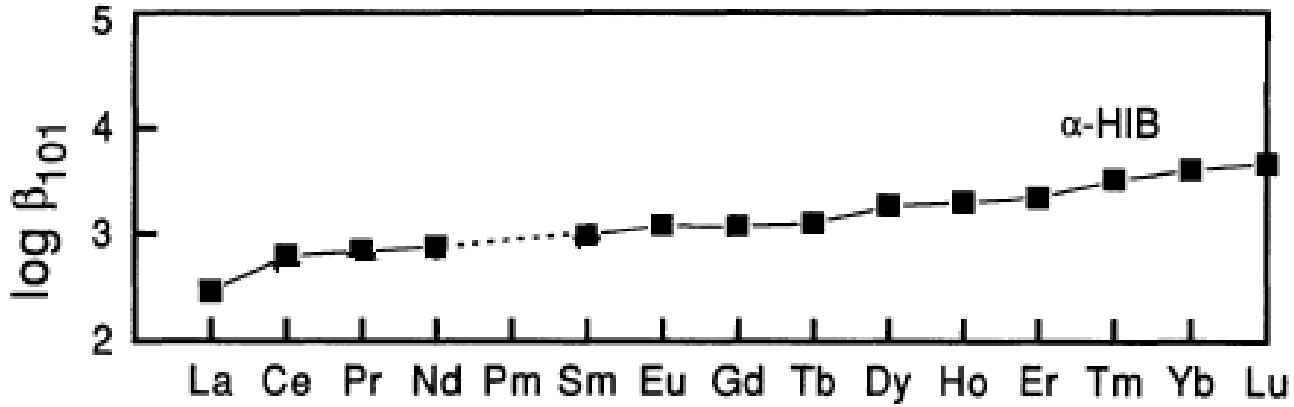
J. Peter et al., Coordination Chemistry Review, 2020, 406.

How we separate lanthanides?/ Why it is difficult?

57	58	59	60	61	62	63	64	65	66	67	68	69	70	71
La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Lanthanum	Cerium	Praseodymium	Neodymium	Promethium	Samarium	Europium	Gadolinium	Terbium	Dysprosium	Holmium	Erbium	Thulium	Ytterbium	Lutetium
138.905	140.116	140.908	144.242	144.913	150.36	151.964	157.25	158.925	162.500	164.930	167.259	168.934	173.055	174.967

Possible Coordination Modes of HIBA with Metal Ions





Separation of neighboring lanthanides?

57	58	59	60	61	62	63	64	65	66	67	68	69	70	71
La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Lanthanum 138.905	Cerium 140.116	Praseodymium 140.908	Neodymium 144.242	Promethium 144.913	Samarium 150.36	Europium 151.964	Gadolinium 157.25	Terbium 158.925	Dysprosium 162.500	Holmium 164.930	Erbium 167.259	Thulium 168.934	Ytterbium 173.055	Lutetium 174.967

Lanthanum Ytterbium

Gadolinium Terbium

neighbouring radiolanthanides

easier

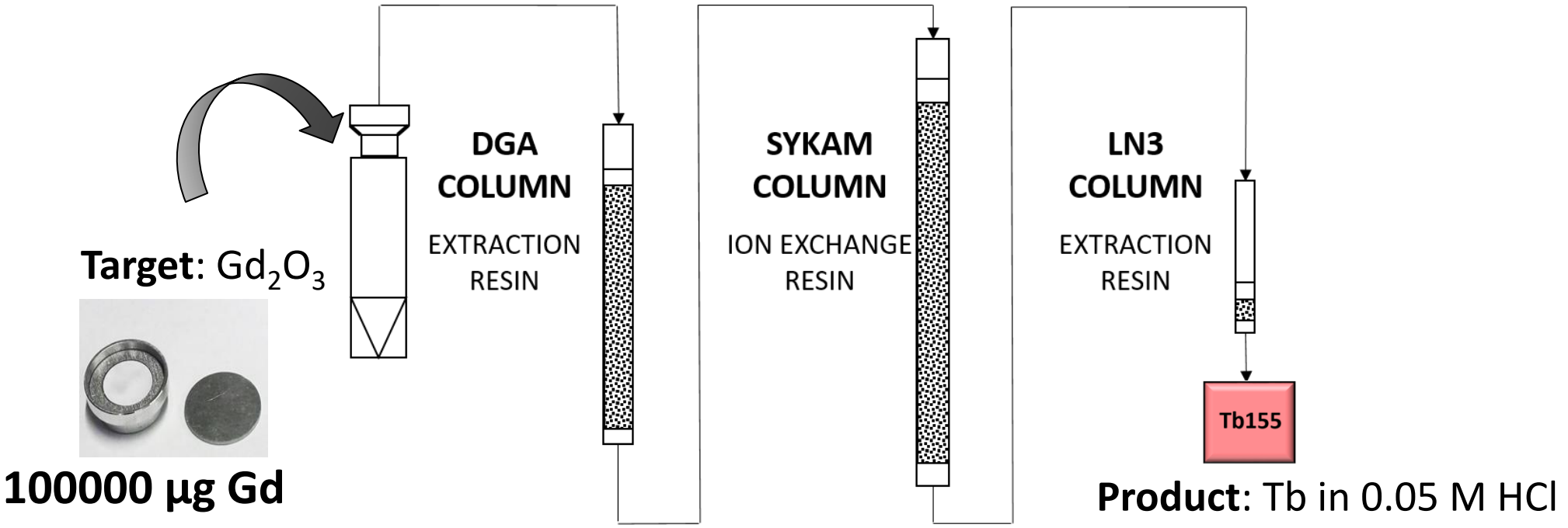
challenging

Lanthanides Separation: Devil in the details

Slight differences in the following parameters significantly affect the separation of the radiolanthanides, particularly for the neighboring radiolanthanides.

- **pH of the loading solution**
- **concentration of the eluents**
- **pH of the eluents**
- **column dimensions**
- **the particle size and homogeneity of the resins**
  (resolution increases with small particle size, but it will increase the back pressure)
- **flow rate** (for loading and elution)
- …

Separation of Terbium-155



Target: Gd_2O_3

100000 µg Gd

0.75 µg ^{155}Tb

Product: Tb in 0.05 M HCl

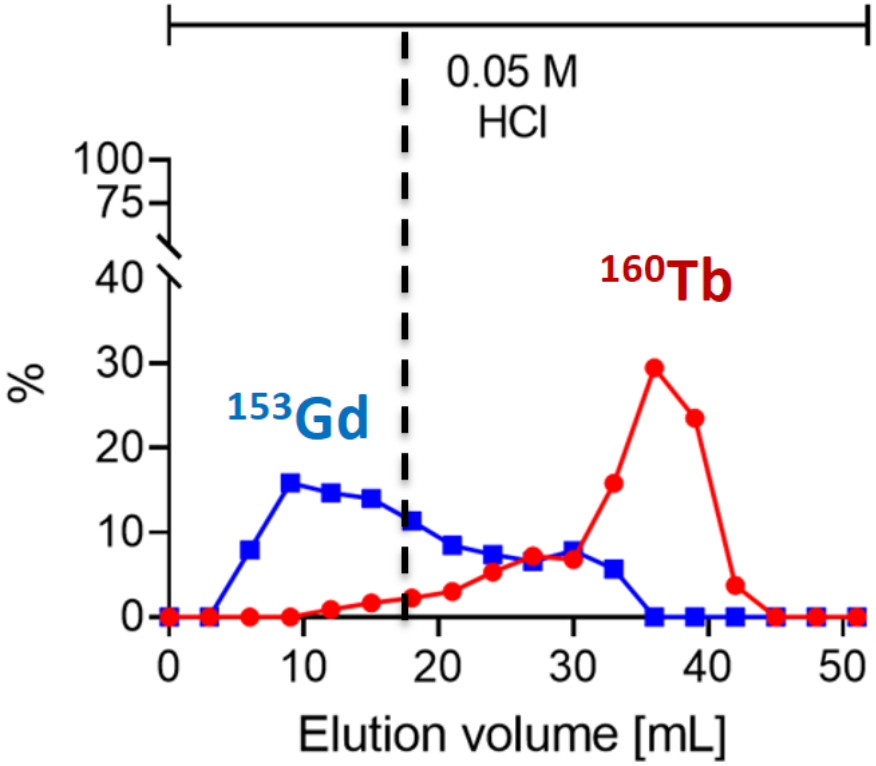
Favaretto et al., EJNMMI Radiopharmacy and Chemistry, 6 (2021) 37.

Experiments using gamma emitter tracers

Loading solution: 5 mL 7 M HNO_3
(5 µg Tb and 40 mg Gd)

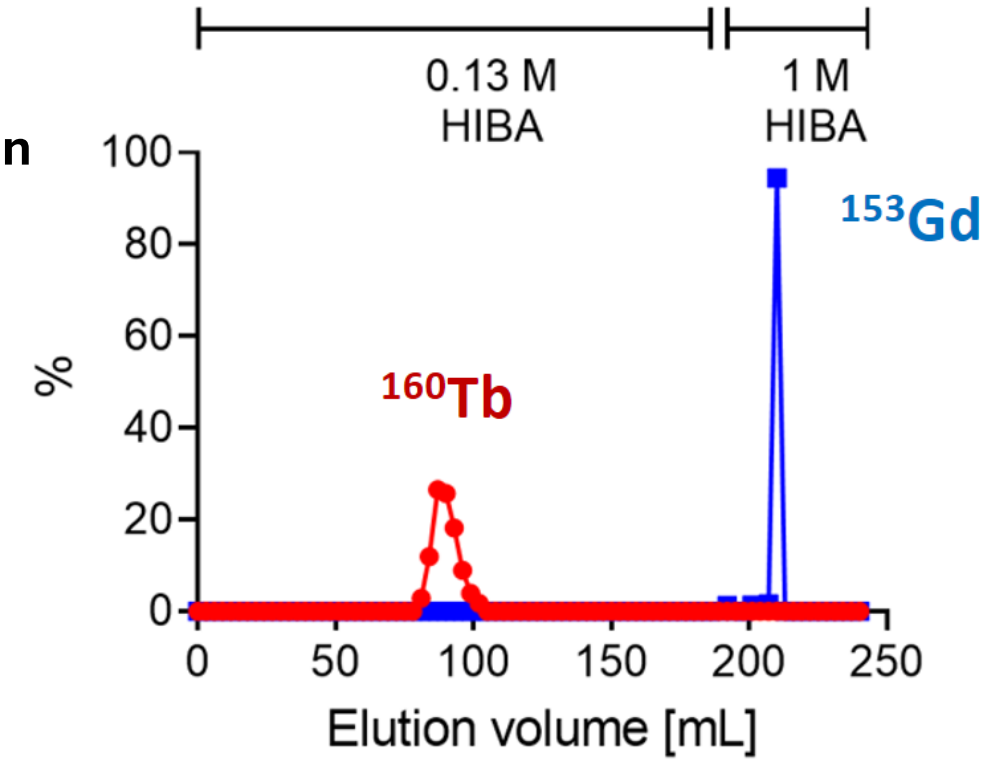
Loading solution: Tb fractions in 0.05 M HCl

DGA Resin



Tb fraction

Sykam Resin



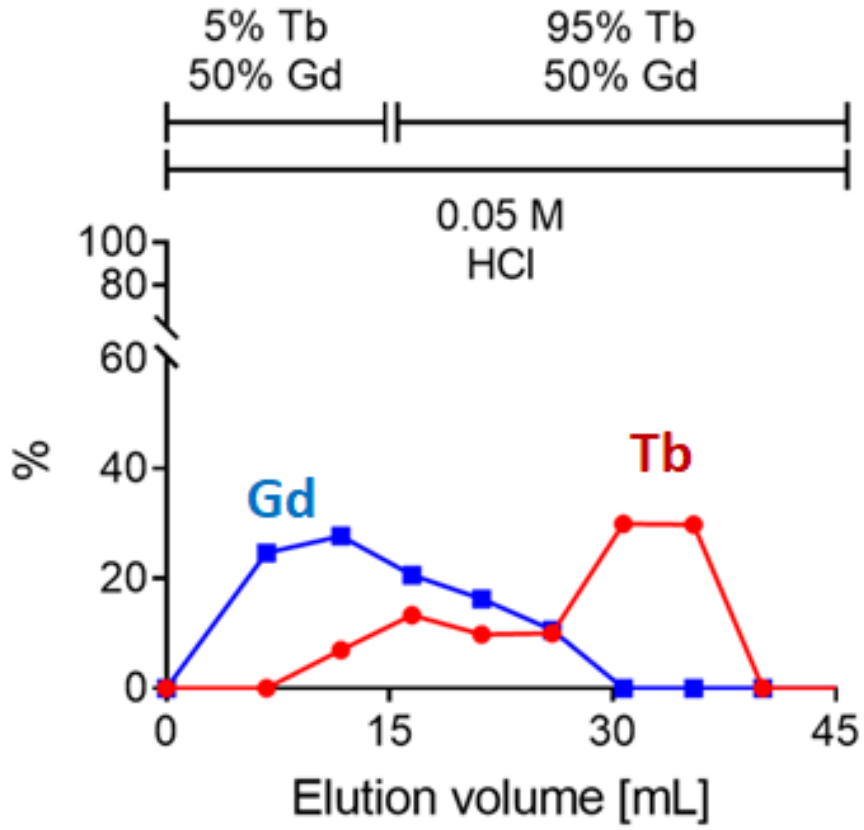
Experiments using ICP-OES standards

PSI

Loading solution: 5 mL 7 M HNO_3
(5 µg Tb and 40 mg Gd)

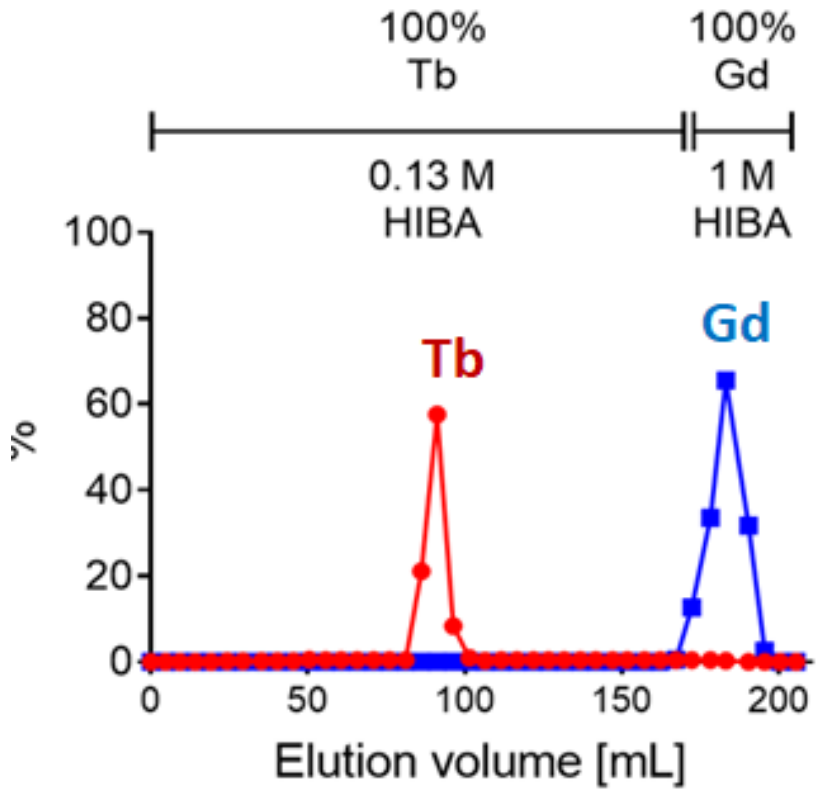
Loading solution: Tb fractions in 0.05 M HCl

DGA Resin



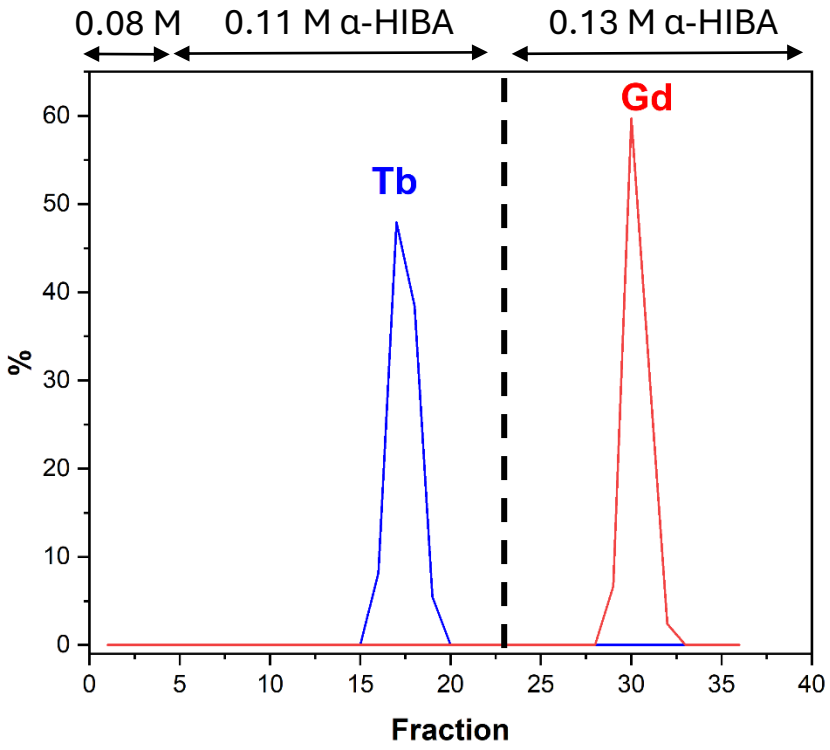
Tb fraction

Sykam Resin

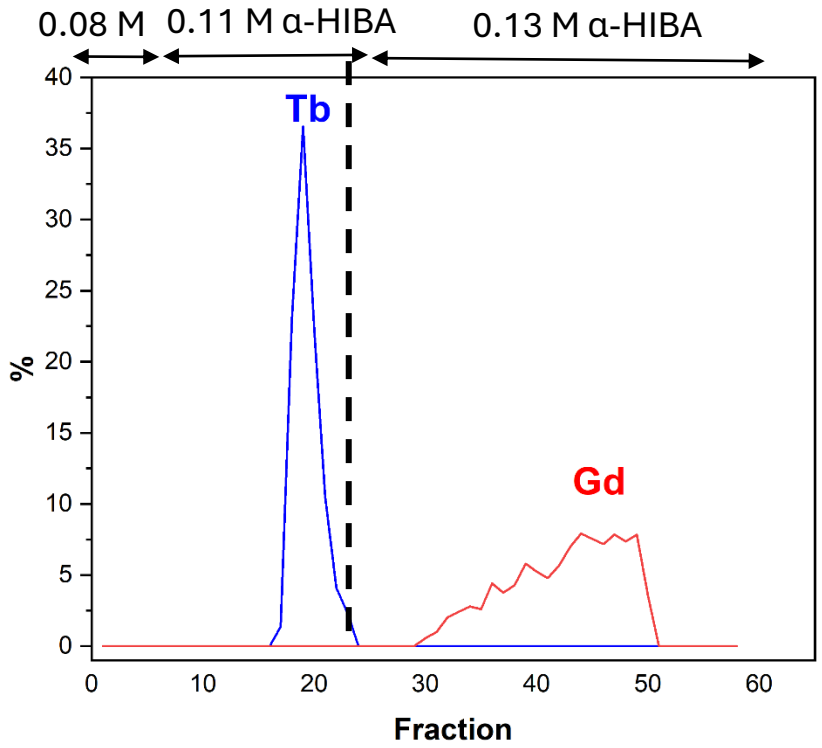


The Effect of Target Mass

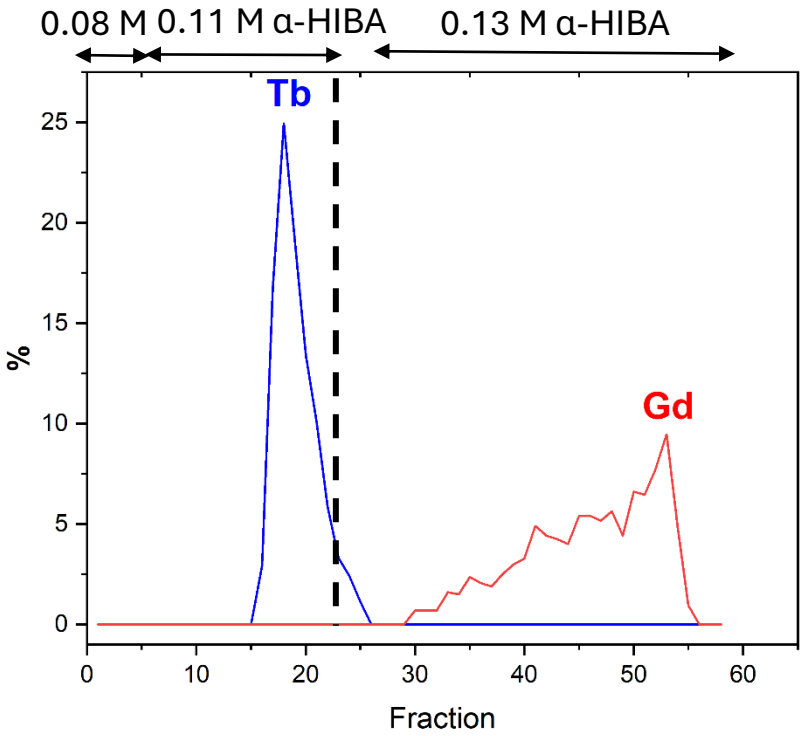
Separation system: Sykam - HIB



5 µg Tb **5 µg** Gd



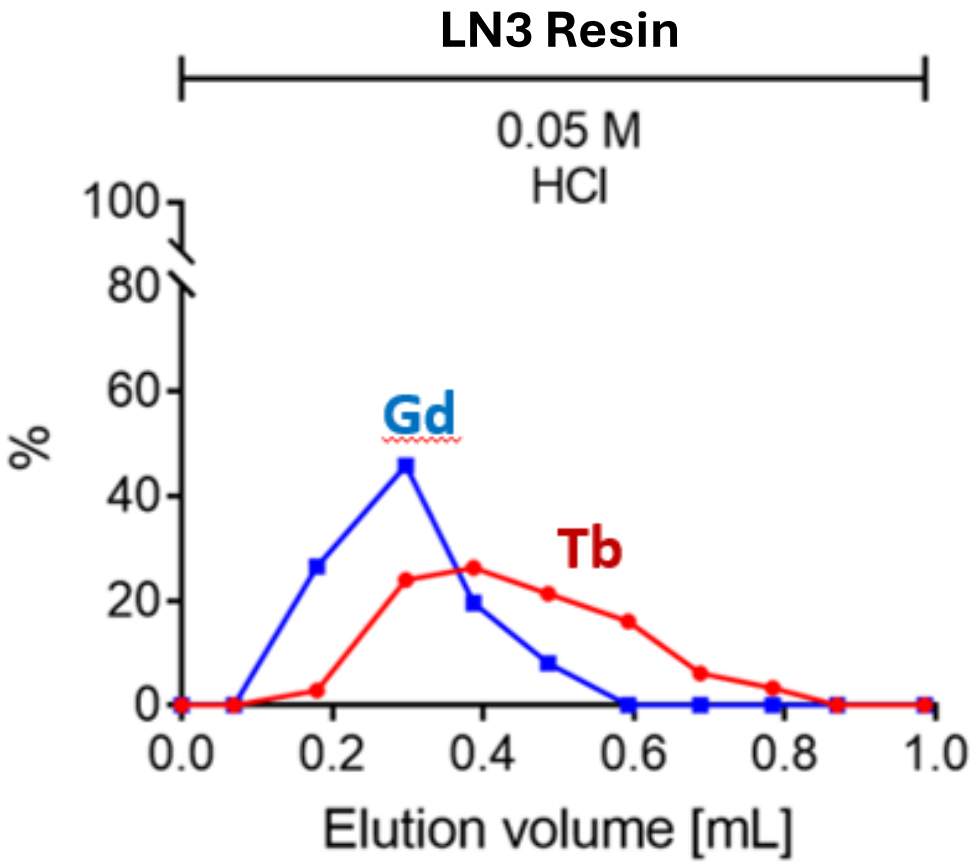
5 µg Tb **50 mg** Gd

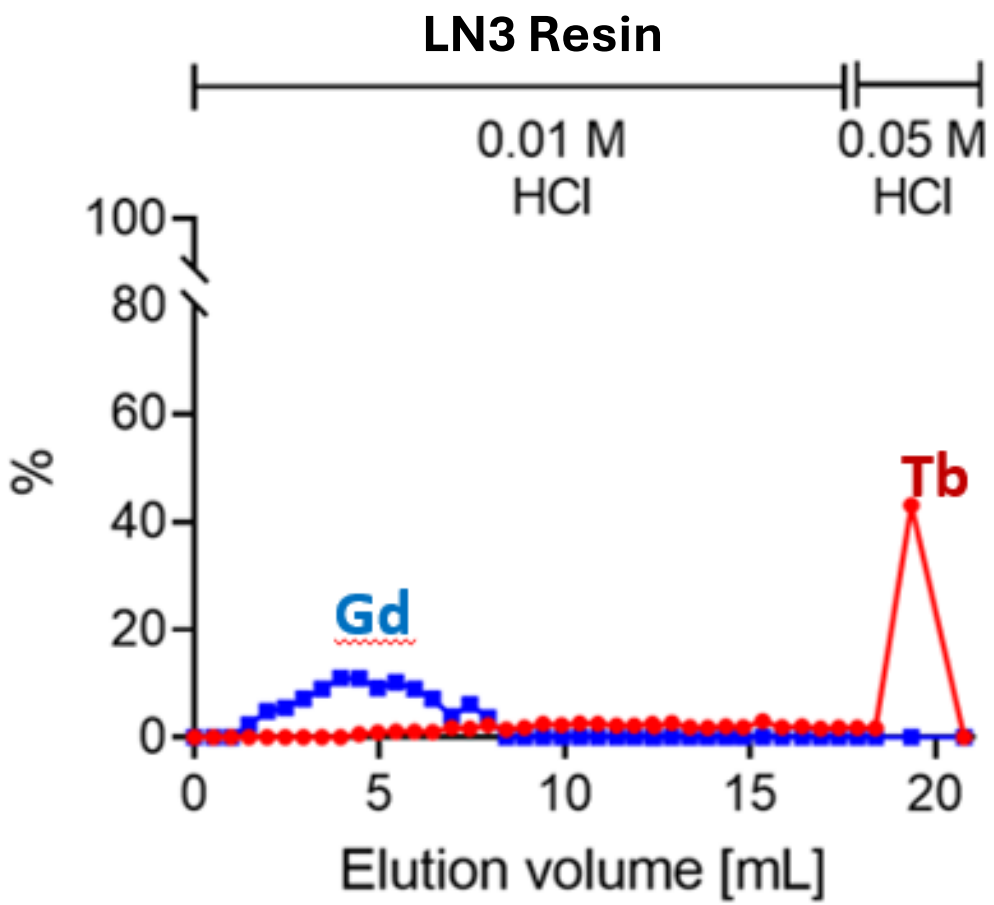


5 µg Tb **100 mg** Gd

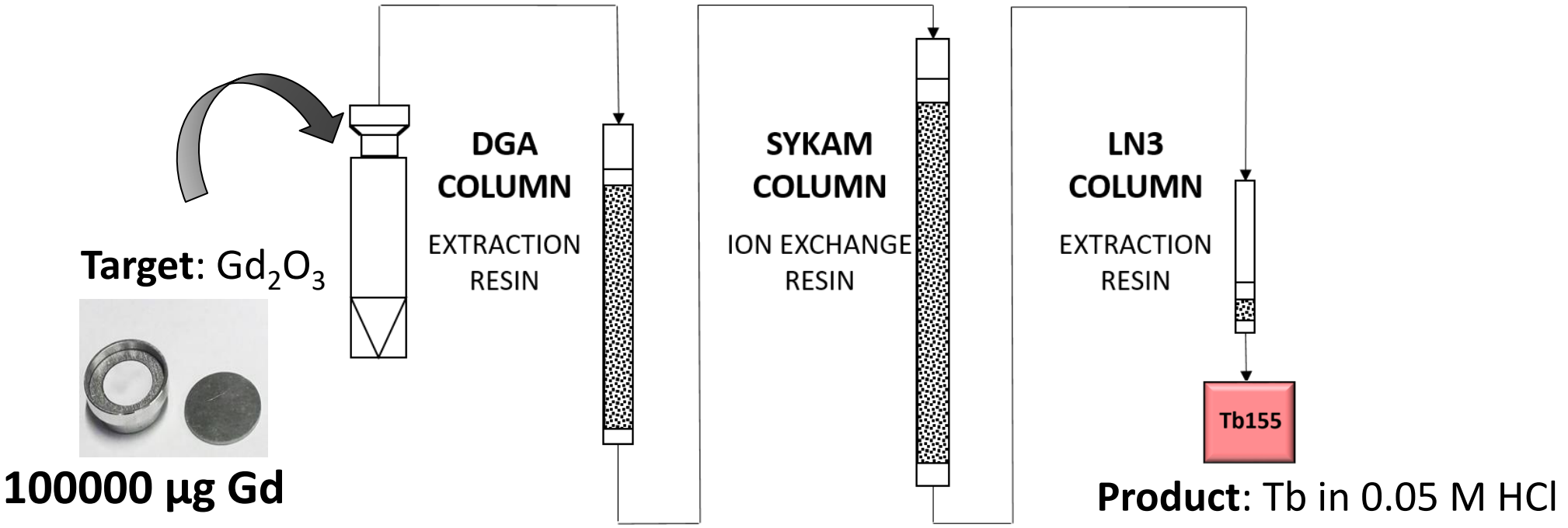
Fine-tuning

Loading solution: 5 µg Tb and 5 µg Gd in 0.13 M α-HIBA





Separation of Terbium-155



Target: Gd_2O_3

100000 µg Gd

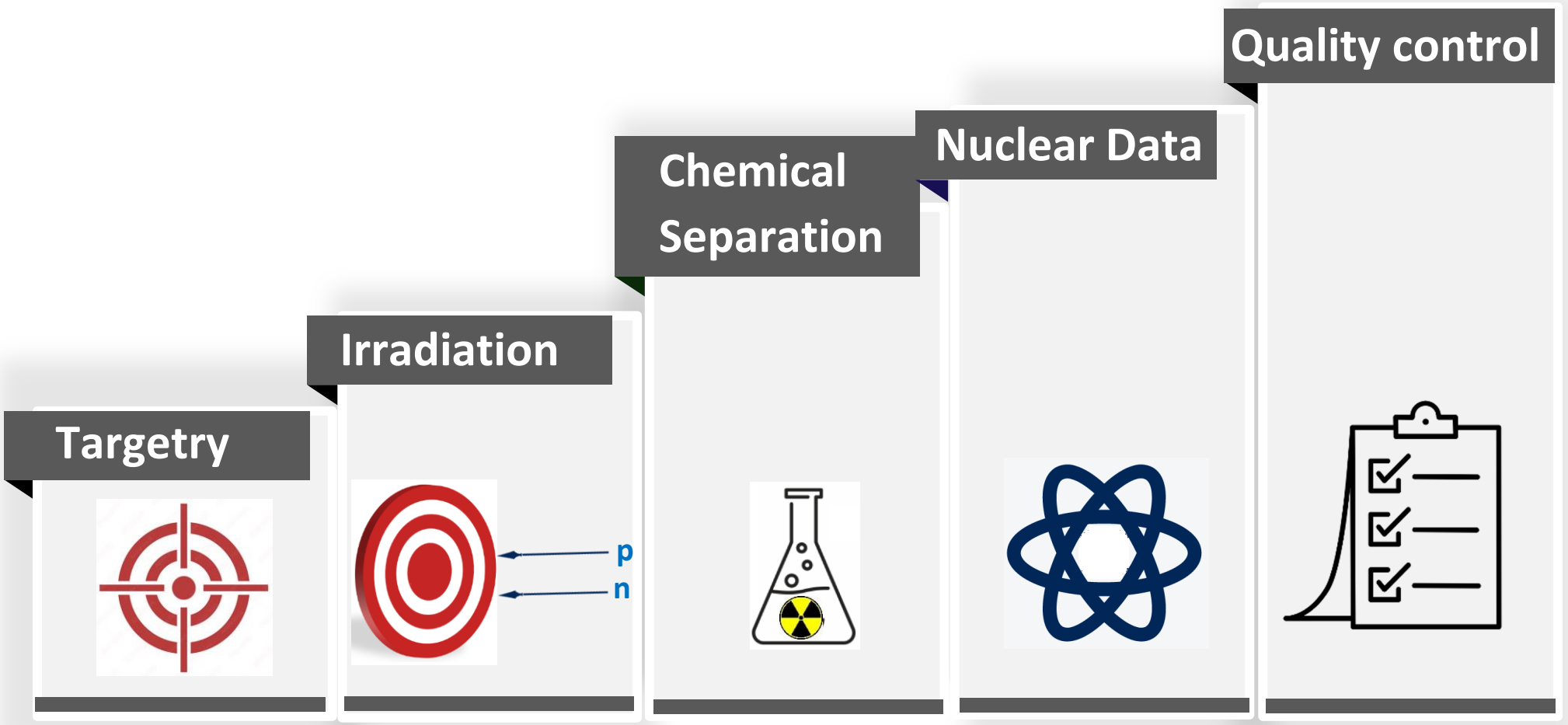
0.75 µg ^{155}Tb

Product: Tb in 0.05 M HCl

Favaretto et al., EJNMMI Radiopharmacy and Chemistry, 6 (2021) 37.

Production of **Mass Separated** Medical Radionuclides

via offline mass separation

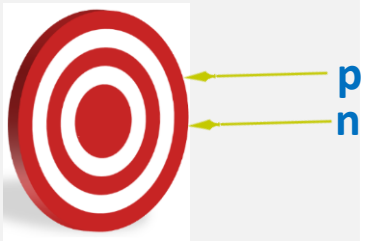


Production of **Mass Separated** Medical Radionuclides

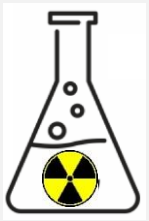
via offline mass separation

Targetry

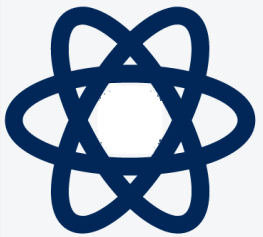
Irradiation



Chemical Separation



Nuclear Data



Quality control

Production of **Mass Separated** Medical Radionuclides

PSI

Quality control

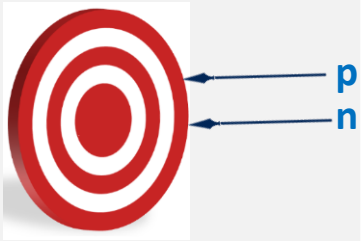
Nuclear Data

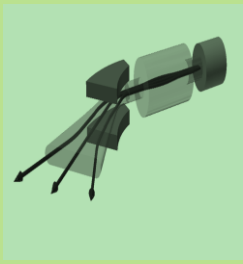
Chemical Separation

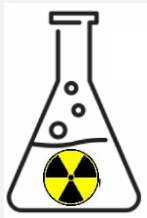
Offline Mass Separation

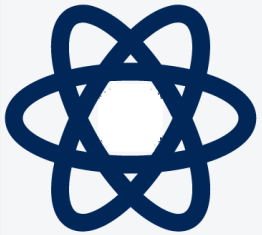
Irradiation

Targetry



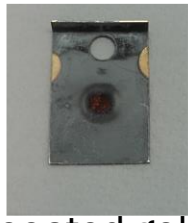






Chemical Separation of **Mass Separated** Medical Radionuclides

For the mass-separated samples, you do not need to separate macro amounts of target materials and the desired radionuclide.



Zn coated gold foil

Al coated gold foil

Characterization of your sample before and after dissolution

- Amount of coating material
- Presence of isobars?
- Other impurities (tailing?)

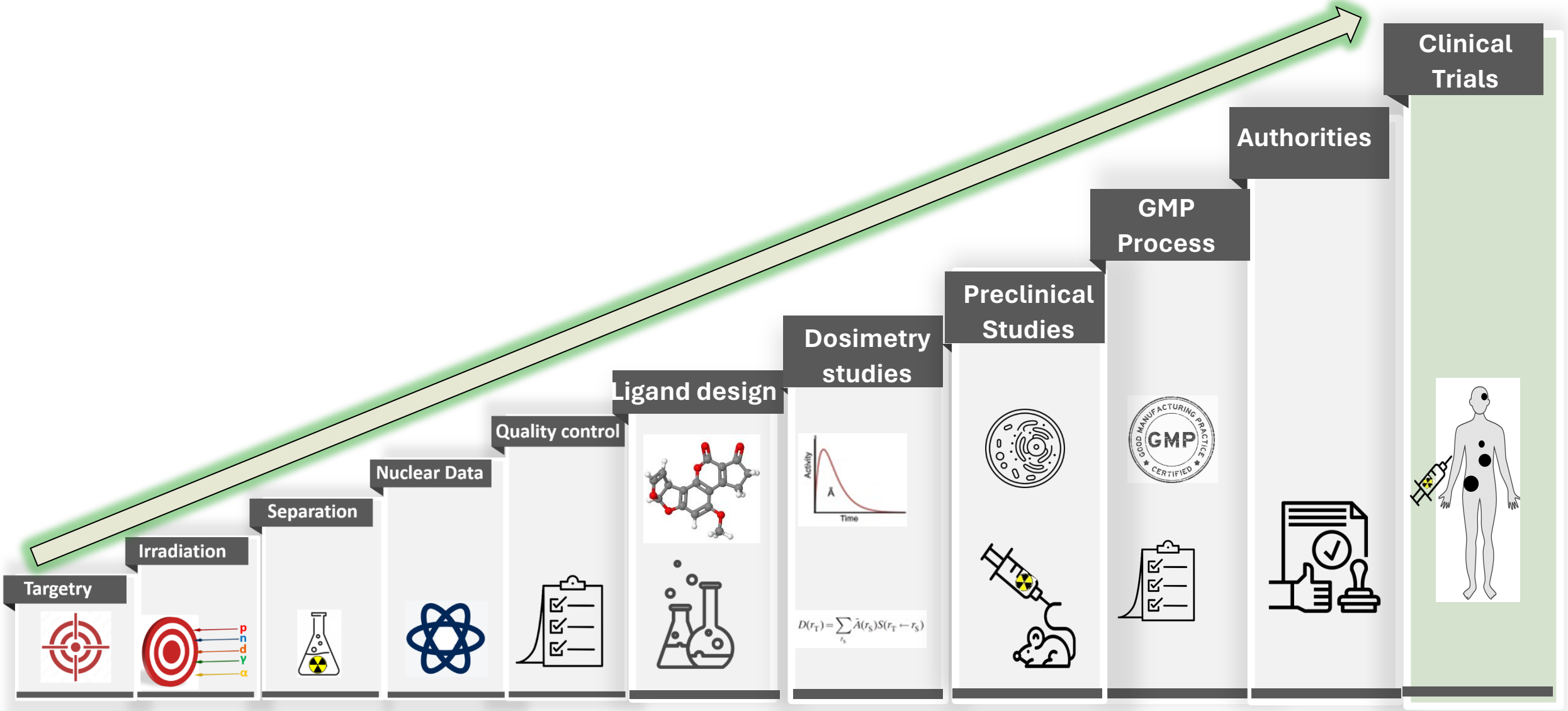
Commercially-available non-carrier added 177Lu (ITM, Germany)
Zn: ≤0.1 µg/GBq with an activity concentration of 37.5 GBq/mL
(80 µL 3 GBq 177Lu can contain 0.3 µg Zn).

Due to the low activity concentration of the mass-separated samples the chemical purity of the final samples should be very high!

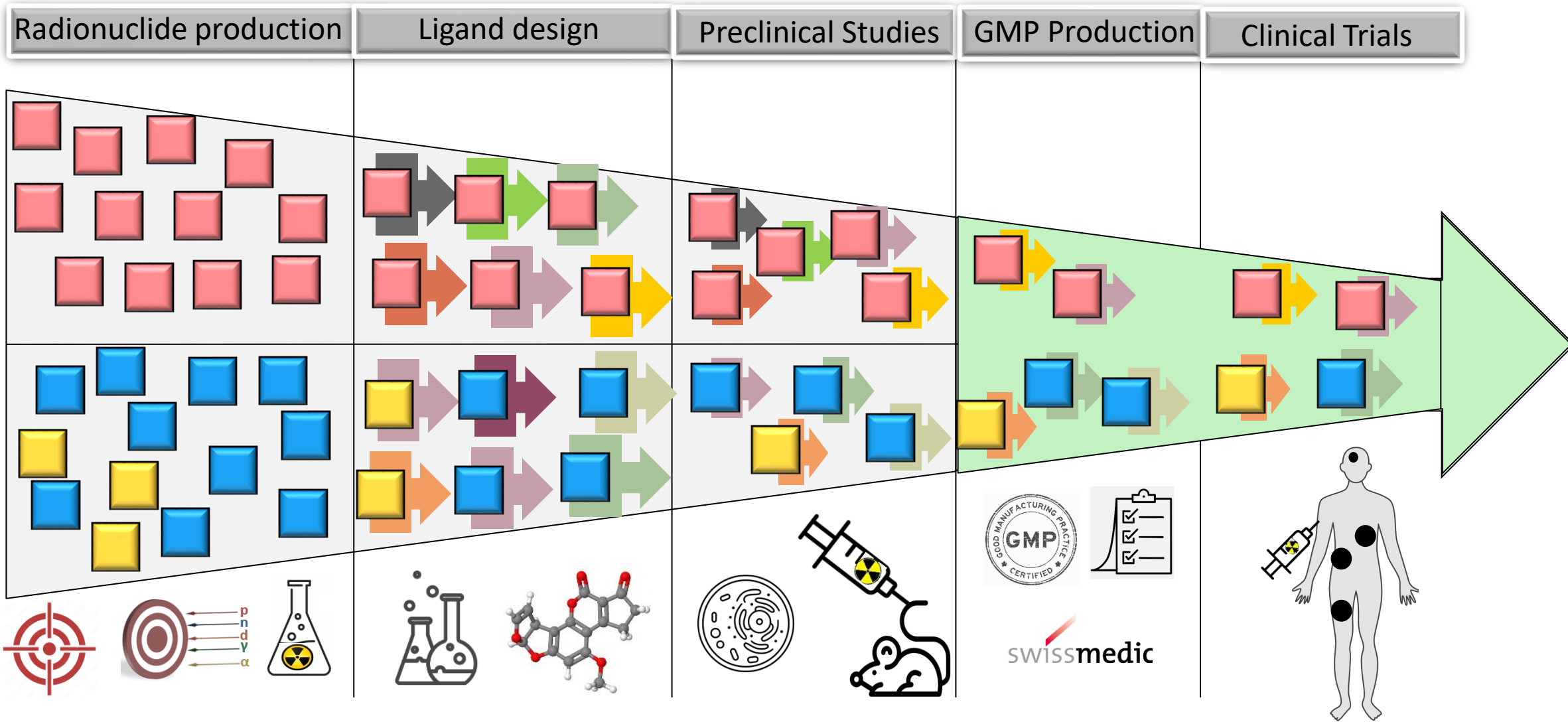
Production of novel medical radionuclides from bench to bedside

Example of Terbium-161

Radiopharmaceutical Development Pipeline



Radiopharmaceutical Development Pipeline



Production of novel radionuclides from bench to bedside

Challenges

Supply Chain
(high development cost)
enriched target material

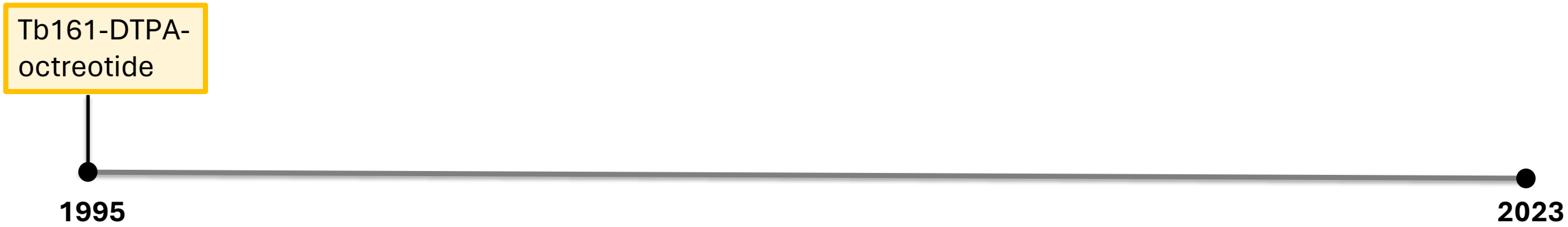
Logistics
presentation of
Clive Naidoo

Production of
patient doses
(scale-up)

Regulatory
issues

Education
and training

Clinical Translation of Tb-161



First Preclinical Study using Tb161

European Journal of Nuclear Medicine

Original article

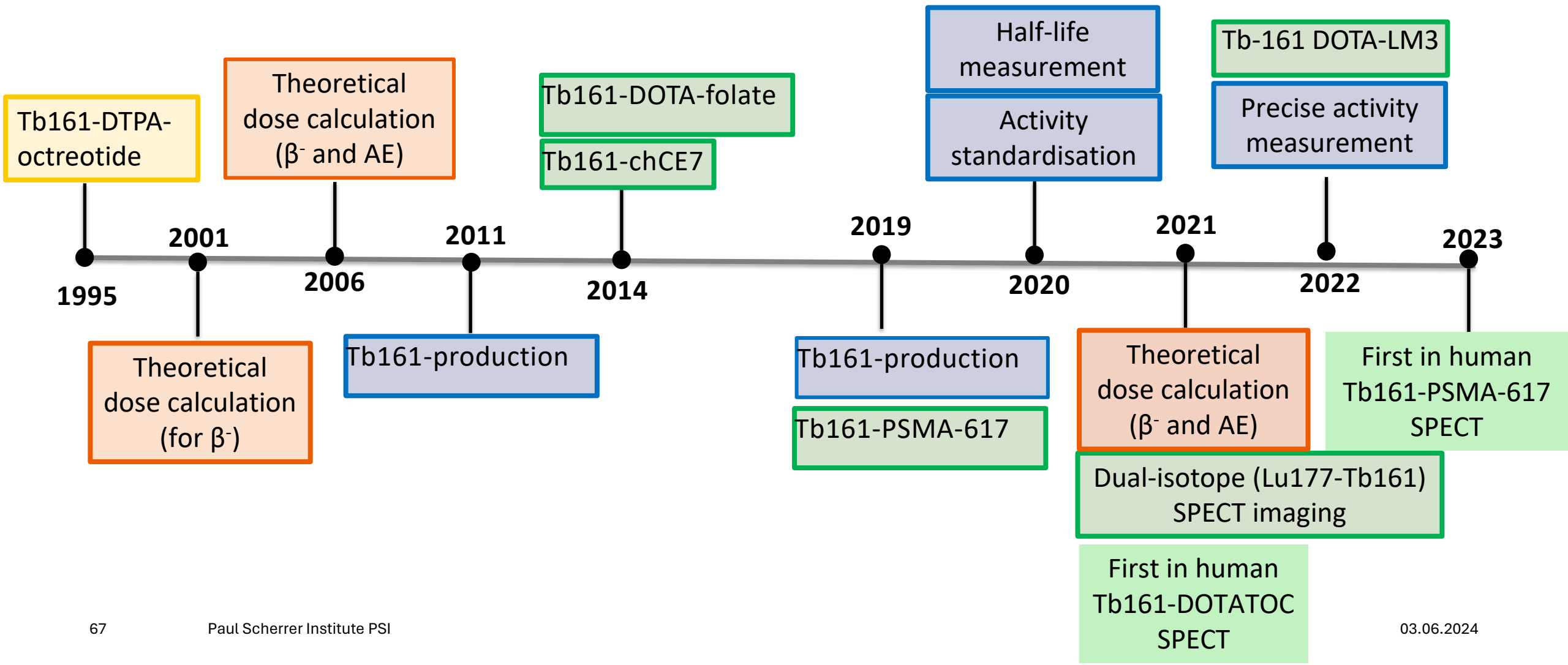
Evaluation in vitro and in rats of ^{161}Tb-DTPA-octreotide, a somatostatin analogue with potential for intraoperative scanning and radiotherapy

Marion de Jong[1], Wout A.P. Breeman[1], Bert F. Bernard[2], Edgar J. Rolleman[1], Leo J. Hofland[2], Theo J. Visser[2], Buddy Setyono-Han[3], Willem H. Bakker[1], Marcel E. van der Pluijm[1], Eric P. Krenning[1]

[1] Department of Nuclear Medicine, University Hospital Rotterdam, 3015 GD Rotterdam, The Netherlands
[2] Department of Internal Medicine III, Erasmus Medical School and University Hospital Rotterdam, Rotterdam, The Netherlands
[3] Dr. Daniël den Hoed Cancer Centre, Rotterdam, The Netherlands

In conclusion: Based on the characteristics of ^{161}Tb (low-energy gamma rays, hard beta rays, and a half-life of nearly 7 days) combined with the in vitro binding studies, biological acticity, and in vivo organ distribution of ^{161}Tb- DTPA-octreotide, the latter may be considered a promising radiopharmaceutical for both intraoperative scanning and radiotherapy. Further studies in patients need to be performed now to see whether ^{161}Tb- DTPA-octreotide can indeed open new therapeutic applications for patients bearing octreotide receptor-positive tumours.

Clinical Translation of Tb-161



Terbium-161 clinical studies

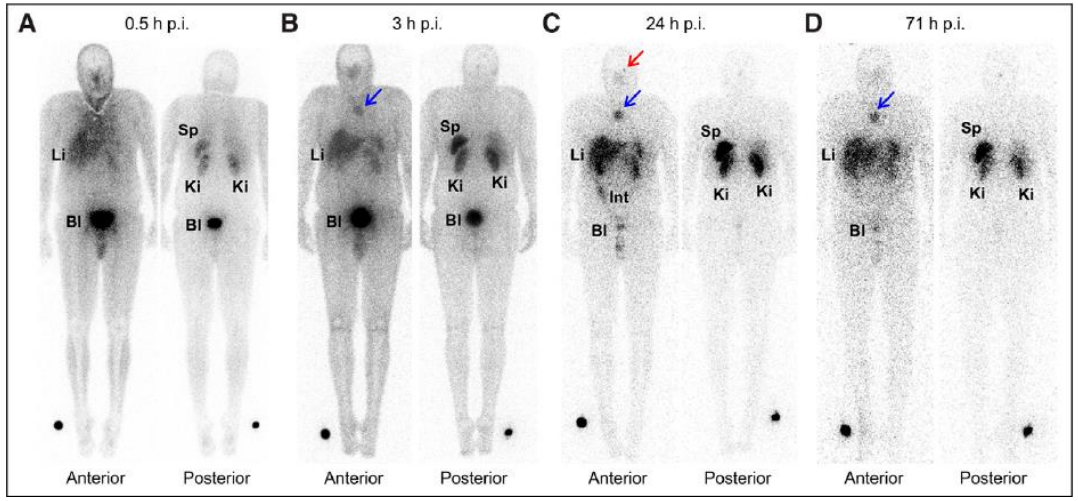
2021

BRIEF COMMUNICATION

First-in-Humans Application of ^{161}Tb: A Feasibility Study Using ^{161}Tb-DOTATOC

Richard P. Baum*[1], Aviral Singh*[1,2], Harshad R. Kulkarni[1], Peter Bernhardt[3,4], Tobias Rydén[3,4], Christiane Schuchardt[1], Nadezda Gracheva[5], Pascal V. Grundler[5], Ulli Köster[6], Dirk Müller[7], Michael Pröhl[7], Jan Rijn Zeevaart[8], Roger Schibli[5,9], Nicholas P. van der Meulen[5,10], and Cristina Müller[5]

[1]Theranostics Center for Molecular Radiotherapy and Precision Oncology, ENETS Center of Excellence, Zentralklinik Bad Berka, Bad Berka, Germany; [2]GROW–School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands; [3]Department of Radiation Physics, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [4]Department of Medical Physics and Medical Bioengineering, Sahlgrenska University Hospital, Gothenburg, Gothenburg, Sweden; [5]Center for Radiopharmaceutical Sciences ETH-PSI-USZ, Paul Scherrer Institute, Villigen-PSI, Switzerland; [6]Institut Laue Langevin, Grenoble, France; [7]Department of Radiopharmacy, Zentralklinik Bad Berka, Bad Berka, Germany; [8]Radiochemistry, South African Nuclear Energy Corporation (Necsa), Pelindaba, South Africa; [9]Department of Chemistry and Applied Biosciences, ETH Zurich, Zurich, Switzerland; and [10]Laboratory of Radiochemistry, Paul Scherrer Institute, Villigen-PSI, Switzerland



2023

Journal of Nuclear Medicine, published on February 9, 2023 as doi:10.2967/jnumed.122.265291

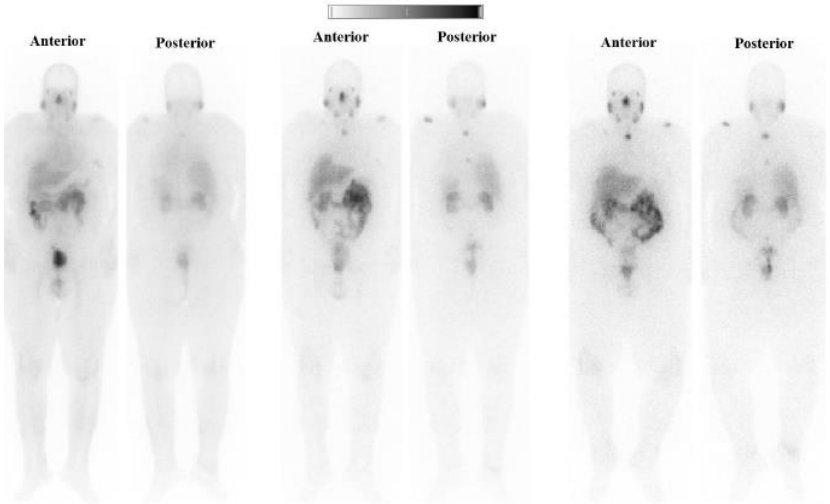
^{161}Tb-PSMA Radioligand Therapy: First-in-human SPECT/CT Imaging

Akram Al-Ibraheem[1], Rahma M. Doudeen[1], Diyaa Juaidi[1], Alaa Abufara[2], Stephan Maus[3]

1- Department of Nuclear Medicine, King Hussein Cancer Center, Amman, Jordan

2- Department of Internal Medicine, King Hussein Cancer Center, Amman, Jordan

3- Department of Nuclear Medicine, Universitätsklinikum des Saarlandes, Homburg, Germany



Tb-161 bench to bedside

Half-life measurement

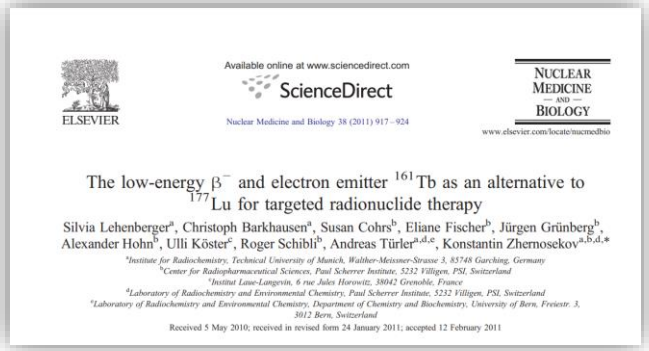
Activity standardisation

Precise activity measurement

2011 — 2019 — 2020 — 2022 — 2023

Tb161-production

Tb161-production



Available online at www.sciencedirect.com

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Nuclear Medicine and Biology 38 (2011) 917–924

NUCLEAR MEDICINE AND BIOLOGY

www.elsevier.com/locate/nucmedbio

ELSEVIER

The low-energy β^- and electron emitter ^{161}Tb as an alternative to ^{177}Lu for targeted radionuclide therapy

Silvia Lehenberger[a], Christoph Barkhausen[a], Susan Cohrs[b], Eliane Fischer[b], Jürgen Grünberg[b], Alexander Hohn[b], Ulli Köster[c], Roger Schibli[b], Andreas Türler[a,d,e], Konstantin Zhernosekov[a,b,d,*]

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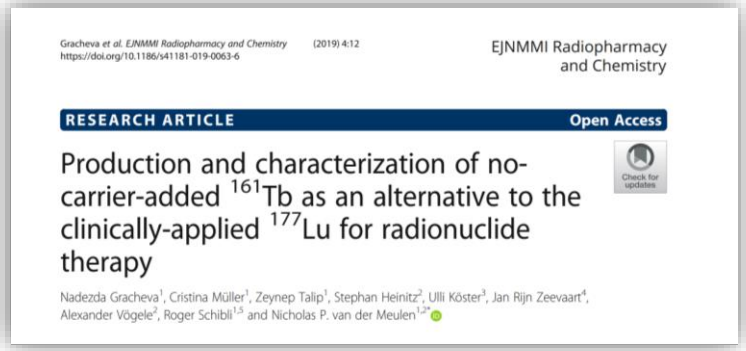
[b]Center for Radiopharmaceutical Sciences, Paul Scherrer Institute, 5232 Villigen, PSI, Switzerland
[c]Institut Laue-Langevin, 6 rue Jules Horowitz, 38042 Grenoble, France
[d]Laboratory of Radiochemistry and Environmental Chemistry, Paul Scherrer Institute, 5232 Villigen, PSI, Switzerland
[e]Laboratory of Radiochemistry and Environmental Chemistry, Department of Chemistry and Biochemistry, University of Bern, Freiestr. 3, 3012 Bern, Switzerland

Received 5 May 2010; received in revised form 24 January 2011; accepted 12 February 2011



Gracheva et al. EJNMMI Radiopharmacy and Chemistry (2019) 4:12
https://doi.org/10.1186/s41181-019-0063-6

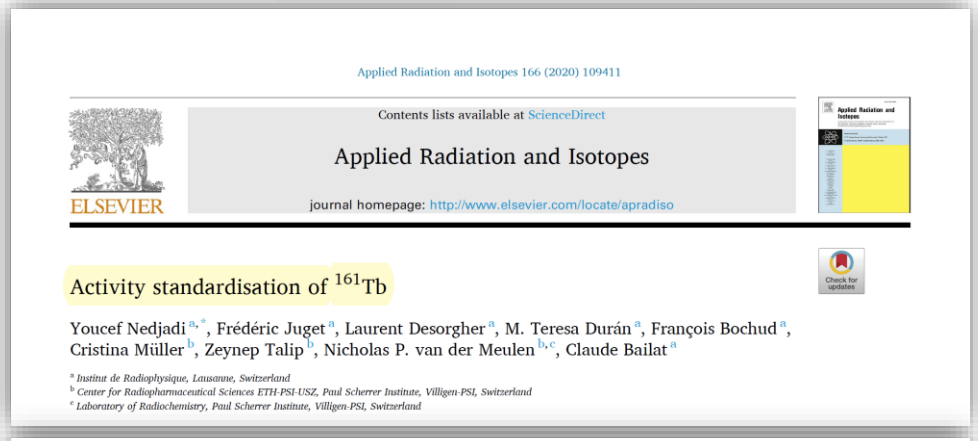
EJNMMI Radiopharmacy and Chemistry

RESEARCH ARTICLE Open Access

Production and characterization of no-carrier-added ^{161}Tb as an alternative to the clinically-applied ^{177}Lu for radionuclide therapy

Nadezda Gracheva[1], Cristina Müller[1], Zeynep Talip[1], Stephan Heinitz[2], Ulli Köster[3], Jan Rijn Zeevaart[4], Alexander Vögele[2], Roger Schibli[1,5] and Nicholas P. van der Meulen[1,2*]

Precise activity measurement of Terbium-161



Applied Radiation and Isotopes 166 (2020) 109411

Contents lists available at ScienceDirect

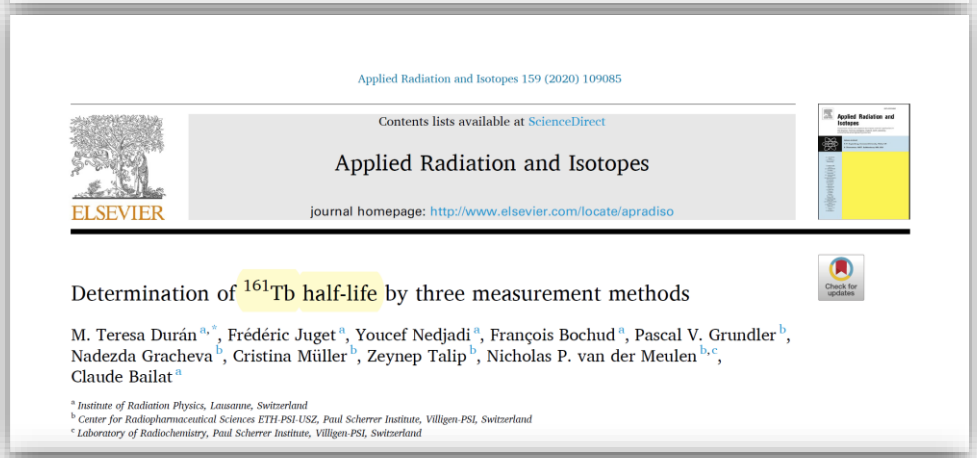
Applied Radiation and Isotopes

journal homepage: http://www.elsevier.com/locate/apradiso

Activity standardisation of ^{161}Tb

Youcef Nedjadi [a,*], Frédéric Juget [a], Laurent Desorgher [a], M. Teresa Durán [a], François Bochud [a], Cristina Müller [b], Zeynep Talip [b], Nicholas P. van der Meulen [b,c], Claude Bailat [a]

[a] Institut de Radiophysique, Lausanne, Switzerland
[b] Center for Radiopharmaceutical Sciences ETH-PSI-USZ, Paul Scherrer Institute, Villigen-PSI, Switzerland
[c] Laboratory of Radiochemistry, Paul Scherrer Institute, Villigen-PSI, Switzerland



Applied Radiation and Isotopes 159 (2020) 109085

Contents lists available at ScienceDirect

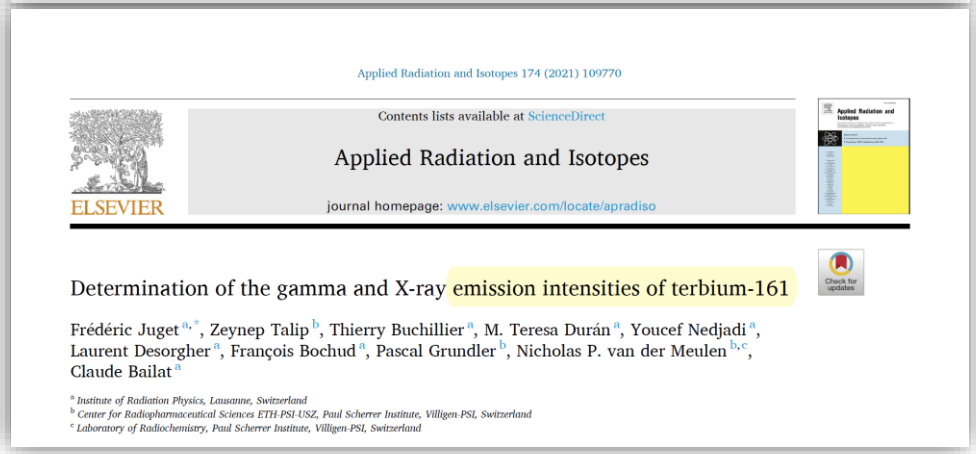
Applied Radiation and Isotopes

journal homepage: http://www.elsevier.com/locate/apradiso

Determination of ^{161}Tb half-life by three measurement methods

M. Teresa Durán [a,*], Frédéric Juget [a], Youcef Nedjadi [a], François Bochud [a], Pascal V. Grundler [b], Nadezda Gracheva [b], Cristina Müller [b], Zeynep Talip [b], Nicholas P. van der Meulen [b,c], Claude Bailat [a]

[a] Institute of Radiation Physics, Lausanne, Switzerland
[b] Center for Radiopharmaceutical Sciences ETH-PSI-USZ, Paul Scherrer Institute, Villigen-PSI, Switzerland
[c] Laboratory of Radiochemistry, Paul Scherrer Institute, Villigen-PSI, Switzerland



Applied Radiation and Isotopes 174 (2021) 109770

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

Determination of the gamma and X-ray emission intensities of terbium-161

Frédéric Juget [a,*], Zeynep Talip [b], Thierry Buchillier [a], M. Teresa Durán [a], Youcef Nedjadi [a], Laurent Desorgher [a], François Bochud [a], Pascal Grundler [b], Nicholas P. van der Meulen [b,c], Claude Bailat [a]

[a] Institute of Radiation Physics, Lausanne, Switzerland
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[c] Laboratory of Radiochemistry, Paul Scherrer Institute, Villigen-PSI, Switzerland

Juget et al. EJNMMI Physics (2022) 9:19
https://doi.org/10.1186/s40658-022-00448-0

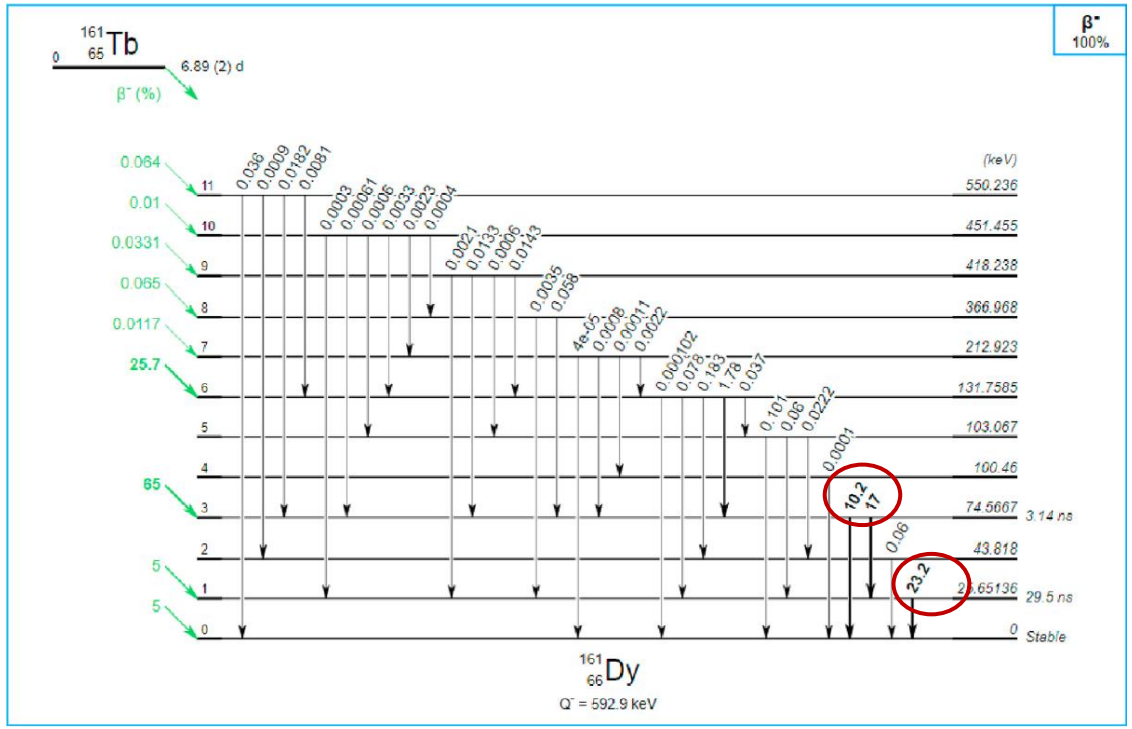
EJNMMI Physics

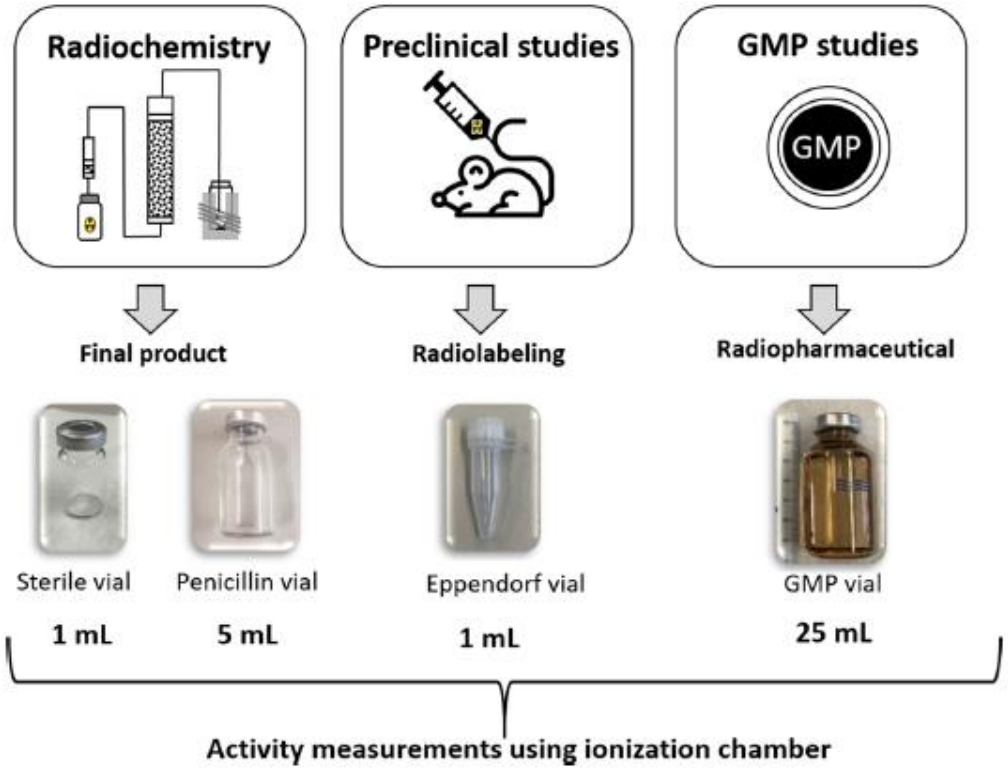
ORIGINAL RESEARCH Open Access

Precise activity measurements of medical radionuclides using an ionization chamber: a case study with Terbium-161

Frédéric Juget[1*], Zeynep Talip[2], Youcef Nedjadi[1], M. Teresa Durán[1], Pascal V. Grundler[2], Jan Rijn Zeevaart[3], Nicholas P. van der Meulen[2,4] and Claude Bailat[1]

Precise activity measurement of Terbium-161





>8.5% >14%

Different calibration factors should be used for each type of vial!

Production of Terbium-161-DOTATOC

Based on GMP guidelines

^{161}Tb-DOTATOC Production Using a Fully Automated Disposable Cassette System: A First Step Toward the Introduction of ^{161}Tb into the Clinic

Chiara Favaretto[1,2], Pascal V. Grundler[1], Zeynep Talip[1], Stefan Landolt[1], Lebogang Sepini[3], Ulli Köster[4], Cristina Müller[1], Roger Schibli[1,2], Susanne Geistlich[1], and Nicholas P. van der Meulen [1,5]

[1]Center for Radiopharmaceutical Sciences, ETH–Paul Scherrer Institute, Villigen-PSI, Switzerland; [2]Department of Chemistry and Applied Biosciences, ETH, Zurich, Switzerland; [3]Radiochemistry, South African Nuclear Energy Corp., Brits, South Africa; [4]Institut Laue-Langevin, Grenoble, France; and [5]Laboratory of Radiochemistry, Paul Scherrer Institute, Villigen-PSI, Switzerland

^{161}Tb is an interesting radionuclide for application in the treatment of neuroendocrine neoplasms' small metastases and single cancer cells because of its conversion and Auger-electron emission. Tb has coordination chemistry similar to that of Lu; therefore, like ^{177}Lu, it can stably radiolabel DOTATOC, one of the leading peptides used for the

Key Words: ^{161}Tb; specifications; DOTATOC; GMP compliant; automated

J Nucl Med 2023; 64:1138–1144
DOI: 10.2967/jnumed.122.265268

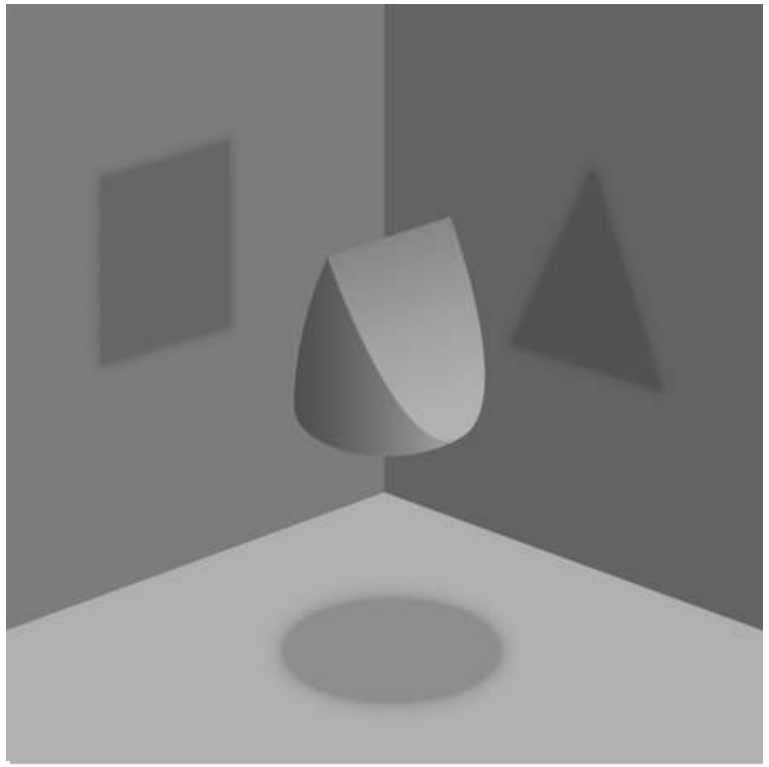
^{161}Tb specifications until end of shelf-life (9 days after end of separation).

Test	$^{161}TbCl_3$ Specification
Appearance (visual inspection)	Clear and colorless solution
Identity (γ-spectrometry)	74.6 ± 1 keV 87.9 ± 1 keV 103.1 ± 1 keV 106.1 ± 1 keV 292.4 ± 1 keV 550.3 ± 1 keV
pH (pH paper)	1–2
Chemical purity (ICP-MS)	Cu: <1.0 µg/GBq Fe: <0.5 µg/GBq Pb: <0.5 µg/GBq Zn: <1.0 µg/GBq
Sterility	Not required
Bacterial endotoxins (LAL Test)	<175 IU/mL (injectable dose)
Radionuclidic purity (γ-ray spectrometry)	^{160}Tb ≤0.1%
Radiochemical purity (TLC)	≥99.0% as $^{161}TbCl_3$

C. Favaretto et al., J Nucl Med, 64 (2023) 1138.

Novel Medical Radionuclides

View from
a producer side



View from
a user side
(preclinical and clinical studies)

Regulatory perspective

Summary

Before starting to develop your separation method: **first, ask the right questions**!!!!

Questions to be asked

- What should be separated? **Characterization of the target**
- Separation time? **Half-life of the desired radionuclide**
- Dissolution of the target? **Loading solution**
- **Available Kd data?** **Selection of the resins**
- Aimed decontamination factors? **Radiolabeling efficiency**
- Aimed separation yields? **EOB and EOS activities**
- Acidity and volume of the final solution? **Usage: preclinical/clinical**

To take into account: minimizing the radioactive waste volume & recycling the target material

Summary

Before starting to develop your method: **first, ask the right questions**!!!!

Most of the time, there is more than one way to separate different elements.

You should adapt your method based on **the usage of your final product**.

If you aim to bring medical radionuclides to the final step (clinical studies), **look at the big picture**.

PRISMAP Radiolanthanides Workshop

3-5 September 2024

Villigen, PSI

https://indico.psi.ch/event/15961/

77

Day 1

Production	Cross Section	Decay Data	Radiochemistry	Mass Seperation
Mikeal Jenssen Paul Schaffer	Thomas Sounalet Saverio Braccini	Frederic Juget Sean Collins Emilio Maugeri	Paul Ellison Michiel Van de Voorde Nick van der Meulen Zeynep Talip	Ulli Köster Robert Eichler Lucia Popescu Thierry Stora

Day 2

Dosimetry	Preclinical	GMP Production	Clinical Studies
Peter Bernhardt Elif Hindie Michel Koole	Cristina Müller Maarten Ooms Antonio Rocha Paulo Michel Ma	Susanne Geistlich Clemens Decristoforo Anna Catherina Senn	Damian Wild Samer Ezziddin

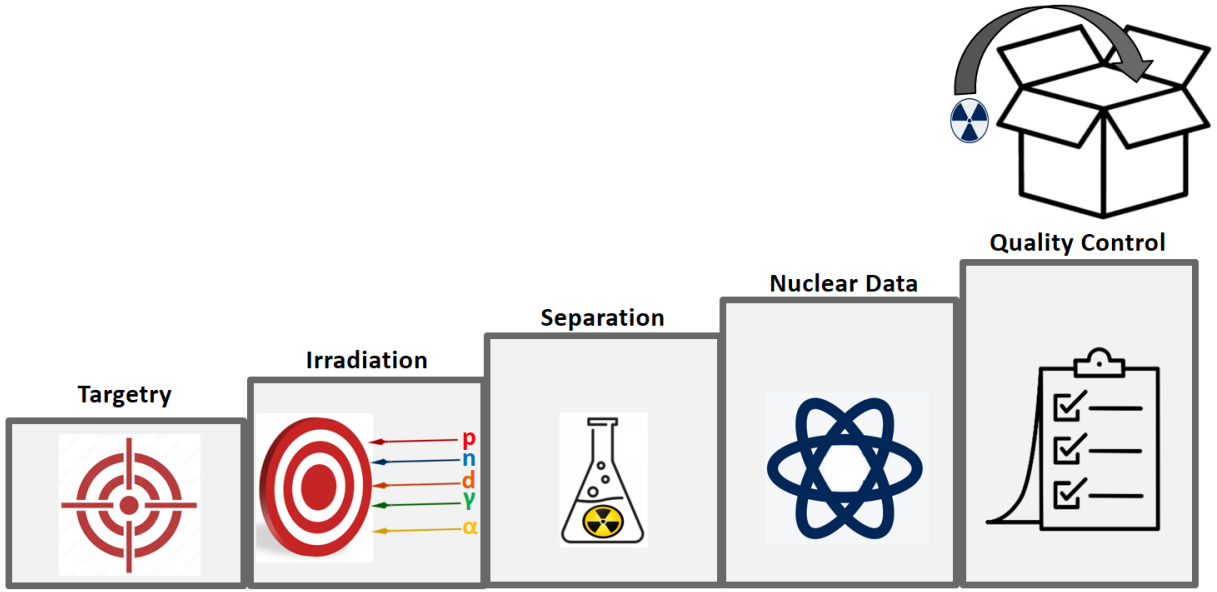
Day 3

Panel Discussion (Clinical translation of Terbium-161)

Presentation: Richard Baum

Panel:
Roger Schibli (Moderator) Richard Baum Damian Wild Samer Ezziddin ITM TerThera

Thank You For Your Attention



Dr. Zeynep Talip

zeynep.talip@psi.ch

PRISMAP School on Radionuclide Production: 31.05.2024