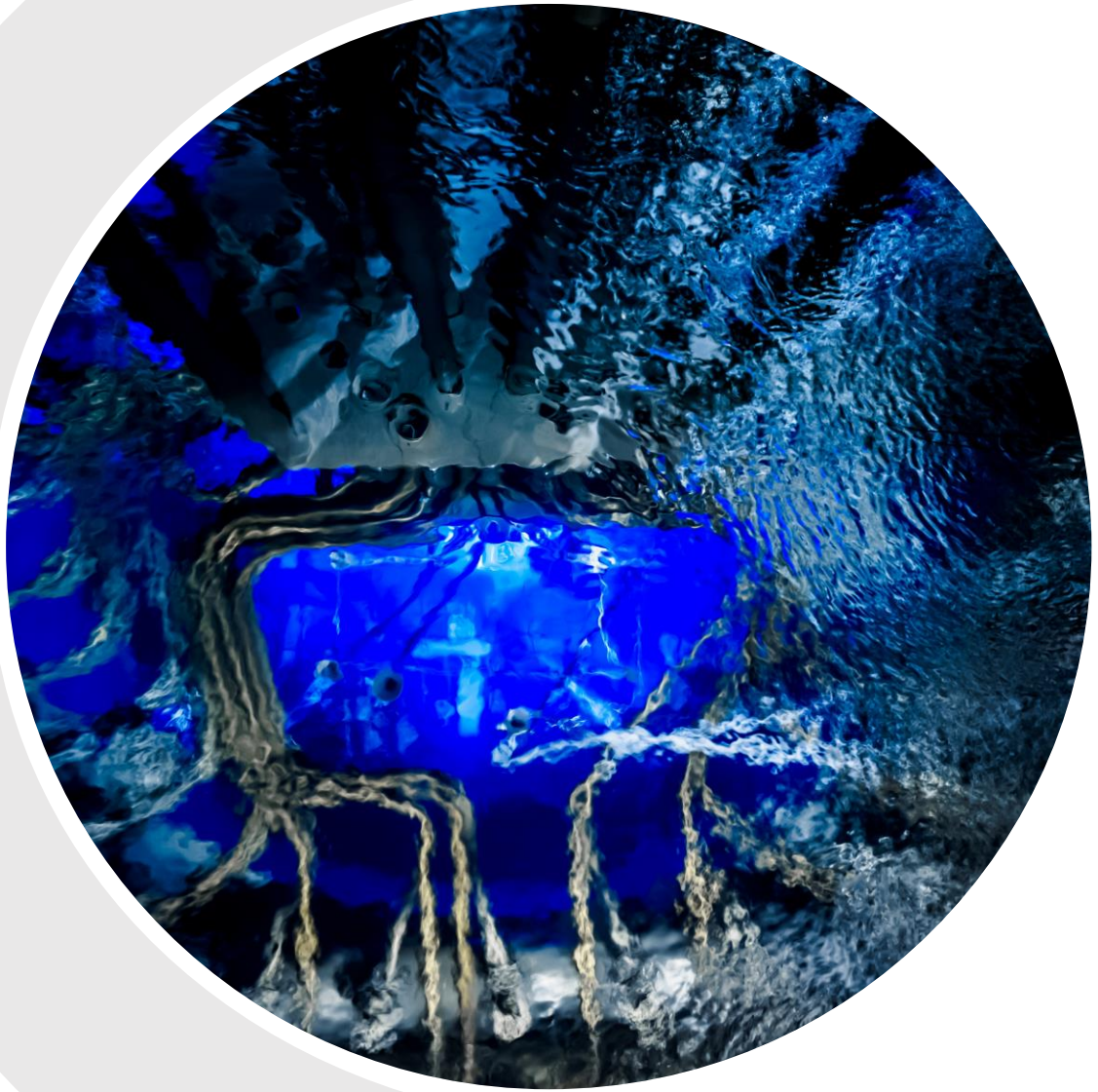


BEYOND CONVENTIONAL RADIONUCLIDES: ACCELERATOR PRODUCTION FOR NEXT-GENERATION THERANOSTICS

MAREK PRUSZYŃSKI, PHD, DSC, PROF. NCBJ
NOMATEN CENTRE OF EXCELLENCE
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UL. SOŁTANA 7, OTWOCK, POLAND

3RD WORKSHOP ON RESEARCH & INNOVATION IN POLAND:
RESEARCH PROGRAMME FOR LINEAR ACCELERATOR – RADIOISOTOPES AND APPLICATIONS
HENRYK NIEWODNICZAŃSKI INSTITUTE OF NUCLEAR PHYSICS
POLISH ACADEMY OF SCIENCES
22-23.10.2026, CRACOW

We acknowledge support from the European Union's Horizon 2020 research and innovation program under the NOMATEN Teaming grant agreement No. 857470 and from the Ministry of Science and Higher Education's initiative „Support for the Activities of Centers of Excellence Established in Poland under the Horizon 2020 Program" under agreement No. MEiN/2023/DIR/3795.

PRODUCTION OF RADIOPHARMACEUTICALS

NOMATEN

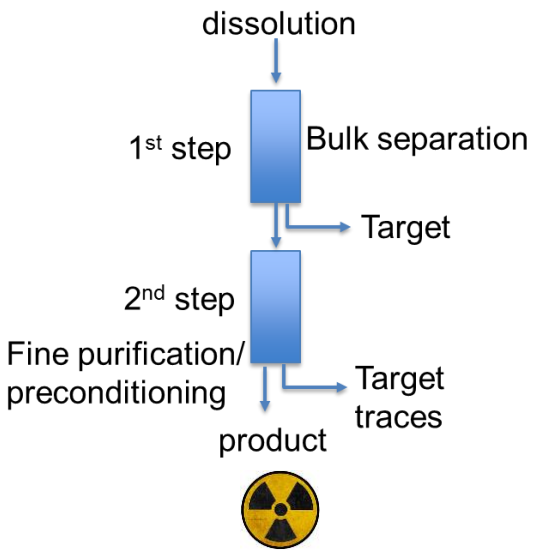
Production → **Radiochemical separation** → **Radiolabelling** → **Application**

neutrons (n,γ)

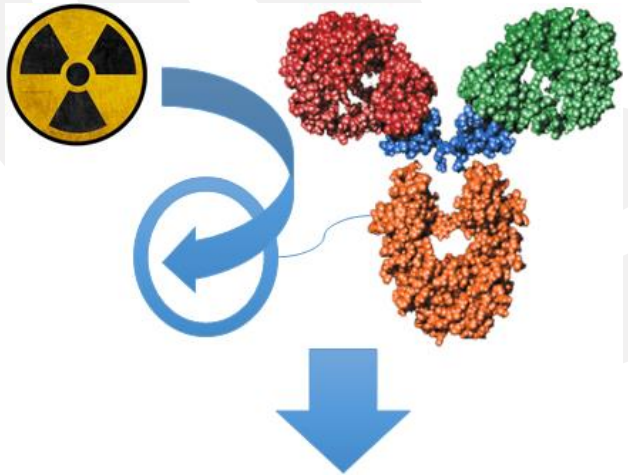


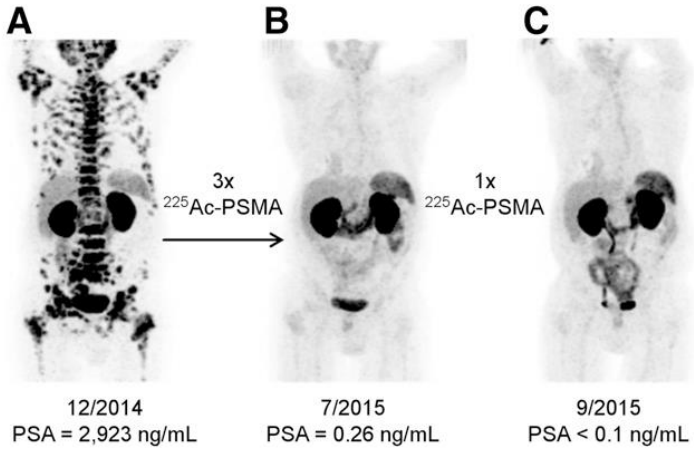
protons/deuterons/alphas (p/d/α,xn)





Ion exchange
Liquid-liquid extraction
Solid phase extraction
Precipitation
Electrochemistry
Distillation
Termochromatography….





*Radchenko V. et al. Solvent Extraction and Ion Exchange, **2021**;39:7, 714-744, DOI: 10.1080/07366299.2021.1874099*

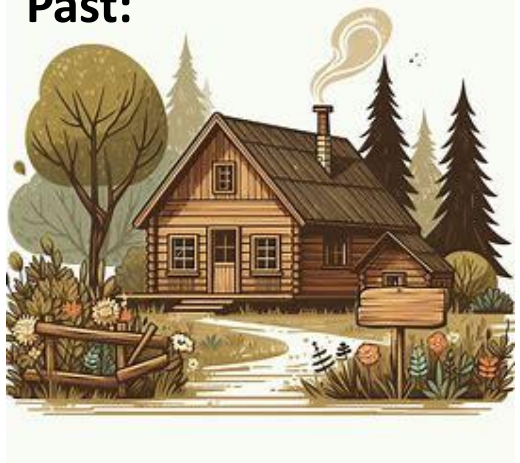
*Kratochwil et al., J. Nuc. Med. July **2016***

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Ministerstwo Nauki i Szkolnictwa Wyższego
European Funds Smart Growth
Republic of Poland
European Union European Regional Development Fund

ACCELERATOR-PRODUCED MEDICAL RADIONUCLIDES

Past:



$^{18}O(p,n)^{18}F$
$^{14}N(p,\alpha)^{11}C$
$^{16}O(p,\alpha)^{13}N$
$^{14}N(d,n)^{15}O$
$^{83}Kr(p,3n)^{81}Rb$
$^{80}Kr(d,n)^{81}Rb$
$^{124}Te(p,2n)^{123}I$
$^{127}I(p,5n)^{123}Xe \rightarrow {}^{123}I$
$^{203}Tl(p,3n)^{201}Pb \rightarrow {}^{201}Tl$
$^{68}Zn(p,2n)^{67}Ga$
$^{112}Cd(p,2n)^{111}In$
$^{209}Bi(\alpha,2n)^{211}At$

Present:



$^{68}Zn(p,2p)^{67}Cu$
$^{72}Ge(p,n)^{72}As$
$^{86}Sr(p,n)^{86}Y$
$^{89}Y(p,n)^{89}Zr$
$^{100}Mo(p,2n)^{99m}Tc$
$^{44}Ca(p,n)^{44}Sc$
$^{40}Ca(\alpha,n)^{43}Sc$
$^{48}Ca(p,2n)^{47}Sc$
$^{103}Rh(p,n)^{103}Pd$
$^{103}Rh(d,2n)^{103}Pd$
$^{114}Cd(\alpha,n)^{117m}Sn$

Future:



$^{54}Fe(d,n)^{55}Co$
$^{nat(56)}Fe(p,2n)^{55}Co$
$^{57}Fe(d,n)^{58m}Co$
$^{58}Fe(p,n)^{58m}Co$
$^{135}Ba(p,n)^{135}La$
$^{191}Ir(p,n)^{191}Pt$
$^{nat}Ir(p,xn)^{191}Pt$
$^{192}Os(\alpha,3n)^{193m}Pt$
$^{192}Os(\alpha,n)^{195m}Pt$
$^{197}Au(p,n)^{197m/g}Hg$
$^{197}Au(d,n)^{197m/g}Hg$
$^{119}Sn(p,n)^{119}Sb$
$^{165}Ho(p,n)^{165}Er$
$^{165}Ho(d,2n)^{165}Er$

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THERANOSTIC PAIR OF SCANDIUM RADIONUCLIDES

	^{43}Sc (β^+)	^{44}Sc (β^+)	^{47}Sc (β^-)
$t_{1/2}$	3.89 h	3.97 h	3.35 d
β emission	88%	95%	100%
$E_{\beta av}$	476 keV	632 keV	162 keV
Production	^{nat}Ca(α,p)^{43}Sc ^{nat}Ca(α,n)^{43}Ti →^{43}Sc ^{42}Ca(d,n)^{43}Sc ^{43}Ca(p,n)^{43}Sc	generator ^{44}Ti/^{44}Sc ^{44}Ca(p,n)^{44}Sc	^{47}Ti(n,p)^{47}Sc ^{50}Ti(p,α)^{47}Sc ^{48}Ca(p,2n)^{47}Sc ^{46}Ca(n,γ)^{47}Ca → ^{47}Sc
Main γ quantum [keV]	372.8 (23%)	1157.0 (99%)	159.4 (68%)

JRC EUROPEAN COMMISSION

Ispra, Italy

ichtj

Irradation conditions

Scanditronix MC 40:

- intensity – 2 μA
- time – 30 min
- $^{44}CaCO_3$ target – 2 mg

NOMATEN

Protons enrgy on target[MeV]	^{44}Sc (kBq)	^{44m}Sc (kBq)	%^{44m}Sc
5.57→ 0	25.8	0.02	0.081
7.28→ 0	4240	0.94	0.022
7.88→ 0	4350	2.6	0.060
8.89→ 0	27000	43	0.159
9.83→ 0	31000	57.8	0.186
10.70→ 0	9370	23.00	0.245
13.20→ 0	13600	76.00	0.559
17.50→ 0	4600	40	0.869

S. Krajewski, I. Cydzik, K. Abbas, A. Bulgheroni, F. Simonelli, U. Holzwart and A. Bilewicz,(**2013**)
Cyclotron production of ^{44}Sc for clinical application Radiochim. Acta 101, 333–338





HIL Heavy Ion Laboratory — **U -200 & GE-PETrace**

ARRONAX — **IBA Cyclone 70XP**

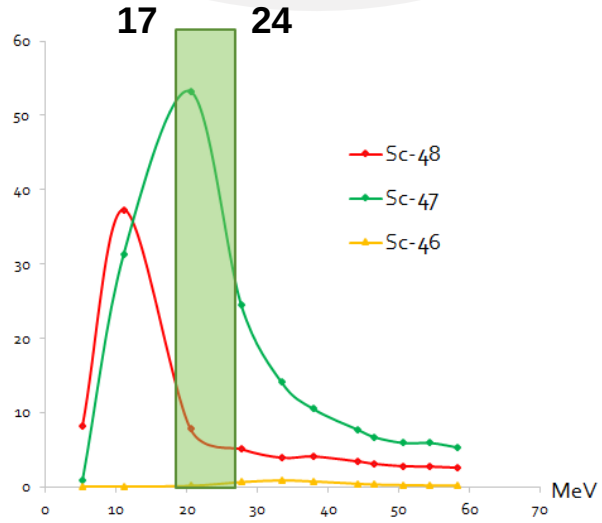
THE HENRYK NIEWODNICZAŃSKI INSTITUTE OF NUCLEAR PHYSICS POLISH ACADEMY OF SCIENCES — **AIC-144**

NCBJ POLATOM

^{48}Ca(p,2n) ^{47}Sc

< 16 MeV ^{48}Ca(p,n)^{48}**Sc**

> 30 MeV ^{48}Ca(p,3n)^{46}**Sc**



2015-2017, NCBIR, PBS3/A9/28/2015 „Preparation of radiopharmaceuticals based on scandium radionuclides for positron emission tomography - PET-SKAND", Institute of Nuclear Chemistry and Technology, Warsaw University – Heavy Ions Laboratory, POLATOM – National Center of Nuclear Research

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Ministerstwo Nauki i Szkolnictwa Wyższego

European Funds Smart Growth

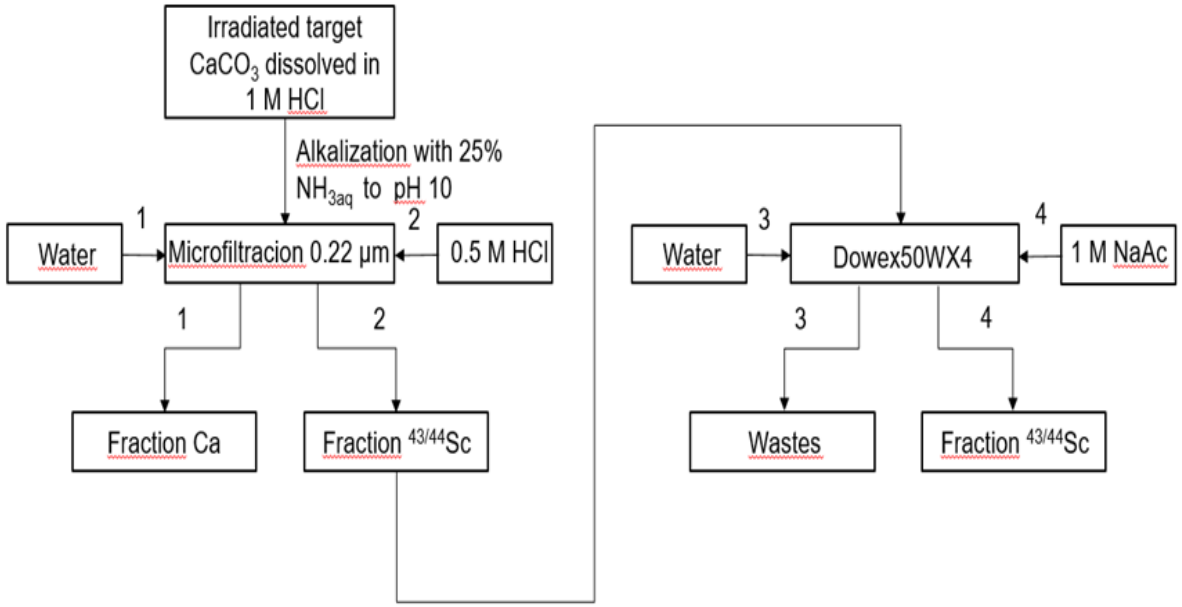
Republic of Poland

European Union European Regional Development Fund

THERANOSTIC PAIR OF SCANDIUM RADIONUCLIDES

Separation of $^{43/44/47}Sc$ from the $CaCO_3$ targets & Ca target material recovery

Method	Eluent of Ca	Eluent of $^{43/47}Sc$	Recovery $^{43/47}Sc$	Recovery $CaCO_3$	Reference
Chelex -100 chelating resin	0.01 M HCl	0.1M HCl	85%	87%	Bilewicz et al. Radiochim Acta 2012
UTEVA extraction resin	10 M HCl	H_2O	79%	90%	Valdovinos, et al. Appl Radiat Isot 2012
DGA extraction resin	3 M HCl	0.1M HCl	89 %	83%	Müller et al. J Nucl Med 2014
Filtration (0.22µm) after formation of $Sc(OH)_3$	25% NH_{3aq}	0.5M HCl	96%	93%	Katsuyuki et al. Appl Radiat Isot 2016
Dowex – 50 for purification, concentration and change of enviroment	-	1M NH_4OAc, pH 4.5	92%	-	Pruszynski et al. Appl Radiat Isot 2010



K. Minegishi et al. *Applied Radiation and Isotopes* **2016**, 116:8–12

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THERANOSTIC PAIR OF COBALT RADIONUCLIDES

^{55}Co

$T_{½}$ = 17.53 h

Decay: β^+ (76%) and EC

E_γ: 477 keV; 931,3 keV (75%), 1408 keV

^{54}Fe(d,n)^{55}Co
5 – 15 MeV

99.58% ^{54}Fe

21.123 ± 0.971 mg

74.675 ± 3.475 $\frac{mg}{cm^2}$

E_d: 8 MeV

^{55}Co: 12.7 ± 2.9 $\frac{MBq}{\mu Ah}$

+ very high radionuclidic purity
- deuteron beam, enriched ^{54}Fe

nat(56)Fe(p,2n)^{55}Co
20 -30 MeV

91.8% ^{56}Fe

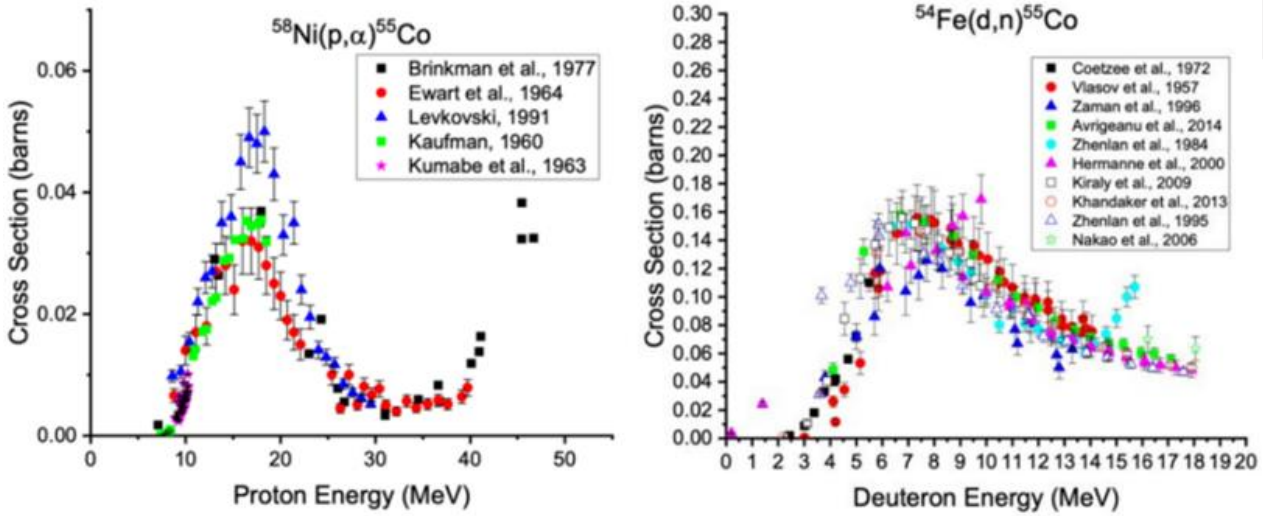
368.336 mg

469.218 $\frac{mg}{cm^2}$

E_p: 16.5 MeV

^{55}Co: 13.125 $\frac{MBq}{\mu Ah}$

+ high production yield
- long-lived ^{56}Co contamination



+ 10 – 20 MeV relatively low proton energy
- long-lived ^{57}Co contamination

Barrett et al. Diagnostics **2021**;11(7):1235

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THERANOSTIC PAIR OF COBALT RADIONUCLIDES

^{58m}Co

$T_{½}$ = 9.04 h
Decay: Auger e- and internal-conversion electrons
K: 17,2 keV, 73,0 %
L: 24,0 keV, 24,0 %
M: 24,8 keV, 3,4 %
Auger x3: < 8keV
LET: 2-18 keV/µm

Barrett et al. Diagnostics **2021**;11(7):1235

^{58}Fe(p,n)^{58m}Co
8 – 11 MeV

99. 68% ^{58}Fe
7 $\frac{mg}{cm^2}$
E_p: 10.1 MeV
^{58m}Co: 10.7 $\frac{MBq}{\mu Ah}$

Reaction	Threshold [MeV]
^{58}Fe(p,n)^{58}Co	3.14 ± 0.04
^{58}Fe(p,2n)^{57}Co	11.87 ± 0.06
^{58}Fe(p,3n)^{56}Co	23.44 ± 0.14

+ established proton route, good radionuclidic purity
- expensive enriched ^{58}Fe target

^{57}Fe(d,n)^{58m}Co
6 – 9 MeV

95.06% ^{57}Fe
E_d: 8.2 MeV
^{58m}Co: 13.5 ± 3.1 $\frac{MBq}{\mu Ah}$

+ effective production, thin enriched target
- deuterons, ^{57}Co contamination

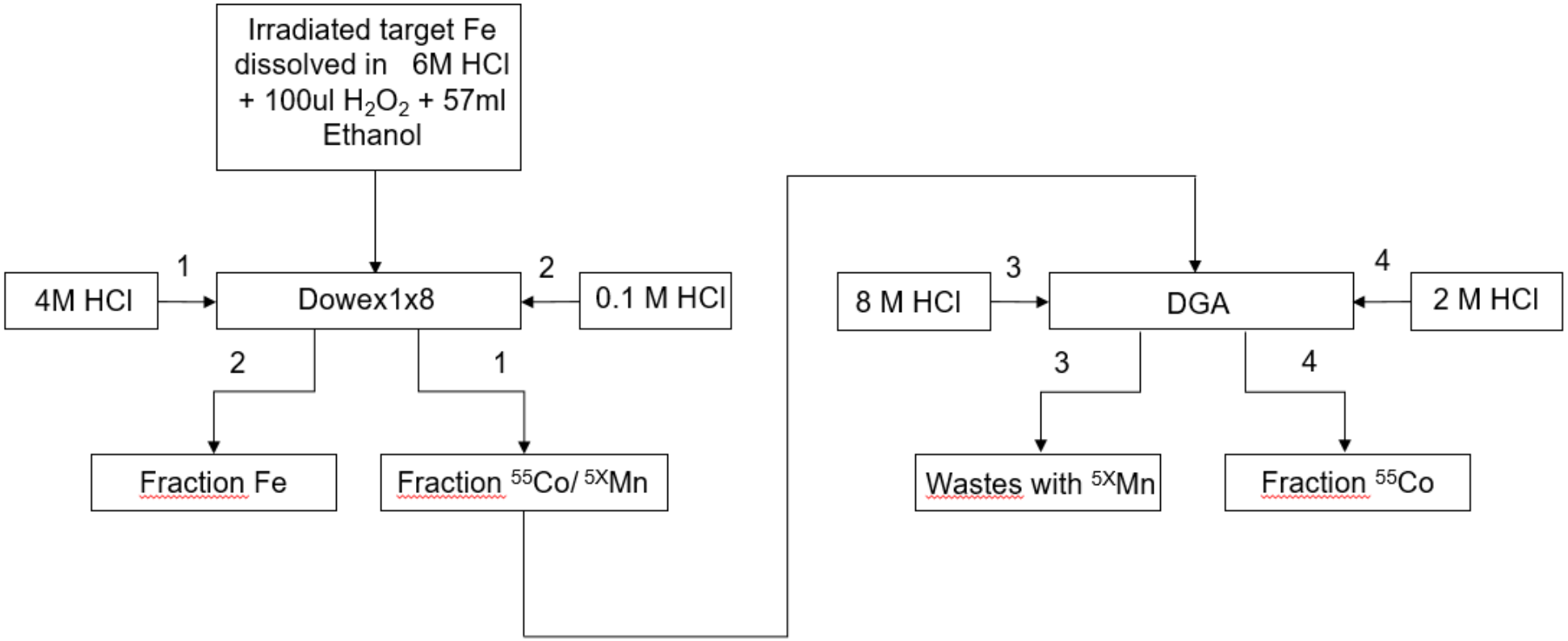
^{55}Mn(α,n)^{58m}Co

+ alternative production route
- alpha beam

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THERANOSTIC PAIR OF COBALT RADIONUCLIDES

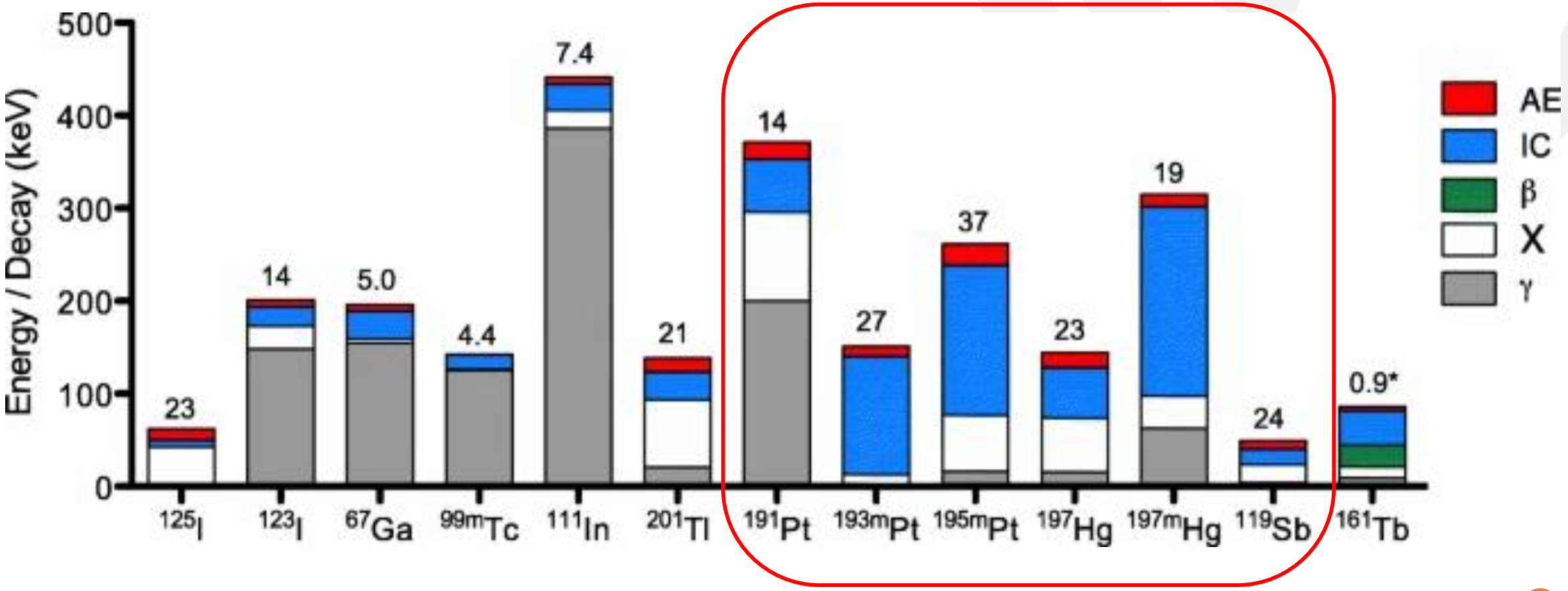
Separation of $^{55/58m}$Co from metallic Fe & target material recovery



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AUGER & CONVERSION ELECTRONS EMITTERS

Many suitable candidates for Targeted Auger Electron Therapy can be produced with small to medium energy protons (10-20 MeV) *via* simple (p,n) reaction



Ku, A., Facca, V.J., Cai, Z. et al. Auger electrons for cancer therapy – a review. EJNMMI Radiopharm. Chem. **2019**;4:27
https://doi.org/10.1186/s41181-019-0075-2

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PLATINUM RADIONUCLIDES

^{188}Pt

$T_{½}$ = 10.2 d
Decay: EC & Auger

^{189}Pt

$T_{½}$ = 10.9 h
Decay: EC & Auger

^{191}Pt

$T_{½}$ = 2.83 d
Decay: EC / Auger / X-rays

^{191}Ir(p,n)^{191}Pt: enriched Ir-191, low-energy protons
^{193}Ir(p,3n)^{191}Pt: enriched Ir-193, protons 25 – 30 MeV
^{nat}Ir(p,xn)^{191}Pt: natural Ir, protons up to 30 MeV

^{193m}Pt

$T_{½}$ = 4.33 d
Decay: Isomeric Transition, conversion & Auger

^{192}Os(α,3n)^{193m}Pt: enriched Os-192, alpha-beam 24 – 28 MeV
^{193}Ir(d,2n)^{193m}Pt: enriched Ir-193, deuterons 11 – 18 MeV

^{195m}Pt

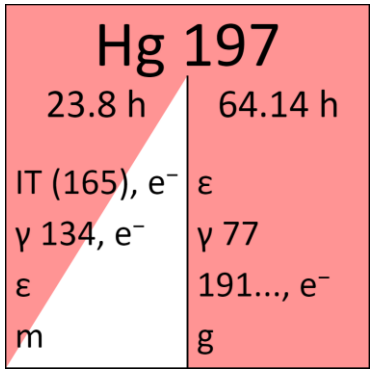
$T_{½}$ = 4.02 d
Decay: Isomeric Transition, conversion & Auger

^{192}Os(α,n)^{195m}Pt: enriched Os-192, alpha-beam 18 – 24 MeV

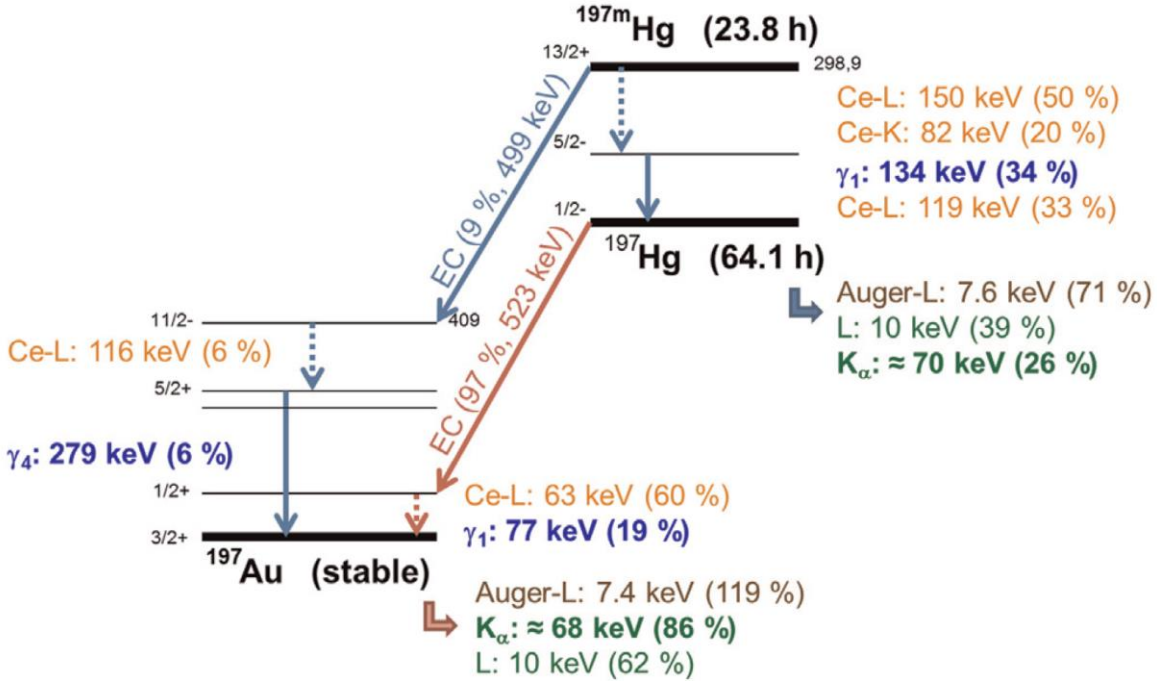
Production parameter	^{193m}Pt	^{195m}Pt
Alpha-particle energy interval	28 → 24 MeV	24 → 18 MeV
Calculated thick-target yield	0.25 MBq/μAh	0.013 MBq/μAh
Reported batch production	8.7 MBq	Approximately 1 MBq

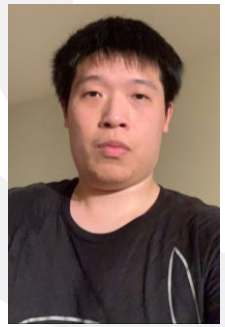
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MERCURY RADIONUCLIDES



10th Karlsruhe Nuclide Chart;
M. Walther et al., Appl. Radiat. Isotopes, 2015





Shaohuang Chen



Yumeela Ganga-Sah

- **^{197m}Hg**

– Half-life: 23.8 h
– Main gamma emission: 134 keV (34%)

- **^{197g}Hg**

– Half-life: 64.1 h
– Main gamma emission: 77 keV (19%)
– Main AE-emission: 7.4 keV (119%)

- Gamma emission from ^{197m}Hg and AE-emission from ^{197g}Hg make a theranostic pair

Alchemists' inverted dream

^{197}Au(p,n)$^{197m/g}$Hg: natural gold, protons 10 – 15 MeV
^{197}Au(d,2n)$^{197m/g}$Hg: natural gold, deuterons to be optimised

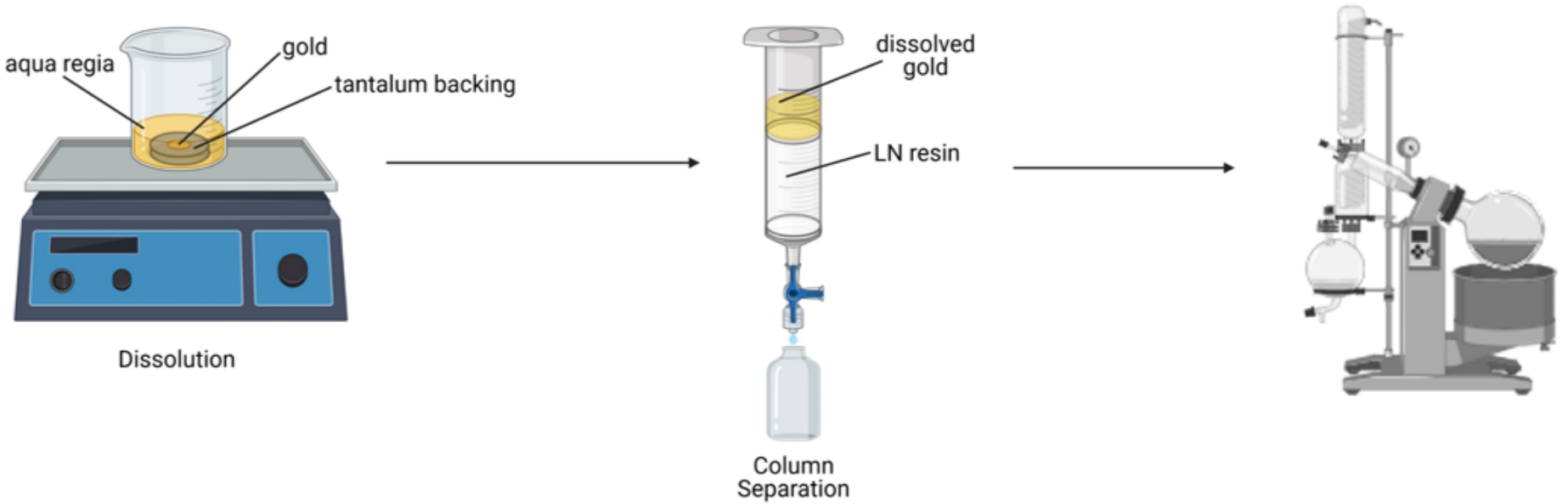
^{194}Pt(α,n)$^{197m/g}$Hg: enriched Pt-194, alphas
^{195}Pt(α,2n)$^{197m/g}$Hg: enriched Pt-195, alphas

*Randhawa P et al.Current Radiopharmaceuticals **2021**; 14 (4)*
https://dx.doi.org/10.2174/1874471014999210111201630

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MERCURY RADIONUCLIDES

Separation of $^{197m/g}$Hg from Au target material

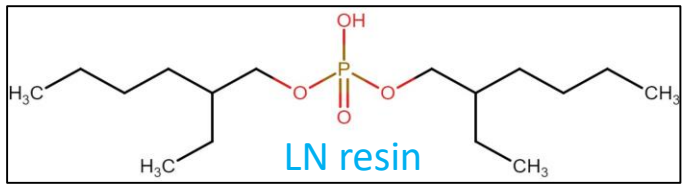


Dissolution

- Heating at 90 °C
- Gold dissolves in up to 6 h

Separation

- Eluent: 6 M HCl
- Mercury quickly eluted
- Gold was retained on LN resin



Evaporation

- Heating at 160 °C
- Solution → near dryness → conditioned with 0.01 M HCl (2x)
- Final volume: 200 – 400 µL

Filosofov D, et l.. Nucl Med Biol. ***2021****;94-95:1-19.*

M. Walther et al., AIP Conf. Proc., ***2017***

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ANTIMONY RADIONUCLIDES

^{117}Sb

$T_{½}$ = 2.8 h
Decay: EC & β⁺
γ: 158.6 keV (85.9%)

^{117}Sn(p,n)^{117}Sb
^{115}In(α,2n) ^{117}Sb

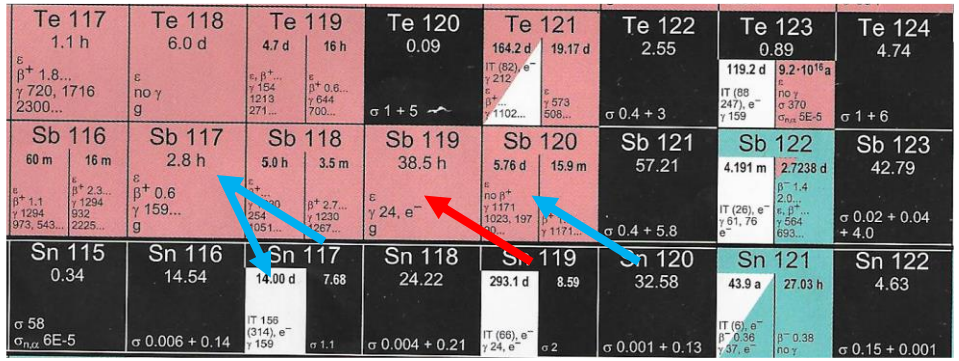
Sb 119
38.19 h

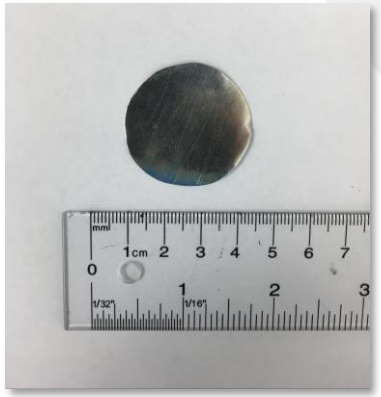
ε
γ 24, Ae^-
g

^{119}Sb

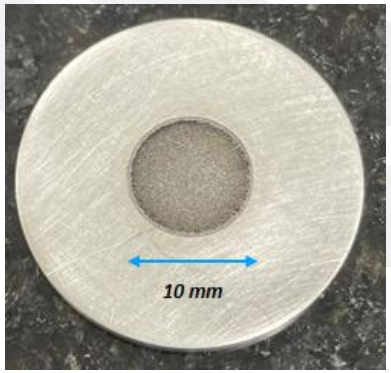
$T_{½}$ = 38.19 h
Decay: EC / Auger

^{119}Sn(p,n)^{119}Sb
^{119}Sn(d,2n)^{119}Sb
^{120}Sn(p,2n)^{119}Sb
^{121}Sb(p,3n)^{119}Te -> ^{119}Sb





^{nat}Sn foil target



^{119}Sn electroplated target (Ag backing)



Aivija Grundmane

^{nat}Sn consists of 10 stable Sn isotopes, provides different radioantimony tracers for method development

Target mass	**~ 400 mg**	**25 – 150 mg**
Irradiation conditions	≤ 5 µA, 1 h	≤ 30 µA, 4 h
Estimate ^{119}Sb produced	~ 50 MBq or **~ 2 ng**	~ 1 GBq or **~ 40 ng**

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ANTIMONY RADIONUCLIDES

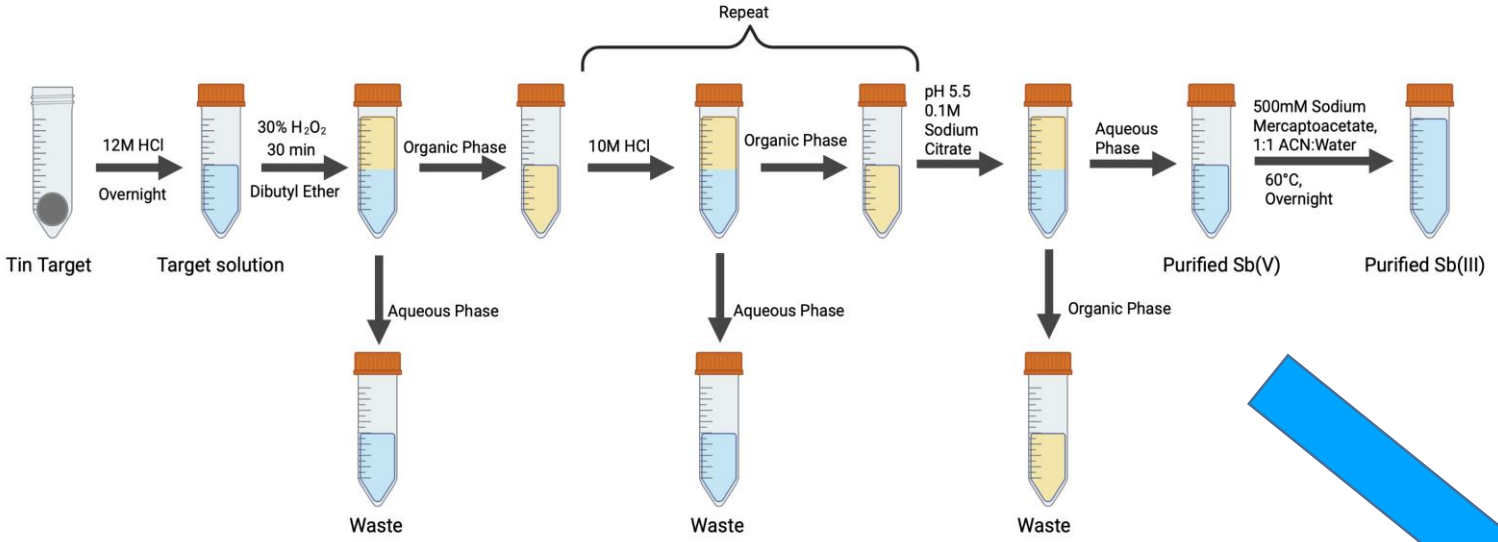
Separation of ^{119}Sb from Sn target material

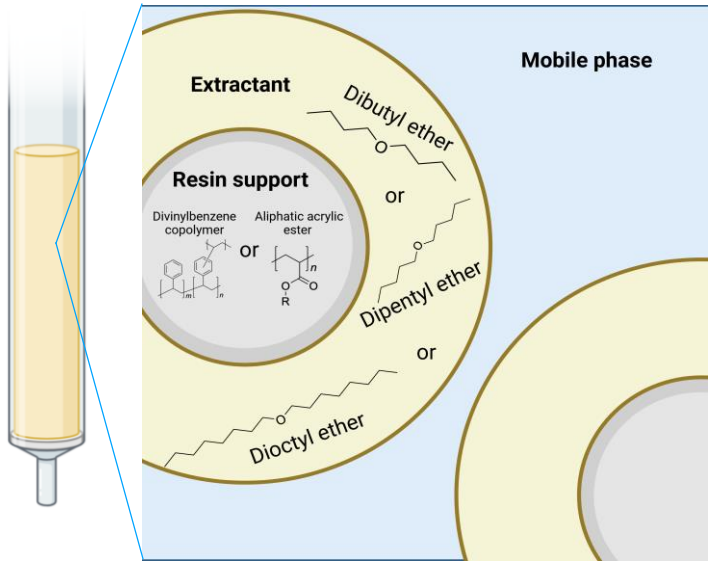


In collaboration with:

Thomas Kostelnik

TRIUMF



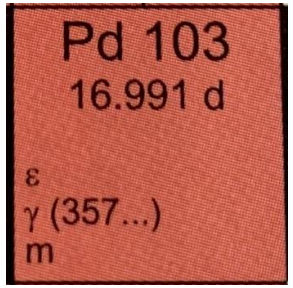


- Removes > 99.95% of the tin target
- > 75% recovery of radioantimony

*Kostelnik T. I et al. Nuclear Medicine and Biology, 122–123, (**2023**), https://doi.org/10.1016/j.nucmedbio*

We acknowledge support from the European Union's Horizon 2020 research and innovation program under the NOMATEN Teaming grant agreement No. 857470 and from the Ministry of Science and Higher Education's initiative „Support for the Activities of Centers of Excellence Established in Poland under the Horizon 2020 Program" under agreement No. MEiN/2023/DIR/3795.

PALLADIUM RADIONUCLIDES



^{103}Pd

$T_{½}$ = 16.99 h

Decay: EC & Auger (^{103m}Rh)

^{103}Rh(p,n)^{103}Pd

^{103}Rh(d,2n)^{103}Pd

^{100}Ru(α,n)^{103}Pd

^{101}Ru(α,2n)^{103}Pd

^{102}Ru(3He,2n)^{103}Pd

^{109}Pd

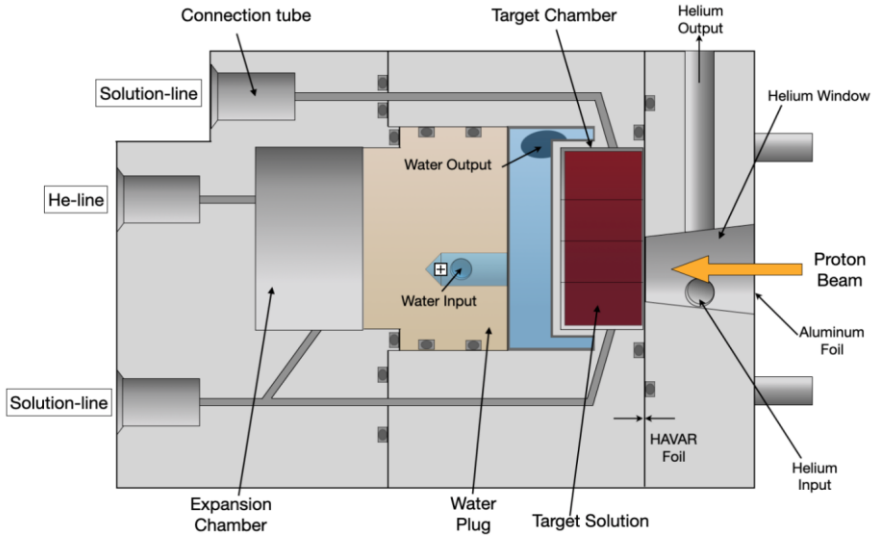
$T_{½}$ = 13.7 h

Decay: β^-

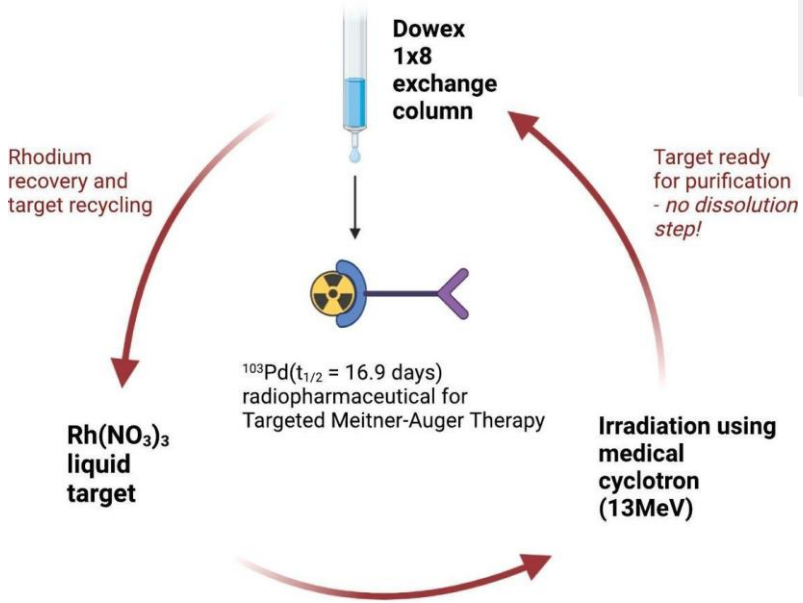
^{108}Pd(n,γ)^{109}Pd

^{110}Pd(p,pn)^{109}Pd

- Liquid targets made by dissolving rhodium nitrate hydrate salt in de-ionized water
- Irradiated using 12 MeV proton beam at the TR-13 cyclotron at TRIUMF



Liquid target design



Liquid target production procedure



Viktoria Krol

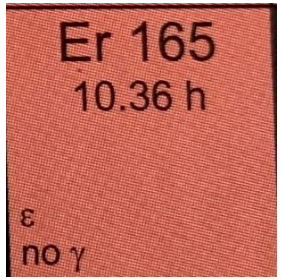


Conny Hoehr

*Viktoria Krol et al. Nuclear Medicine and Biology, 118–119, **2023**, https://doi.org/10.1016/j.nucmedbio*

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ERBIUM RADIONUCLIDES



^{165}Er

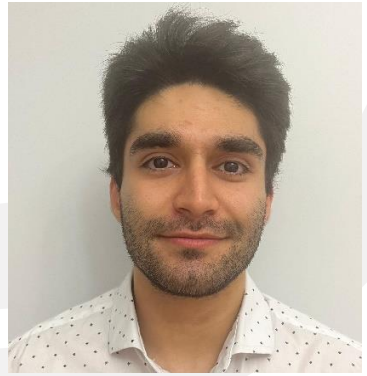
$T_{½}$ = 10.36 h
Decay: EC (100%); pure Auger
no gammas

^{165}Ho(p,n)^{165}Er
^{165}Ho(d,2n)^{165}Er
^{166}Ho(p,2n)^{165}Tm -> ^{165}Er
^{nat}Er(p,xn)^{165}Tm -> ^{165}Er

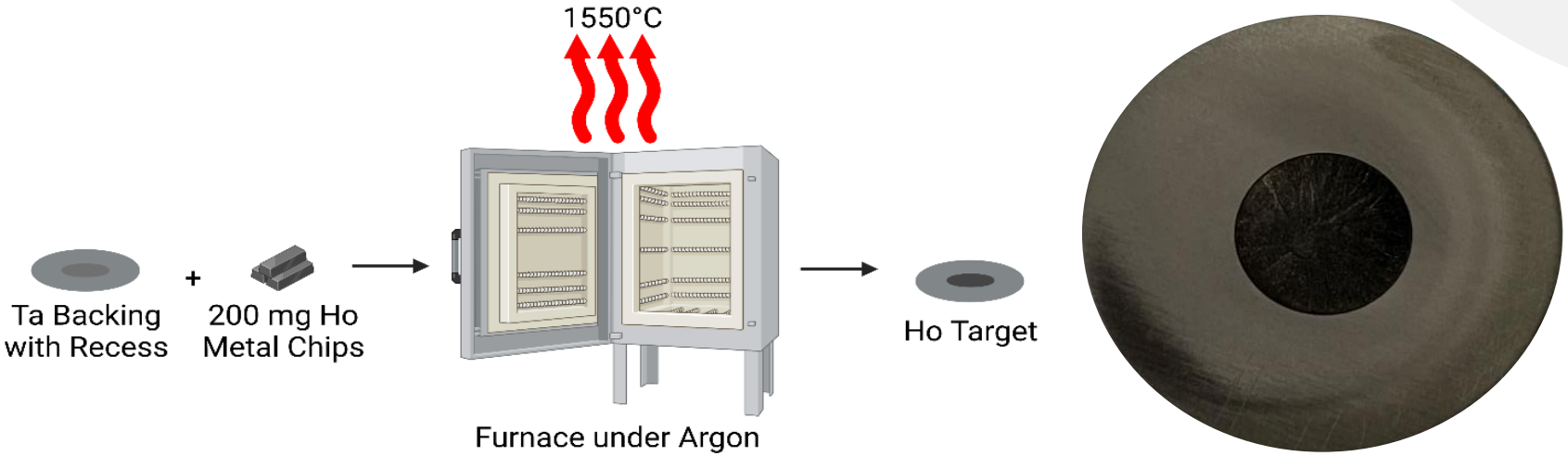
^{169}Er

$T_{½}$ = 9.39 d
Decay: β^-

^{168}Er(n,γ)^{169}Er



Behrad Saeedi



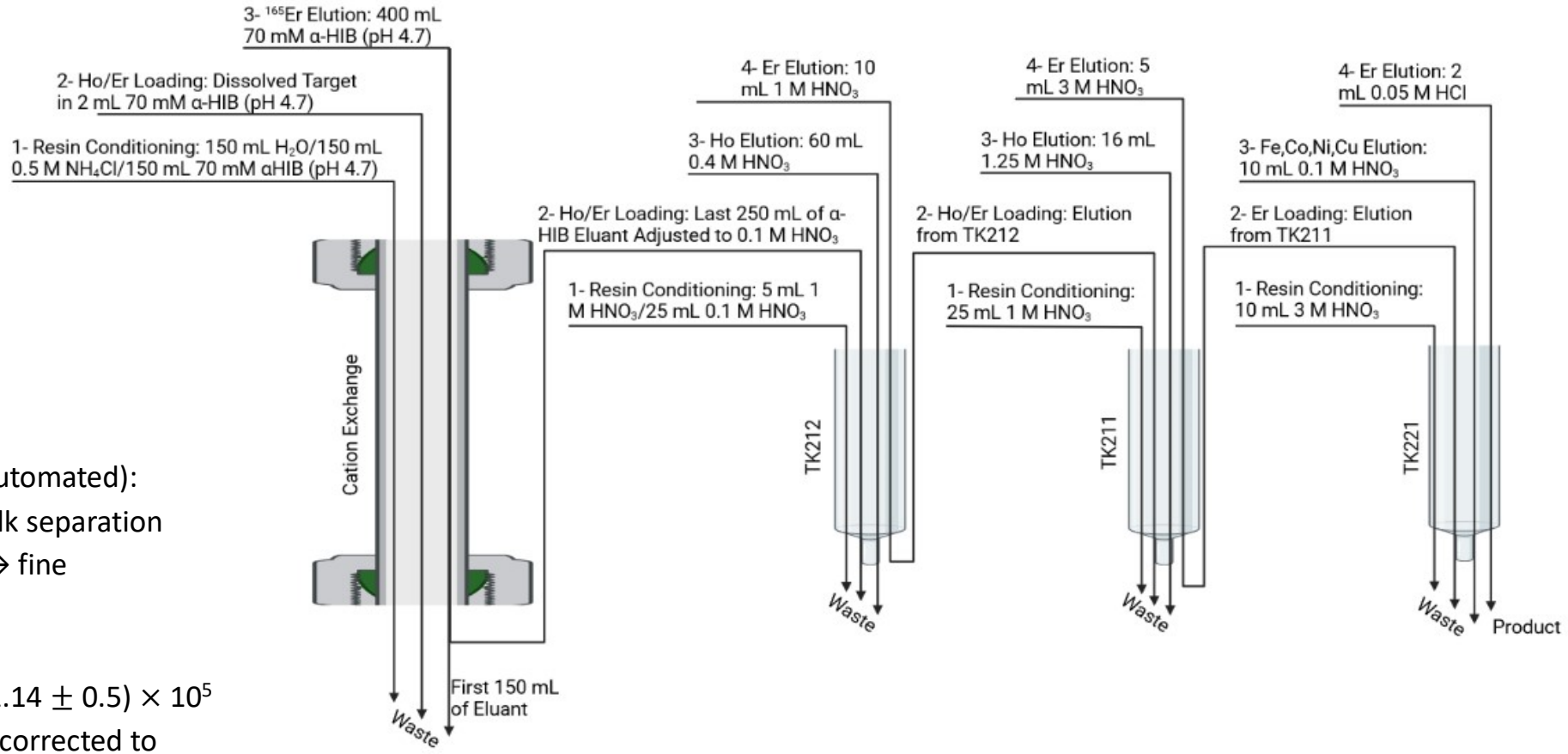
Irradiation for 2 h at 30 μA at TR-13 (12.8 MeV) results in over 1 GBq of ^{165}Er

*Saeedi B. et al. ACS Inorg Chemistry accepted (January 25, **2024**), Invited front cover*

We acknowledge support from the European Union's Horizon 2020 research and innovation program under the NOMATEN Teaming grant agreement No. 857470 and from the Ministry of Science and Higher Education's initiative „Support for the Activities of Centers of Excellence Established in Poland under the Horizon 2020 Program" under agreement No. MEiN/2023/DIR/3795.

ERBIUM RADIONUCLIDES

Separation of ^{165}Er from Ho target material



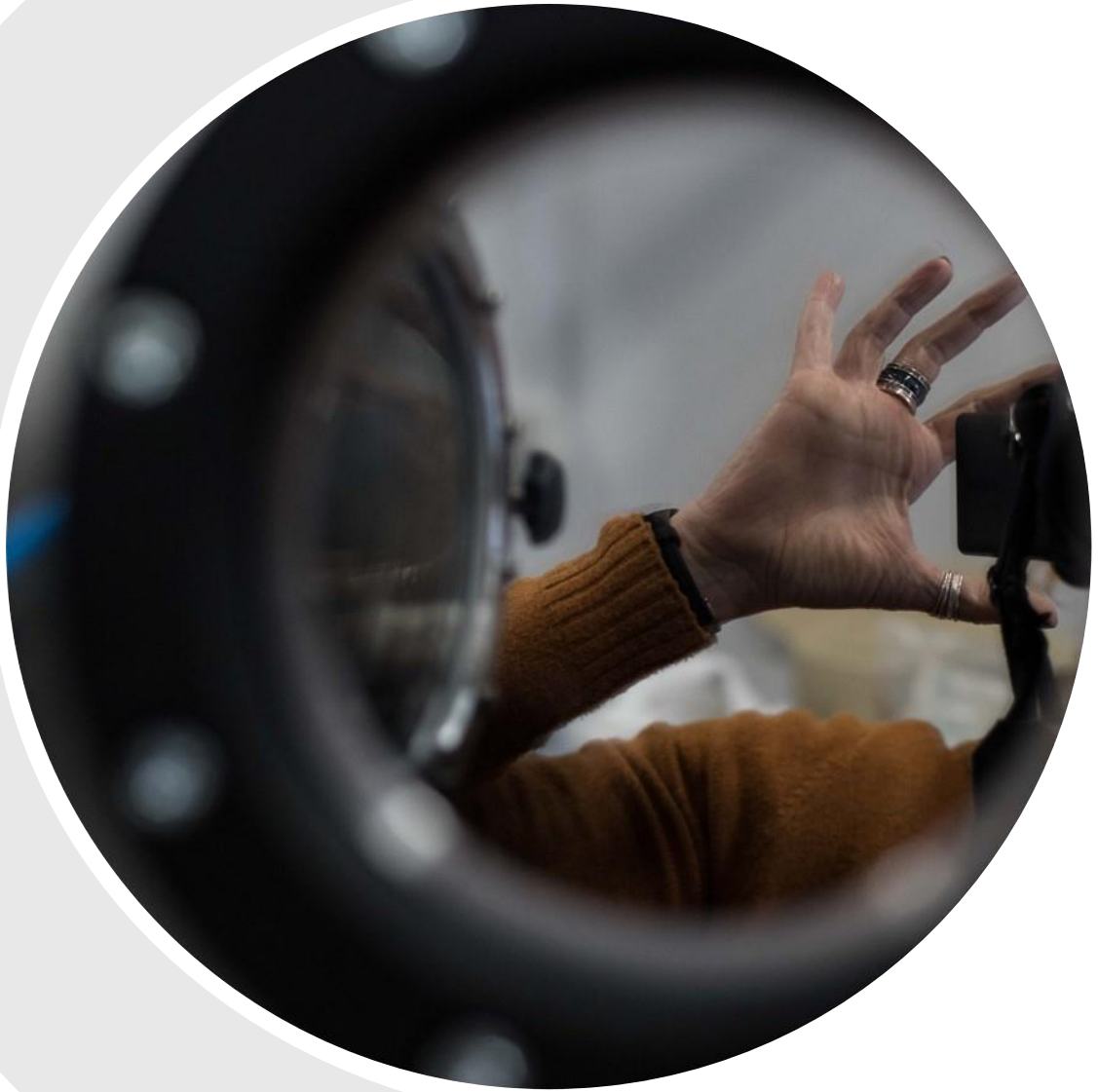
- novel separation method (semi-automated):

- 50W-X8 cation exchange resin → Bulk separation
- combination of TK resins (Triskem) → fine purification and media conversion

- separation 4.5 ± 0.5 hours
- overall separation factor (SF) of $(1.14 \pm 0.5) \times 10^5$
- 79.8 ± 6.2% ^{165}Er recovery (decay corrected to EoB)

*Saeedi B. et al. ACS Inorg Chemistry accepted (January 25, **2024**), Invited front cover*

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THANK YOU

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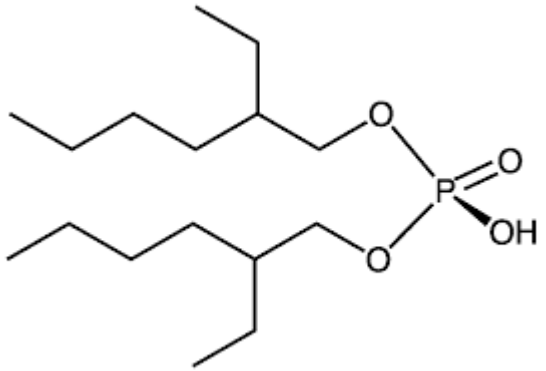
HTTPS://NOMATEN.NCBJ.GOV.PL/NOVEL-RADIOPHARMACEUTICALS-MEDICAL-PURPOSES

We acknowledge support from the European Union's Horizon 2020 research and innovation program under the NOMATEN Teaming grant agreement No. 857470 and from the Ministry of Science and Higher Education's initiative „Support for the Activities of Centers of Excellence Established in Poland under the Horizon 2020 Program" under agreement No. MEiN/2023/DIR/3795.

Separation of $^{197/197m}$Hg from target material

1. Dissolving the target (100 - 200 mg Au) in aqua regia at 90 ° C
2. Dilution of the target solution with 6M HCl
3. Application of the target solution on the Ln-Resin column
4. Mercury cations elution 6M HCl (Predicted recovery of 90% in 2 mL)
5. Gold washout with 0.01M HCl
6. After elution, evaporation of the mercury solution and dilution with 0.1M HCl

Ln-Resin: (Di (2-ethylhexyl) orthophosphoric acid (HDEHP)



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M. Walther, O. Lebeda, S. Preusche, H.-J. Pietzsch, J. Steinbach (2017) Theranostic mercury part 1: A new Hg/Au separation by a resin based method, AIP Conference Proceedings,