Production of Radiolanthanides for Medical Applications in the USA

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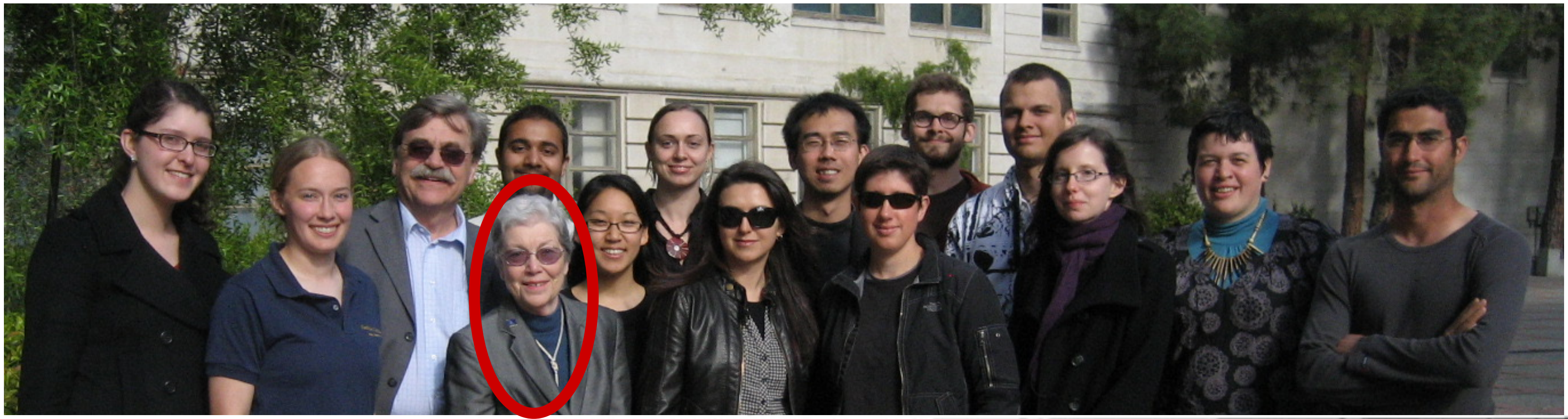
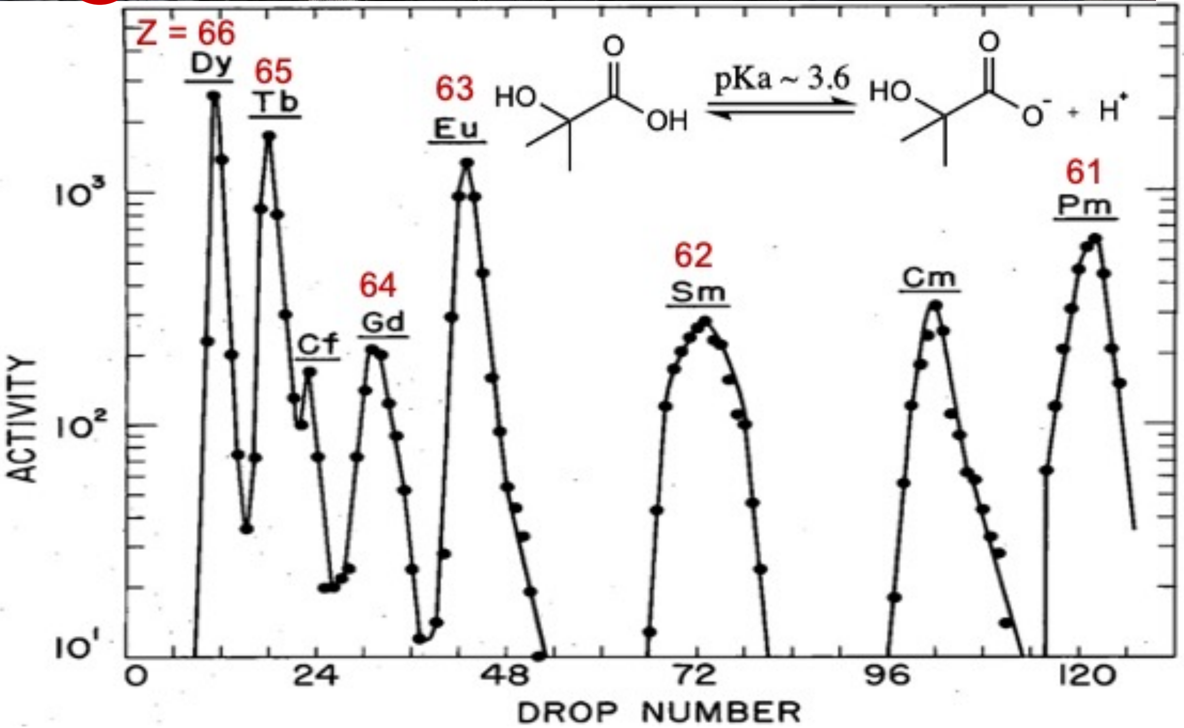
The PRISMAP Radiolanthanides Workshop
Paul Scherrer Institute
Villigen, Switzerland
September 4, 2024

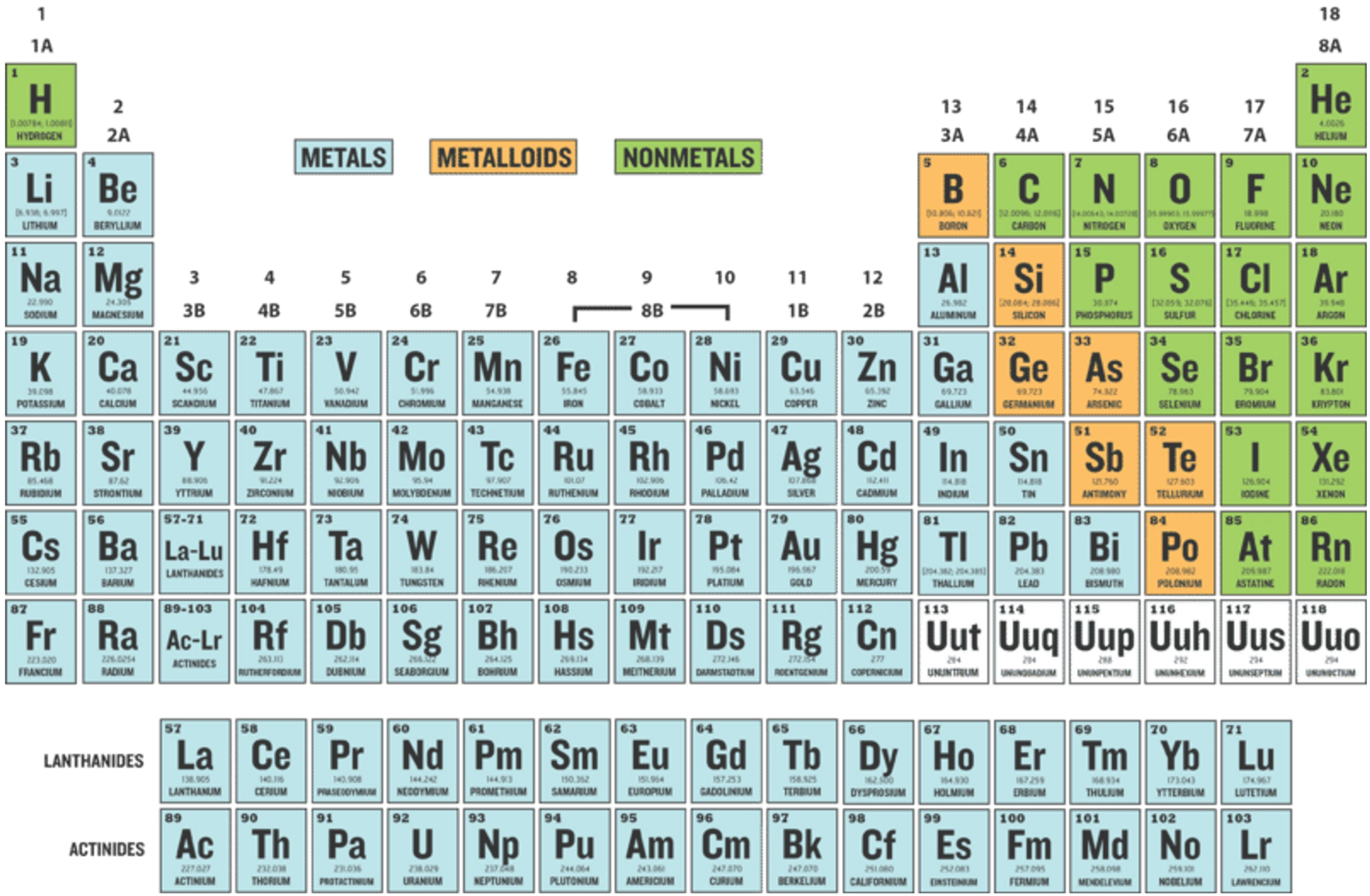
Darleane Hoffman – pioneering radiolanthanide chemist





Louise Smith and Hoffman, *J Inorg Nucl Chem* **3:** 243-247 (1956).

Periodic Table of the Elements



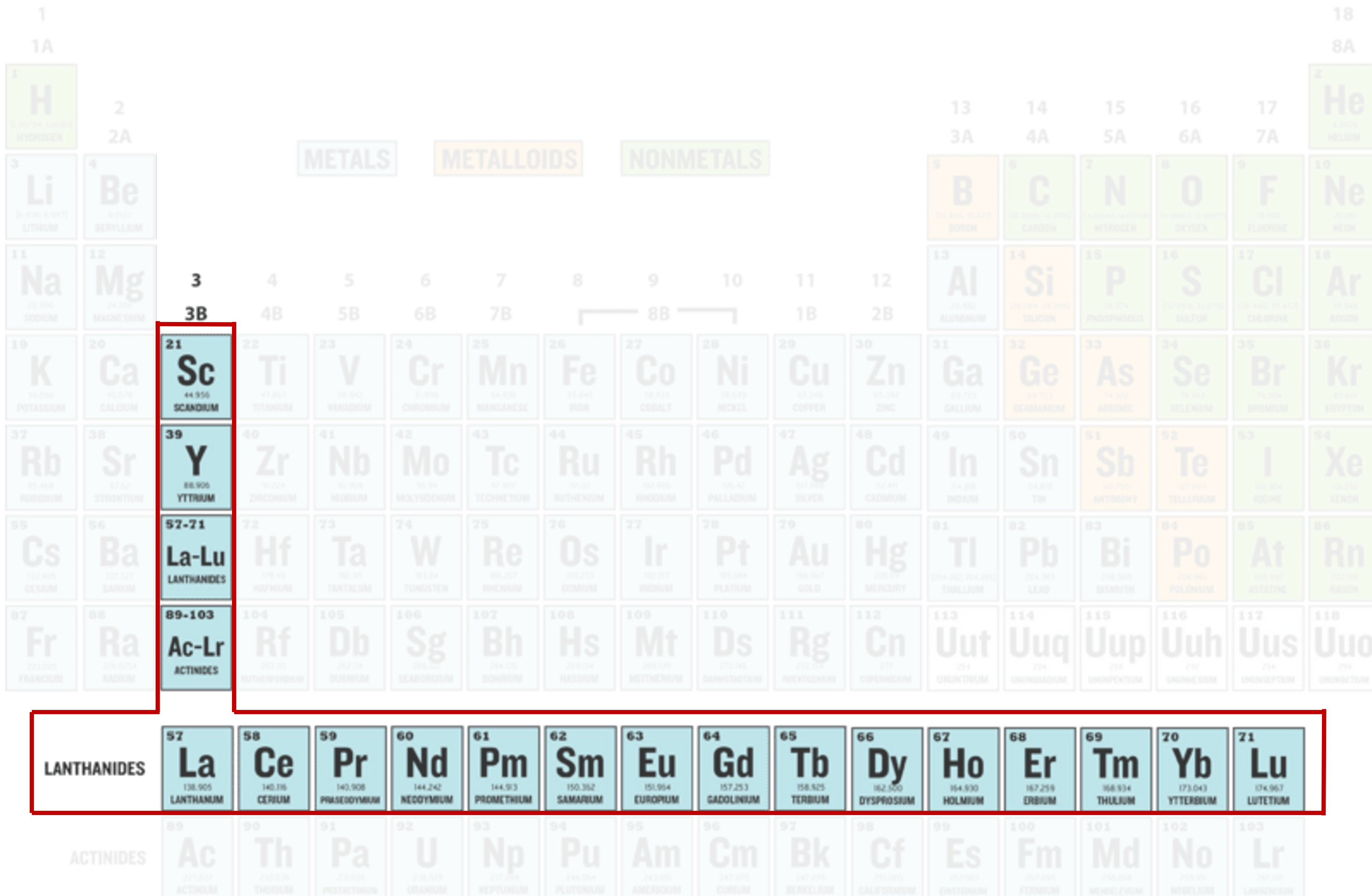
Periodic Table of the Elements

METALS | METALLOIDS | NONMETALS

1 1A	2 2A	3 3B	4 4B	5 5B	6 6B	7 7B	8 8B	9 8B	10 8B	11 1B	12 2B	13 3A	14 4A	15 5A	16 6A	17 7A	18 8A
1 H [1.00784; 1.00811] HYDROGEN																	2 He 4.0026 HELIUM
3 Li [6.938; 6.997] LITHIUM	4 Be 9.0122 BERYLLIUM											5 B [10.806; 10.821] BORON	6 C [12.0096; 12.0116] CARBON	7 N [14.00643; 14.00728] NITROGEN	8 O [15.99903; 15.99977] OXYGEN	9 F 18.998 FLUORINE	10 Ne 20.180 NEON
11 Na 22.990 SODIUM	12 Mg 24.305 MAGNESIUM											13 Al 26.982 ALUMINUM	14 Si [28.084; 28.086] SILICON	15 P 30.974 PHOSPHORUS	16 S [32.059; 32.076] SULFUR	17 Cl [35.446; 35.457] CHLORINE	18 Ar 39.948 ARGON
19 K 39.098 POTASSIUM	20 Ca 40.078 CALCIUM	21 Sc 44.956 SCANDIUM	22 Ti 47.867 TITANIUM	23 V 50.942 VANADIUM	24 Cr 51.996 CHROMIUM	25 Mn 54.938 MANGANESE	26 Fe 55.845 IRON	27 Co 58.933 COBALT	28 Ni 58.693 NICKEL	29 Cu 63.546 COPPER	30 Zn 65.392 ZINC	31 Ga 69.723 GALLIUM	32 Ge 69.723 GERMANIUM	33 As 74.922 ARSENIC	34 Se 78.963 SELENIUM	35 Br 79.904 BROMIUM	36 Kr 83.801 KRYPTON
37 Rb 85.468 RUBIDIUM	38 Sr 87.62 STRONTIUM	39 Y 88.906 YTTRIUM	40 Zr 91.224 ZIRCONIUM	41 Nb 92.906 NIOBIUM	42 Mo 95.94 MOLYBDENUM	43 Tc 97.907 TECHNETIUM	44 Ru 101.07 RUTHENIUM	45 Rh 102.906 RHODIUM	46 Pd 106.42 PALLADIUM	47 Ag 107.868 SILVER	48 Cd 112.411 CADMIUM	49 In 114.818 INDIUM	50 Sn 114.818 TIN	51 Sb 121.760 ANTIMONY	52 Te 127.603 TELLURIUM	53 I 126.904 IODINE	54 Xe 131.292 XENON
55 Cs 132.905 CESIUM	56 Ba 137.327 BARIUM	57-71 La-Lu LANTHANIDES	72 Hf 178.49 HAFNIUM	73 Ta 180.95 TANTALUM	74 W 183.84 TUNGSTEN	75 Re 186.207 RHENIUM	76 Os 190.233 OSMIUM	77 Ir 192.217 IRIDIUM	78 Pt 195.084 PLATIUM	79 Au 196.967 GOLD	80 Hg 200.59 MERCURY	81 Tl [204.382; 204.385] THALLIUM	82 Pb 204.383 LEAD	83 Bi 208.980 BISMUTH	84 Po 208.982 POLONIUM	85 At 209.987 ASTATINE	86 Rn 222.018 RADON
87 Fr 223.020 FRANCIUM	88 Ra 226.0254 RADIUM	89-103 Ac-Lr ACTINIDES	104 Rf 263.113 RUTHERFORDIUM	105 Db 262.114 DUBNIUM	106 Sg 266.122 SEABORGIUM	107 Bh 264.125 BOHRIUM	108 Hs 269.134 HASSIUM	109 Mt 268.139 MEITNERIUM	110 Ds 272.146 DARMSTADTIUM	111 Rg 272.154 ROENTGENIUM	112 Cn 277 COPERNICIUM	113 Uut 284 UNUNTRIUM	114 Uuq 284 UNUNQUADIUM	115 Uup 288 UNUNPENTIUM	116 Uuh 292 UNUNHEXIUM	117 Uus 294 UNUNSEPTIUM	118 Uuo 294 UNUNOCTIUM

LANTHANIDES	57 La 138.905 LANTHANUM	58 Ce 140.116 CERIUM	59 Pr 140.908 PRASEODYMIUM	60 Nd 144.242 NEODYMIUM	61 Pm 144.913 PROMETHIUM	62 Sm 150.362 SAMARIUM	63 Eu 151.964 EUROPIUM	64 Gd 157.253 GADOLINIUM	65 Tb 158.925 TERBIUM	66 Dy 162.500 DYSPROSIUM	67 Ho 164.930 HOLMIUM	68 Er 167.259 ERBIUM	69 Tm 168.934 THULIUM	70 Yb 173.043 YTTERBIUM	71 Lu 174.967 LUTETIUM
ACTINIDES	89 Ac 227.027 ACTINIUM	90 Th 232.038 THORIUM	91 Pa 231.036 PROTACTINIUM	92 U 238.029 URANIUM	93 Np 237.048 NEPTUNIUM	94 Pu 244.064 PLUTONIUM	95 Am 243.061 AMERICIUM	96 Cm 247.070 CURIUM	97 Bk 247.070 BERKELIUM	98 Cf 251.080 CALIFORNIUM	99 Es 252.083 EINSTEINIUM	100 Fm 257.095 FERMIUM	101 Md 258.098 MENDELEVIUM	102 No 259.101 NOBELIUM	103 Lr 262.110 LAWRENCIUM

Lanthanides and their homologues



Radiolanthanides across the United States

^{165}Er, ^{86}Y

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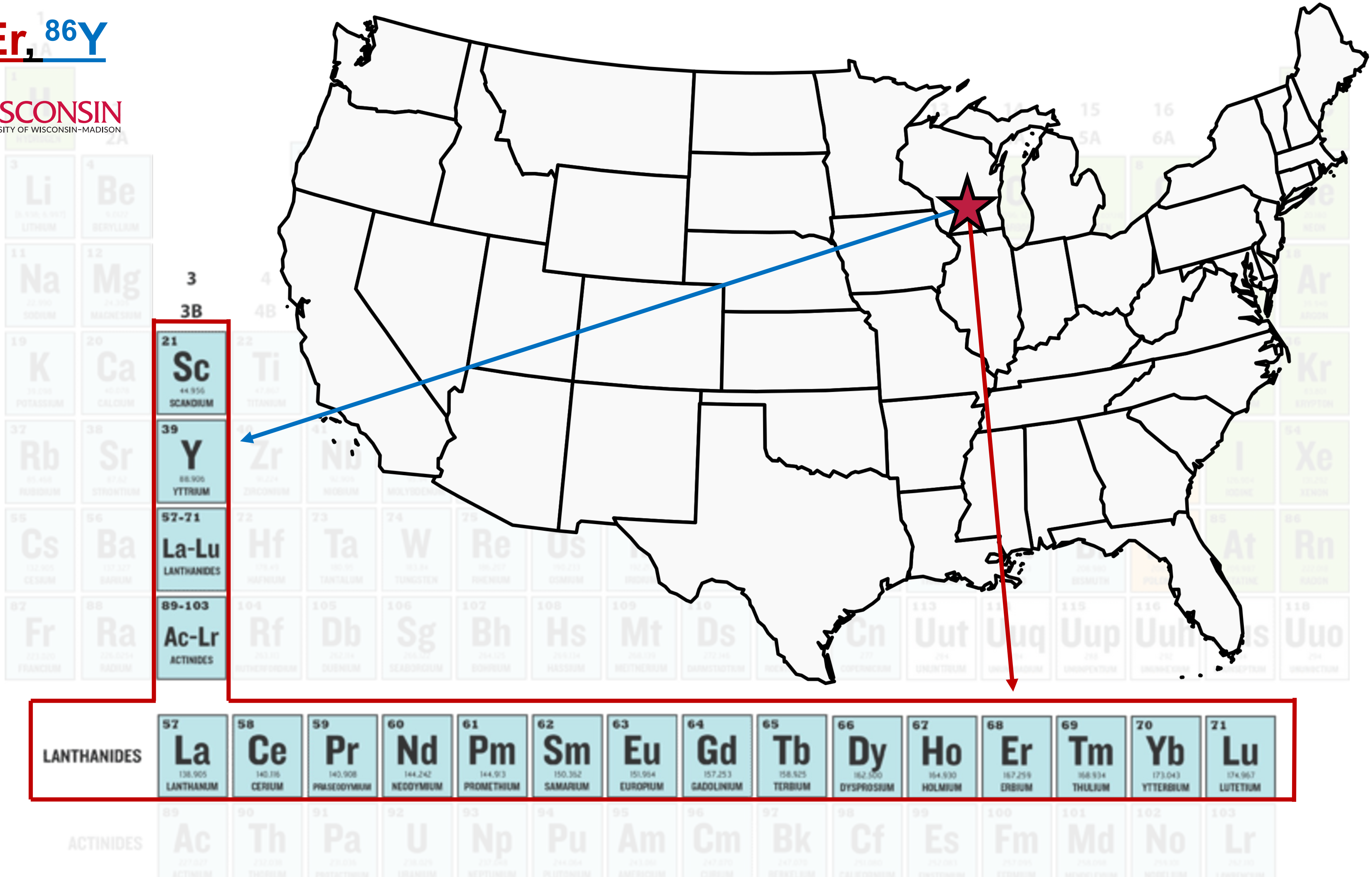

Radiolanthanides across the United States

^{165}Er, ^{86}Y

WISCONSIN
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^{134}Ce/ ^{134}La

Los Alamos
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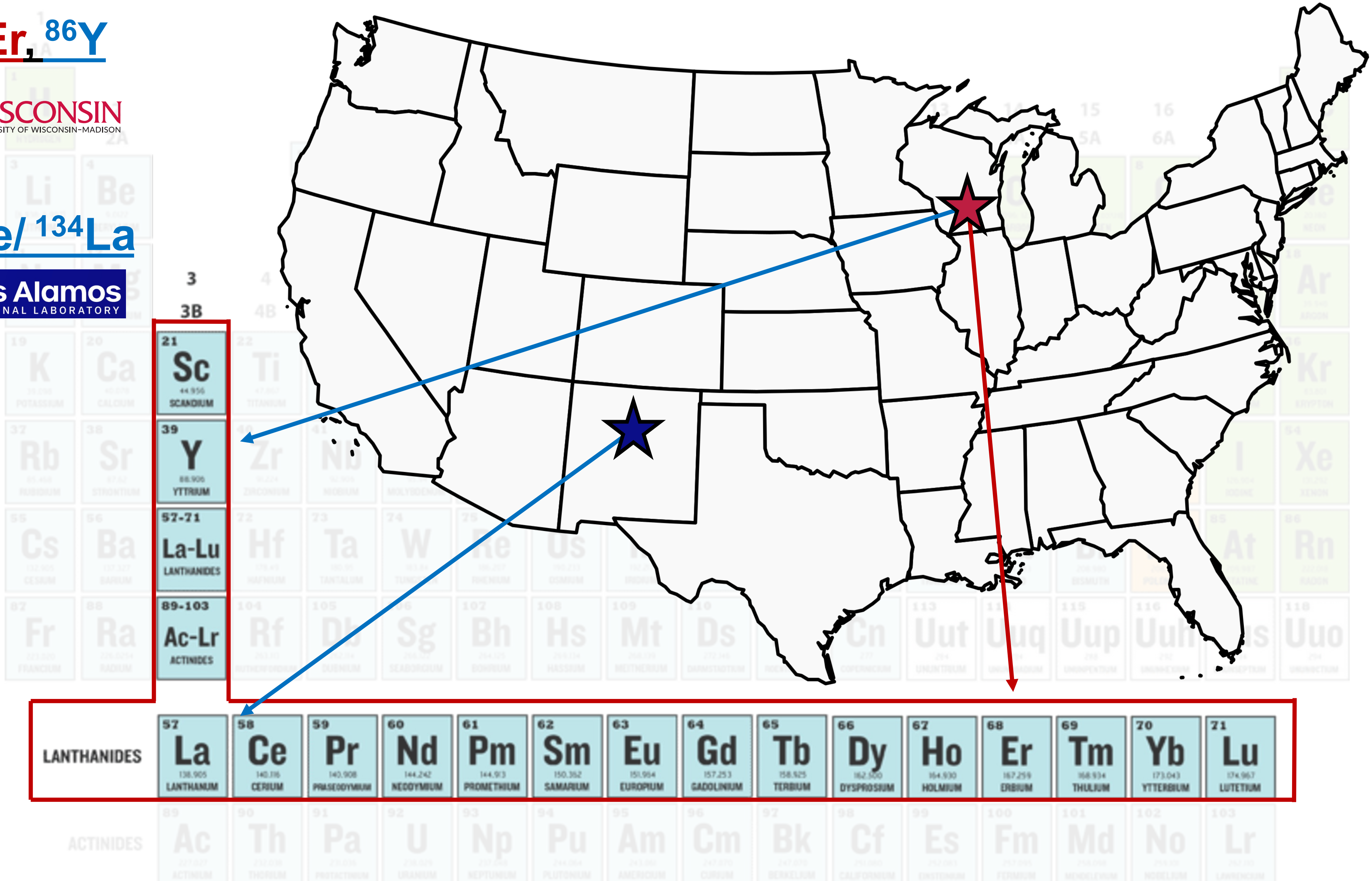
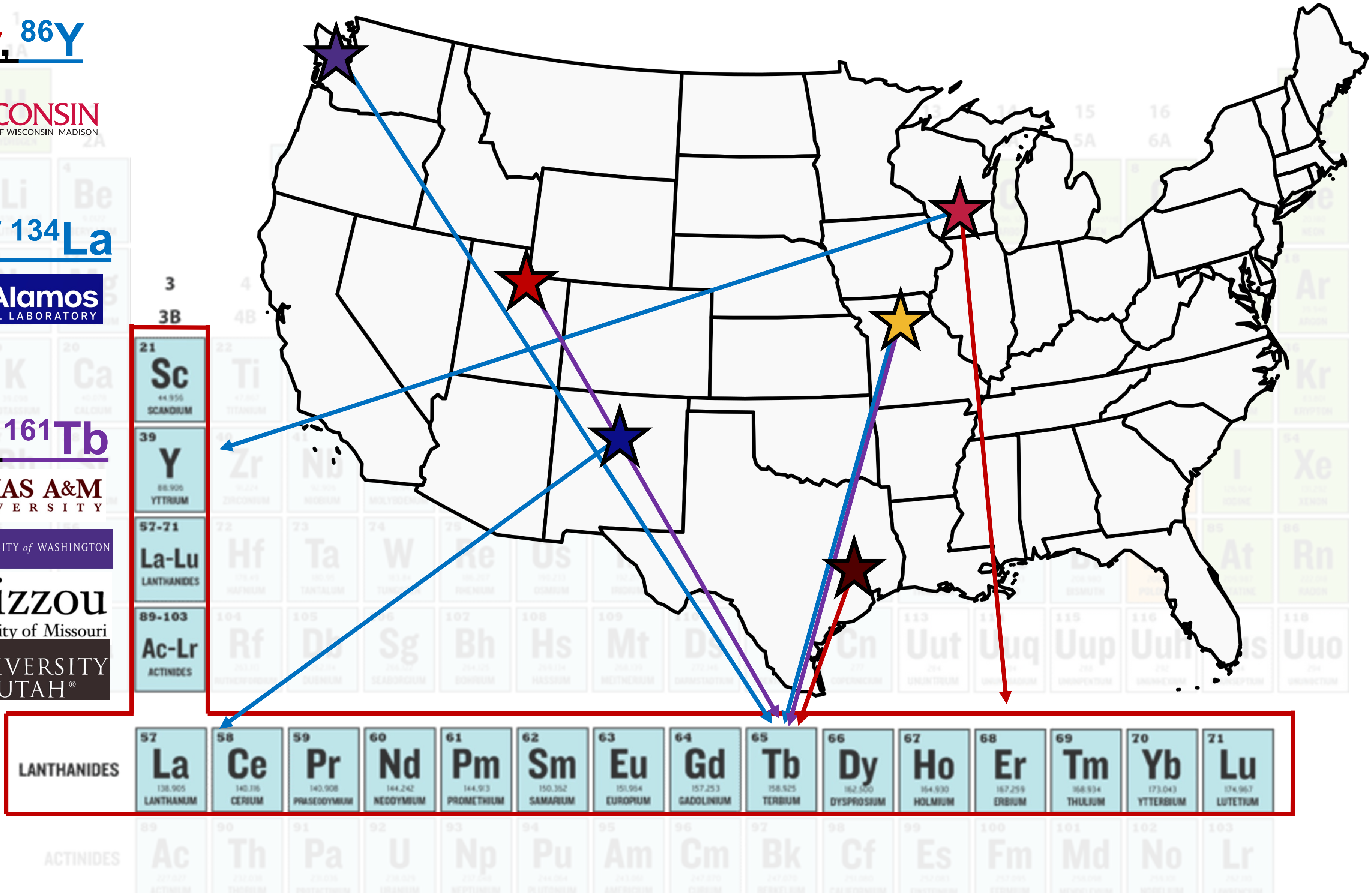


Radiolanthanides across the United States

^{165}Er, ^{86}Y

^{134}Ce/ ^{134}La

149,155,161Tb



^{165}Er at the University of Wisconsin

molecules

MDPI

Article

A High Separation Factor for ^{165}Er from Ho for Targeted Radionuclide Therapy

Isidro Da Silva [1,2], Taylor R. Johnson [1], Jason C. Mixdorf [1], Eduardo Aluicio-Sarduy [1], Todd E. Barnhart [1], R. Jerome Nickles [1], Jonathan W. Engle [1,3] and Paul A. Ellison [1,*]

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Taylor Johnson

Isotope Program
U.S. Department of Energy

Supported by Department of Energy Isotope Program, managed by the Office of Science for Isotope R&D and Production grant DE-SC0020955

$Ho_{(m)}$ target – cyclotron irradiations

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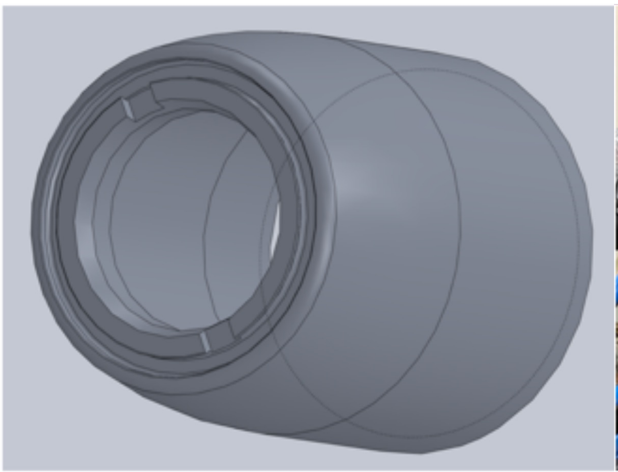
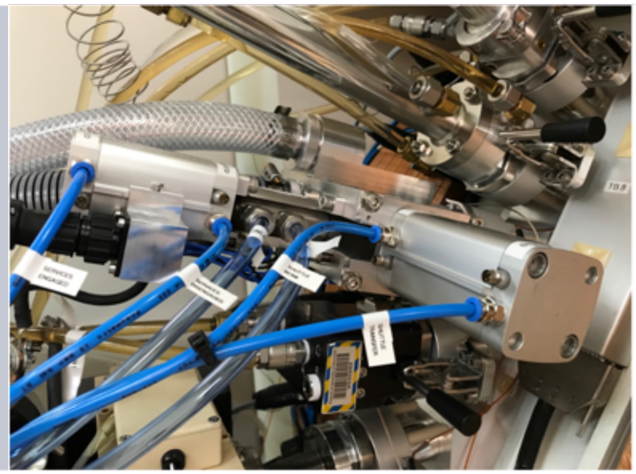
Materials Preparation Center

$^{nat}Ho_{(m)}$ 99.99995% purity from ^{nat}Er (0.5 ppm)



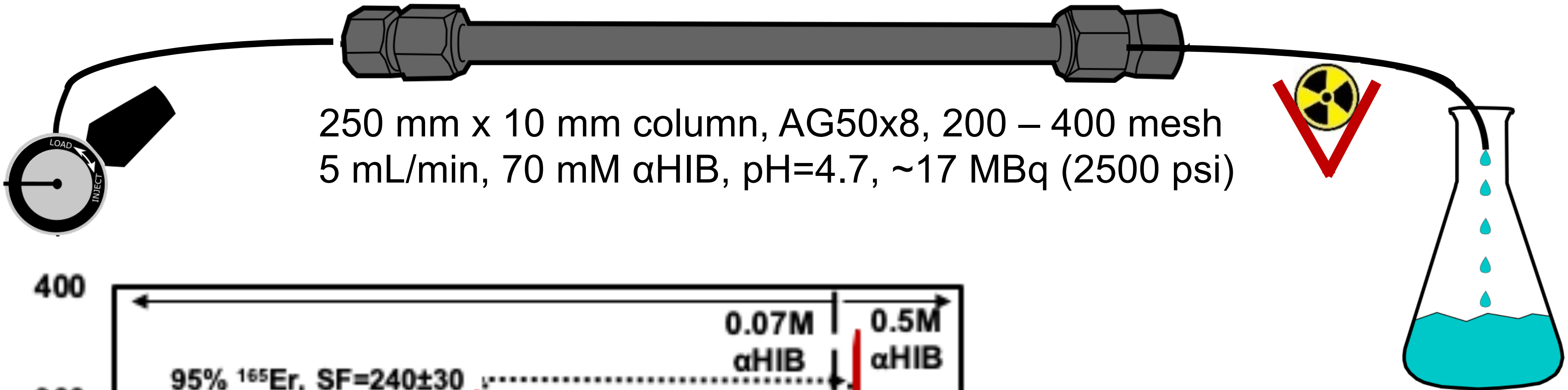


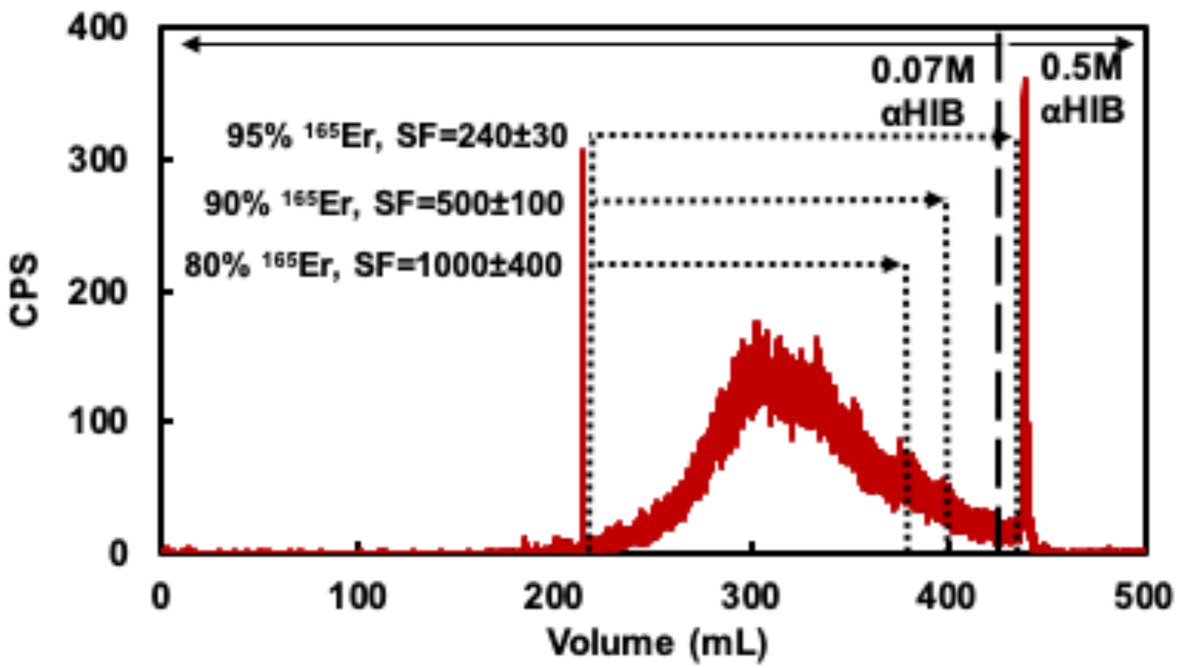
Diam (mm)	Ho Dimensions Thick. (mm)	Mass (mg)	E_{in} (MeV)	E_{out} (MeV)	^{165}Er Physical Yield ($MBq \cdot \mu A^{-1} \cdot h^{-1}$)	n
9.5	280–300	174 ± 8	12.5	7.5	24.1 ± 0.5	5
9.5	200–240	125 ± 6	12.5	8.4–9.1	19.1 ± 1.1	3
7.9	270–280	108 ± 4	12.5	7.8	14.1 ± 1.4	3
7.9	190	69 ± 1	12.5	9.3	12.0 ± 0.9	4

After 40 μA

Da Silva *et al.*, *Molecules* **26:** 7513 (2021).

Ho/^{165}Er separation step 1: CX / αHIB





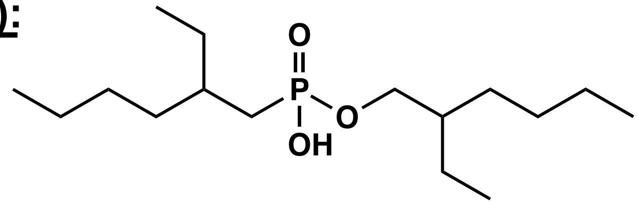
$$SF_{Ho/Er} = \frac{m_{Ho,before}/m_{Ho,after}}{A_{^{165}Er,before}/A_{^{165}Er,after}}$$

174 ± 8 mg Ho: $SF_{Ho/Er}$ = **250 ± 150**, ^{165}Er recovery **(90.5 ± 1.4)%** with (n = 5)

Da Silva *et al.*, *Molecules* **26:** 7513 (2021).

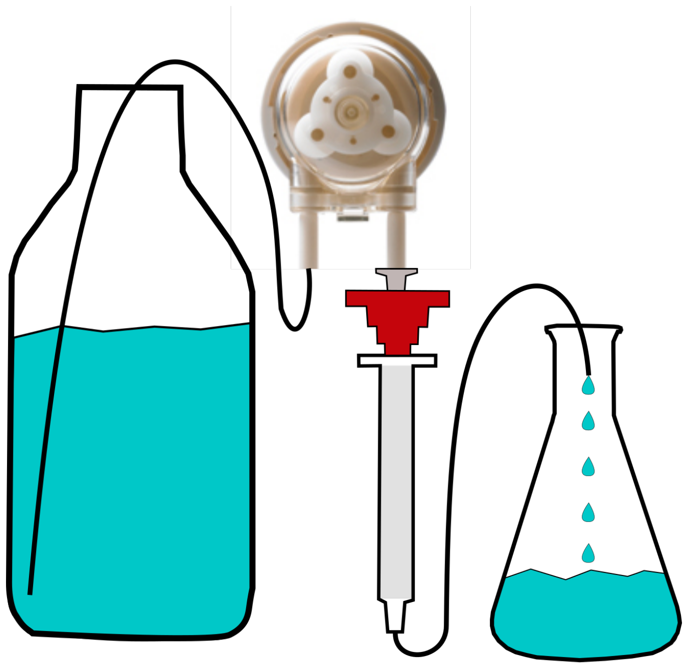
Ho/^{165}Er separation step 2: LN2 EXC

Extraction Chromatography (EXC):



LN2 – HEH(EHP)

1. ^{165}Er in 0.1 M HNO_3, 70 αHIB at 5 mL/min
2. 52 ± 9 mL 0.4 M HNO_3 at 1 mL/min

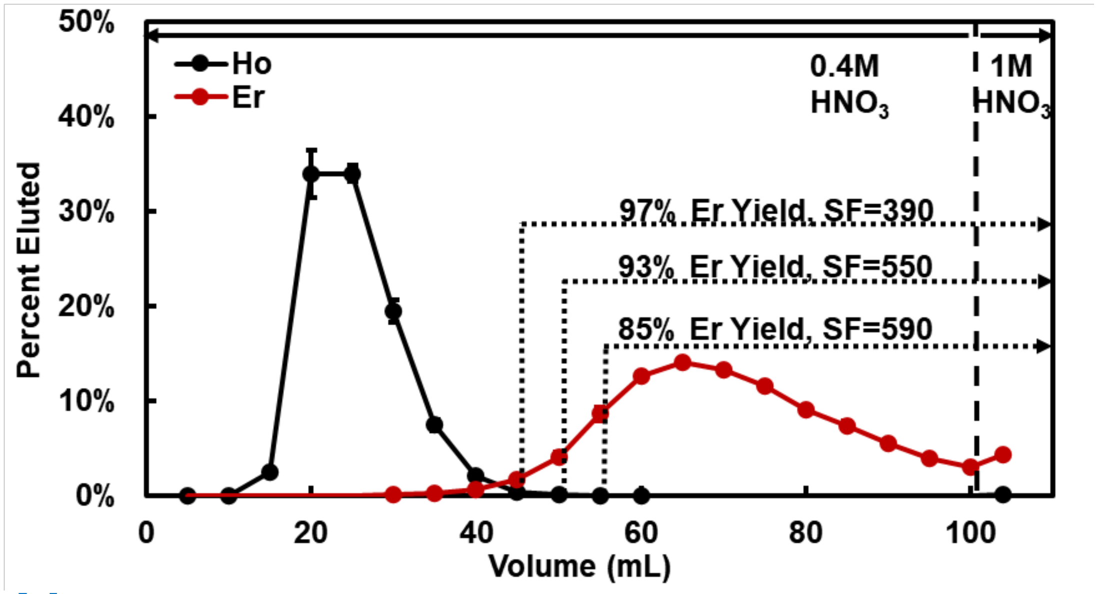


50 mm x 5.5 mm column
500 mg LN2, 20-50 μm

1. No ^{165}Er
2. (99.91 ± 0.06)% Ho, (23 ± 7)% ^{165}Er

Da Silva *et al*., *Molecules* **26:** 7513 (2021).

Ho/^{165}Er separation step 2: LN2 EXC



2. 52 ± 9 mL 0.4 M HNO_3 at 1 mL/min

3. 4 – 5 mL 1 M HNO3 at 1 mL/min

2. (99.91 ± 0.06)% Ho, (23 ± 7)% ^{165}Er

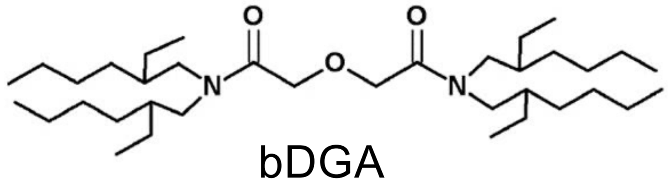
3. (78 ± 6)% Er recovery, $SF_{Ho/Er}$ = 1020 ± 320

570 ± 370 µg Ho → **380 ± 210 ng Ho**

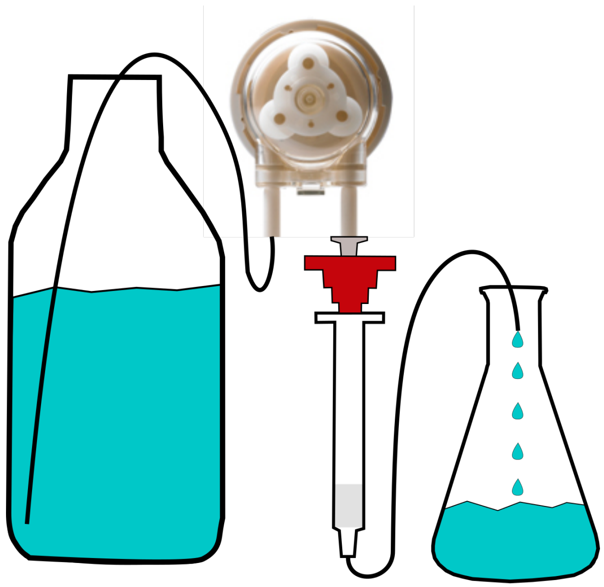
Da Silva *et al.*, *Molecules* **26:** 7513 (2021).

DGA EXC in practice and results

1. ^{165}Er in ~6 mL 5 M HNO_3
2. 15 mL 3 M HNO_3
3. 2 mL 0.5 M HNO_3
4. 1.5 mL 0.01 M HCl



bDGA



10 mm x 5.5 mm column
100 mg bDGA, 50-100 μm

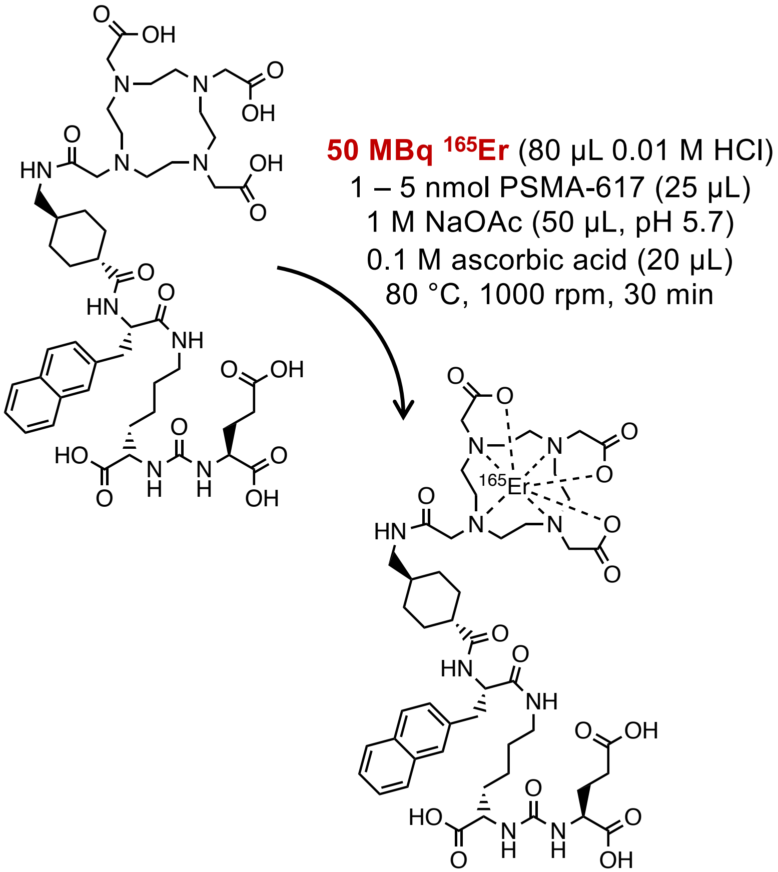
1. No ^{165}Er
2. Trace metal impurities (Fe, Cr, Co, Ni, Cu), no ^{165}Er
3. Lower column acidity, no ^{165}Er
4. (98 ± 1)% ^{165}Er recovery, 1.5 ± 0.1 mL 0.01 M HCl

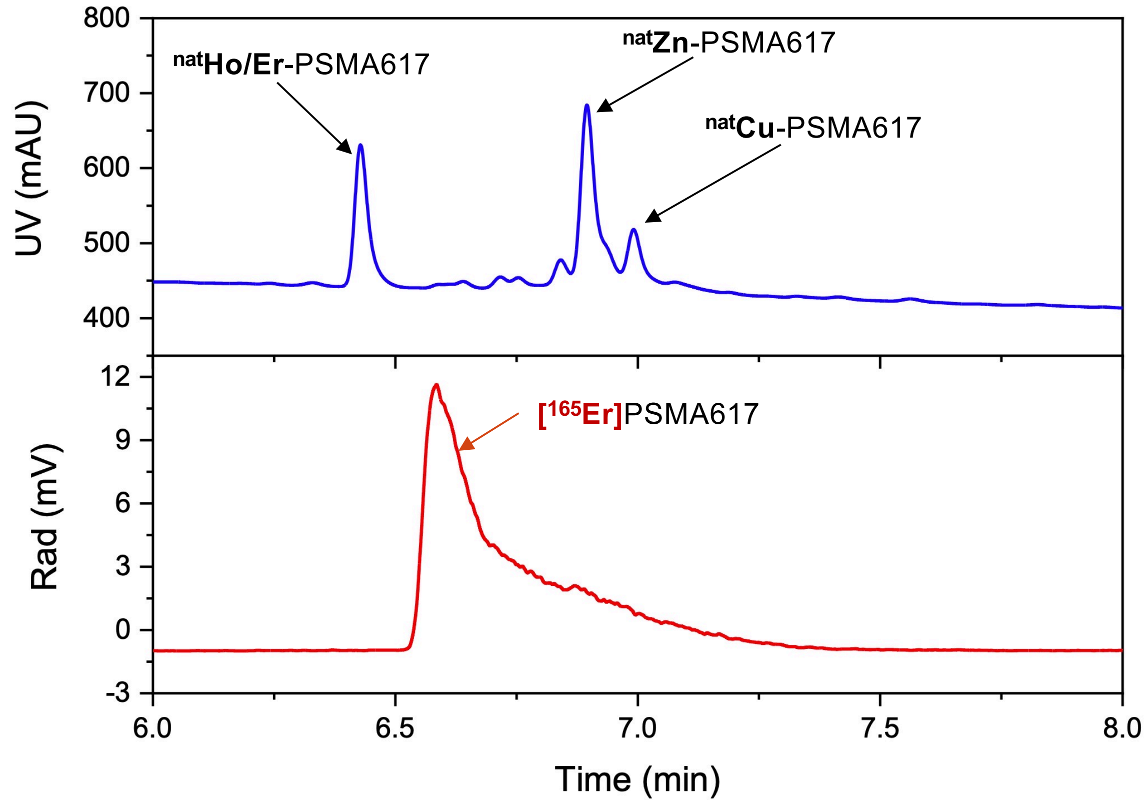
4 mL 1 M HNO_3 → **0.4 – 1.4 mL 0.01 M HCl**

Overall ~5 hour process: **64±2% ^{165}Er recovery**, $SF_{Ho/Er}$ = **$(2.8±1.1)·10^5$**

Da Silva *et al*., *Molecules* **26:** 7513 (2021).

Proof-of-concept [^{165}Er]PSMA-617 synthesis





Agilent InfinityLab Poroshell 120 EC-C18 column 4.6 × 100 mm, 2.7 µm
95:5 – 20:80 of 0.1% TFA in CH_3CN over 15 min

PSMA-617 (nmol)	^{165}Er Activity† (MBq)	Labeling Yield (%)	Labeled MA † (MBq/nmol)	*n*
1	170 ± 88	49 ± 7	82 ± 45	3
2	76	97	37	1
5	250	100	50	1

† Radioactivity and MA decay-corrected to end of bombardment.

Da Silva *et al*., *Molecules* **26:** 7513 (2021).

Positron-emitting ^{86}Y production and isolation

Applied Radiation and Isotopes 142 (2018) 28–31

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

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

Simplified and automatable radiochemical separation strategy for the production of radiopharmaceutical quality ^{86}Y using single column extraction chromatography

Eduardo Aluicio-Sarduy[a], Reinier Hernandez[b], Hector F. Valdovinos[a,1], Christopher J. Kutyreff[a], Paul A. Ellison[a], Todd E. Barnhart[a], Robert J. Nickles[a], Jonathan W. Engle[a,b,*]

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Isotope Program
U.S. Department of Energy

^{86}Y work at UWisc has been supported by US DOE Isotope Program, managed by the Office of Science for Isotope R&D and Production grant DE-SC0020960.

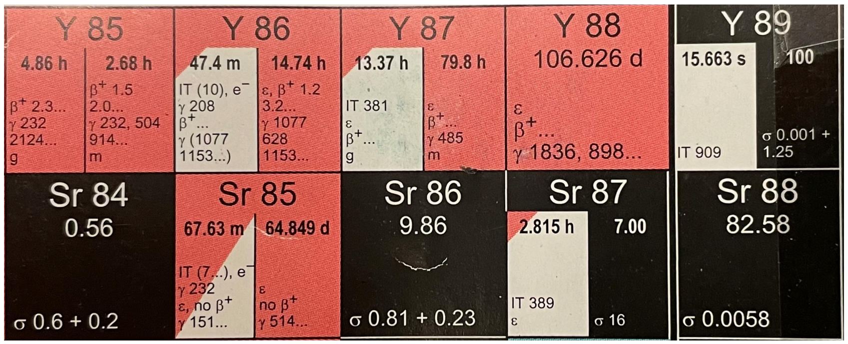
Eduardo Aluicio-Sarduy

Jonathan Engle

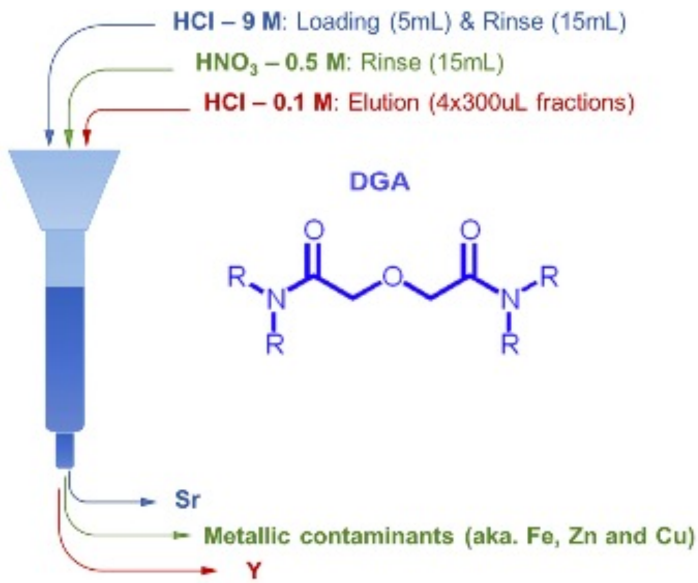
Radionuclide is available to researchers through National Isotope Development Center at www.isotopes.gov

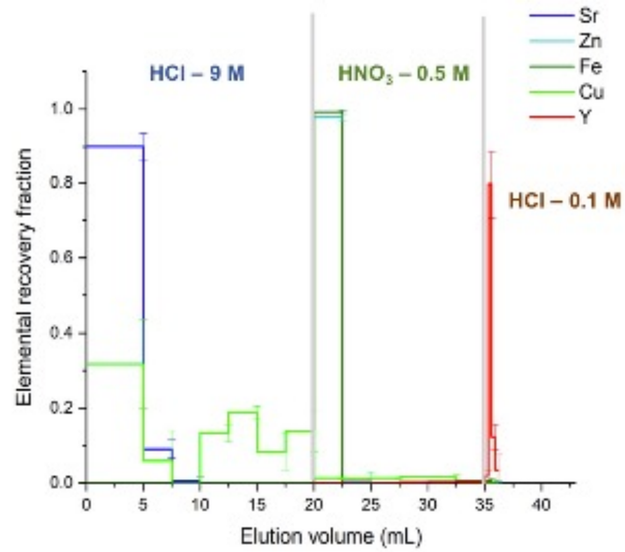
NIDC | NATIONAL ISOTOPE DEVELOPMENT CENTER
MANAGED BY THE U.S. DEPARTMENT OF ENERGY ISOTOPE PROGRAM

Positron-emitting ^{86}Y production and isolation



~150 mg/cm^2 pressed $^{86}SrCO_3$ (or ^{86}SrO)
5 µA (20 µA for SrO), 14 – 15 MeV protons
110 MBq·µA^{-1}·h^{-1} ^{86}Y, >95% RNP at EoC





50 ± 10 MBq/nmol DOTA radiolabeling
98 ± 1% $^{86}SrCO_3$ recycling efficiency

Aluicio-Sarduy *et al.*, *Appl Radiat Isot* **142:** 28-31 (2018).
Aluicio-Sarduy *et al., Nucl Med Biol* **126-127:** 108780 (2023).

LANL/UCB – Positron-emitting $^{134}Ce/^{134}La$

ARTICLES
https://doi.org/10.1038/s41557-020-00598-7
nature chemistry

Developing the ^{134}Ce and ^{134}La pair as companion positron emission tomography diagnostic isotopes for ^{225}Ac and ^{227}Th radiotherapeutics

Tyler A. Bailey[1,2,5], Veronika Mocko[3,5], Katherine M. Shield[1,2,5], Dahlia D. An[2], Andrew C. Akin[3], Eva R. Birnbaum[3], Mark Brugh[3], Jason C. Cooley[3], Jonathan W. Engle[4], Michael E. Fassbender[3], Stacey S. Gauny[2], Andrew L. Lakes[2], Francois M. Nortier[3], Ellen M. O'Brien[3], Sara L. Thiemann[3], Frankie D. White[3], Christiaan Vermeulen[3]✉, Stosh A. Kozimor[3]✉ and Rebecca J. Abergel[1,2]✉

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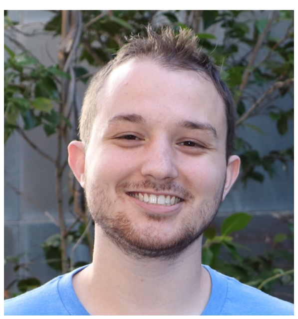
Tyler Bailey (UCB)


Veronika Mocko (LANL)


Rebecca Abergel (UCB)

^{134}Ce work has been supported by US DOE Isotope Program, managed by the Office of Science for Isotope R&D and Production and LA-UR-23-31751.

Radionuclide is available to researchers through National Isotope Development Center at www.isotopes.gov

NIDC NATIONAL ISOTOPE DEVELOPMENT CENTER
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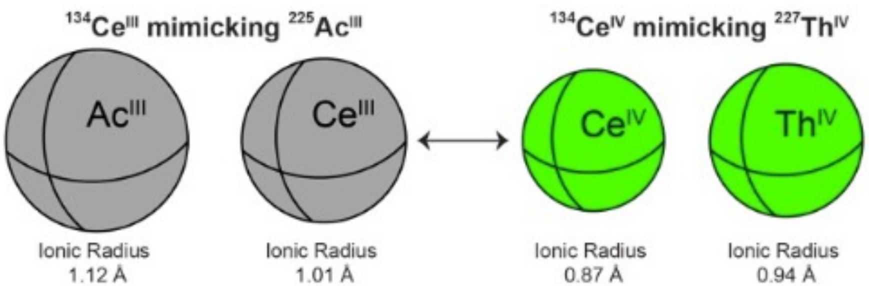
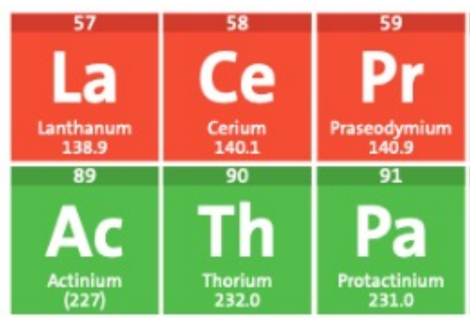
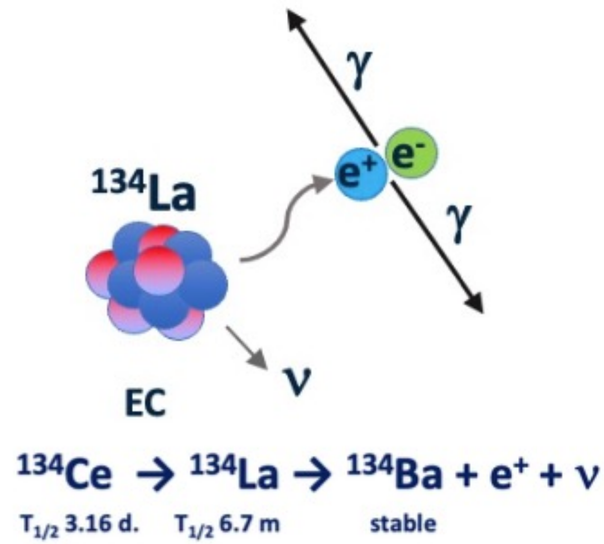
Positron-emitting $^{134}Ce/^{134}La$

Motivation: $^{134}Ce/^{134}La$ as imaging companion for α-radiotherapy

- Increased application of targeted alpha therapy ^{225}Ac ($T_{1/2}$ 9.9d), ^{227}Th ($T_{1/2}$ 18.7d)
- PET radiometals: ^{68}Ga ($T_{1/2}$ 67.7min), ^{64}Cu($T_{1/2}$ 12.7h), ^{132}La($T_{1/2}$ 4.8h), ^{133}La($T_{1/2}$ 3.9h)
  - ^{68}Ga, ^{64}Cu – different chemistry and coordination
  - All too short lived to track biological fate over several days







***In vivo* generator**

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Baily, Mocko, Vermeulen, Kozimor, Abergel, et. al. NATURE CHEM 13. 284 (2021).

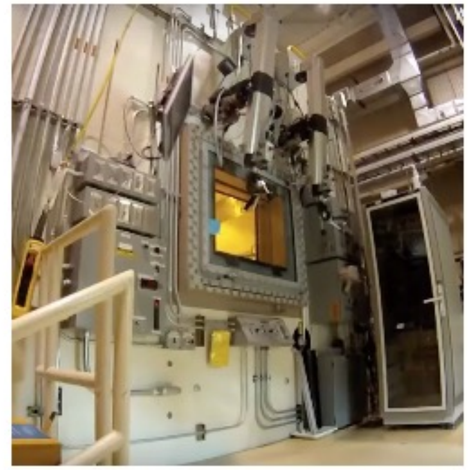
Slide provided courtesy of Veronika Mocko (LANL) – full presentation available at:
https://www.isotopes.gov/sites/default/files/2023-11/DOE_IP_virtual-seminar-series_Ce-134.pdf

Positron-emitting $^{134}Ce/^{134}La$

^{134}Ce production

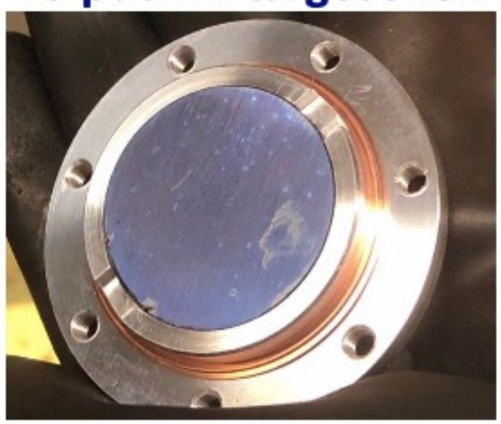
- $^{nat}La\ (p, 6n)^{134}Ce$
- 32 g of La metal (45.7 x 3 mm)
- Incident energy 77.9 MeV, Exit energy 67.8 MeV H^+
- Beam current 100 μA, Cumulative charge ~3000 μA.h

Isotope Production Facility



La metal

La puck in target shell



Irradiated target

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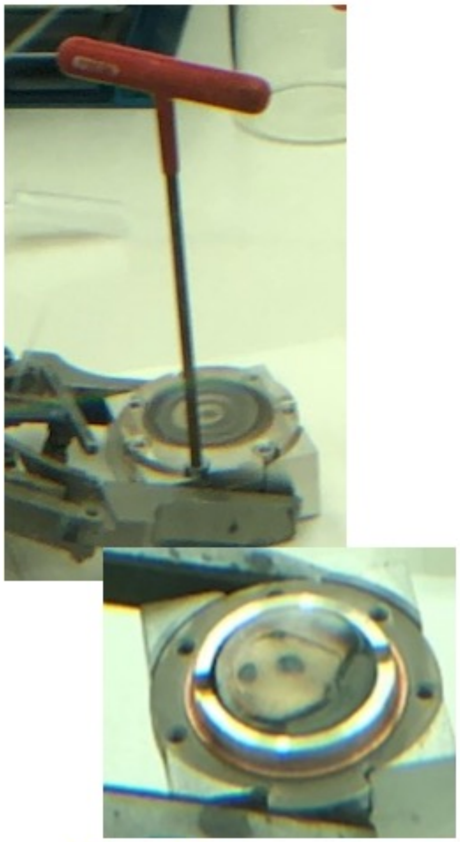
Baily, Mocko, Vermeulen, Kozimor, Abergel, et. al. NATURE CHEM 13. 284 (2021).

Slide provided courtesy of Veronika Mocko (LANL) – full presentation available at:
https://www.isotopes.gov/sites/default/files/2023-11/DOE_IP_virtual-seminar-series_Ce-134.pdf

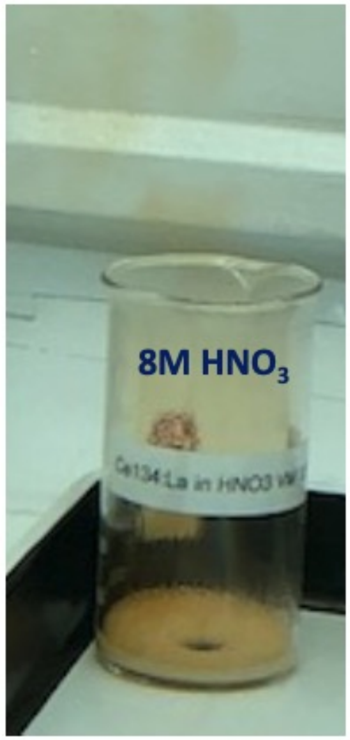
Positron-emitting $^{134}Ce/^{134}La$

^{134}Ce Isolation

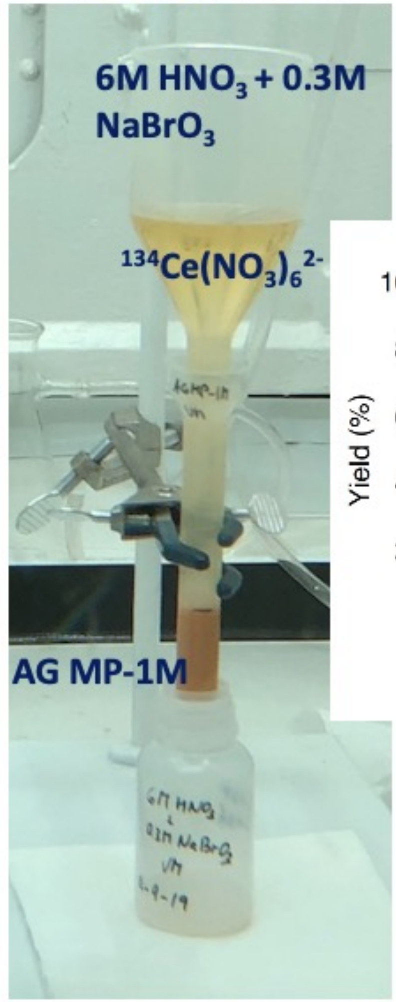
Target opening

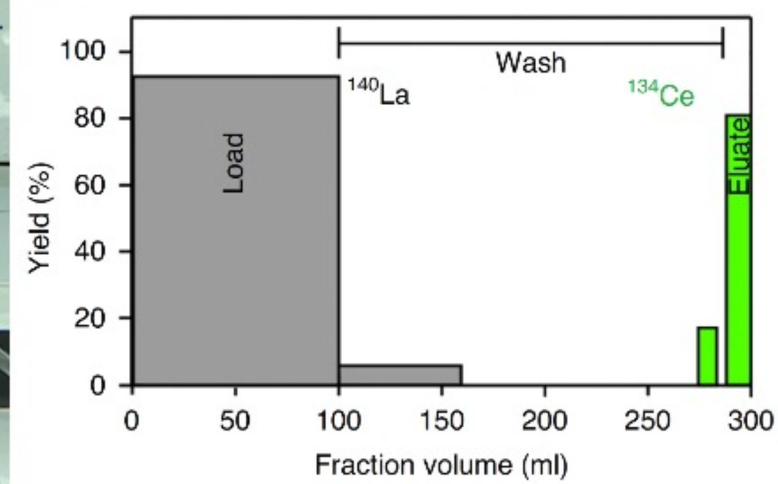


La dissolution



La-Ce separation





^{134}Ce elutes with 50 mM HNO_3
One column rapid separation with high yield > 80%

Los Alamos NATIONAL LABORATORY

Baily, Mocko, Vermeulen, Kozimor, Abergel, et. al. NATURE CHEM 13. 284 (2021).

Slide provided courtesy of Veronika Mocko (LANL) – full presentation available at:
https://www.isotopes.gov/sites/default/files/2023-11/DOE_IP_virtual-seminar-series_Ce-134.pdf

Positron-emitting $^{134}Ce/^{134}La$

^{134}Ce product

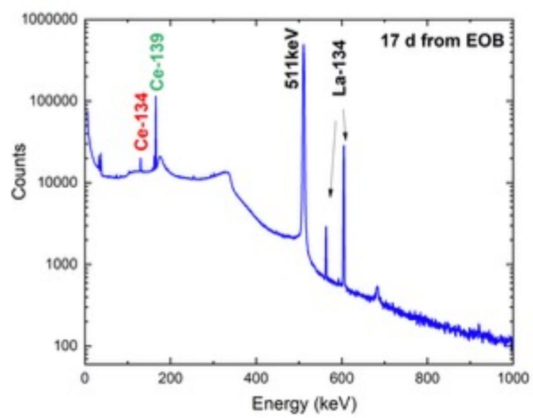
~50 MBq/nmol (by ICP-OES)

Product characterization: gamma spectroscopy & ICP-OES

- Radionuclidic purity >99.8% (excluding ^{135}Ce, ^{137}mCe, ^{139}Ce and daughters)
- ^{135}Ce < 1%, ^{137m}Ce < 5%, ^{139}Ce < 3%
- Specific activity >4,000 Ci/g, typical 8,000-12,000 Ci/g on ship date
- Form: Ce(III) in 0.1 M HCl
- Concentration > 5 mCi/mL, typical 10-20 mCi/mL
- Total Ce 42-101 µg, total Ce concentration 1.4-10.4 µg/mL
- Total La 50-169 µg, total La concentration 1.7- 17.4 µg/mL

~40 GBq ^{134}Ce available to ship ~10 days post EoB

~3·10⁵ La decon. factor



Isotope Program U.S. Department of Energy

NIDC National Isotope Development Center

Product Information

Specifications

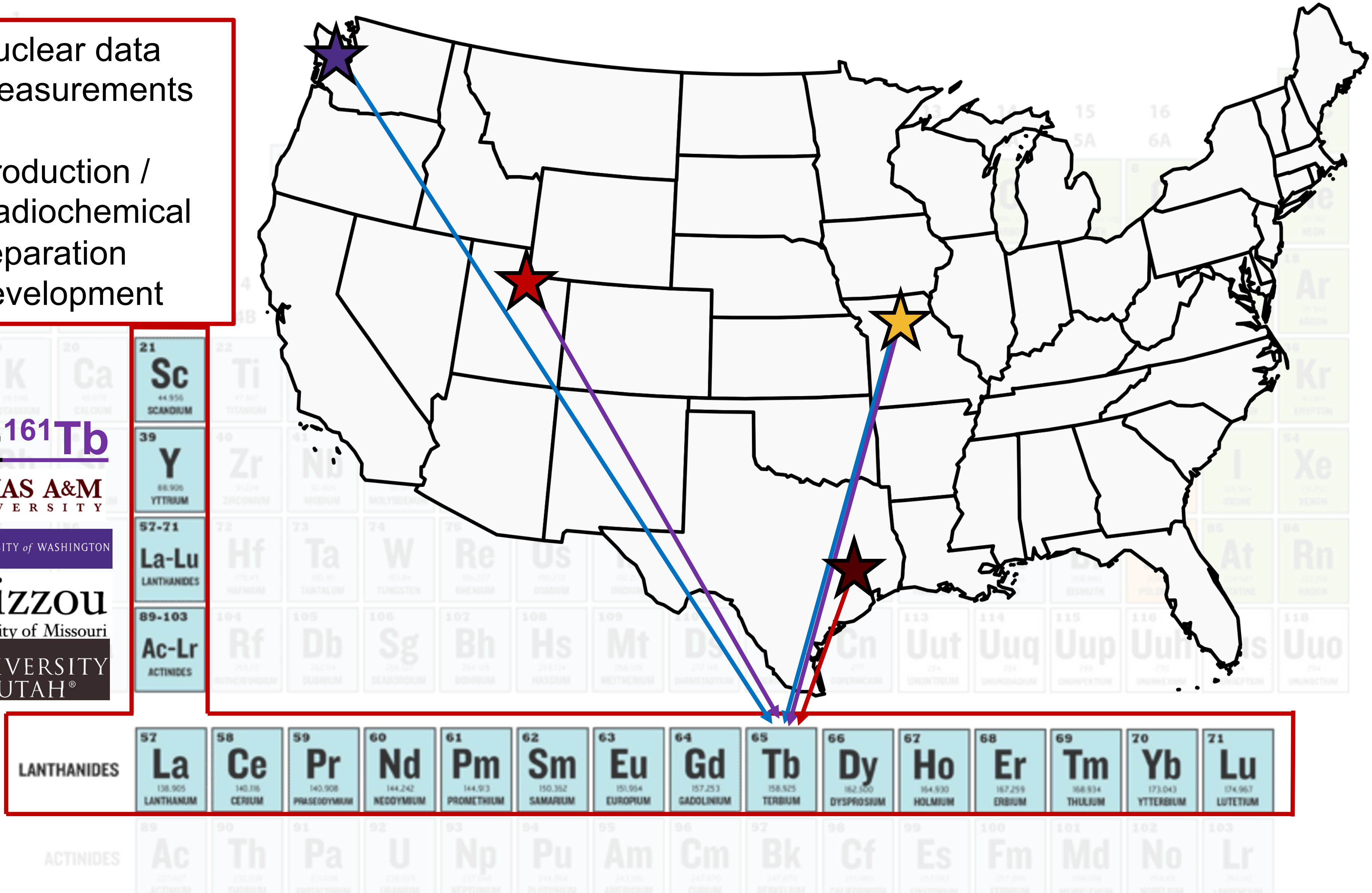
Radioisotope	Ce-134
Half-Life/Daughter	3.16 days to lanthanum-134
Decay	Decay Radiation Information (NNDC)
Chemical Form	Ce(III) in 0.1M HCl
Available Specific Activity	> 4000 Ci/g
Activity Concentration	> 5 mCi/ mL
Radionuclidic Purity	> 99.8% (excluding Ce-135, Ce-137m, Ce-139 and La daughters), Ce-135 < 1%, Ce-137m <5%, Ce-139 <3%
Production Route	Proton irradiation of La target
Processing	Dissolution and ion exchange
Primary Container	Glass crimp- top V-vial
Availability	Monthly
Unit of Sale	Millicuries

Los Alamos National Laboratory

Slide provided courtesy of Veronika Mocko (LANL) – full presentation available at: https://www.isotopes.gov/sites/default/files/2023-11/DOE_IP_virtual-seminar-series_Ce-134.pdf

Radioterbium across the United States

- Nuclear data measurements
- Production / Radiochemical separation development



^{149,155,161}Tb

TEXAS A&M UNIVERSITY

UNIVERSITY of WASHINGTON

Mizzou University of Missouri

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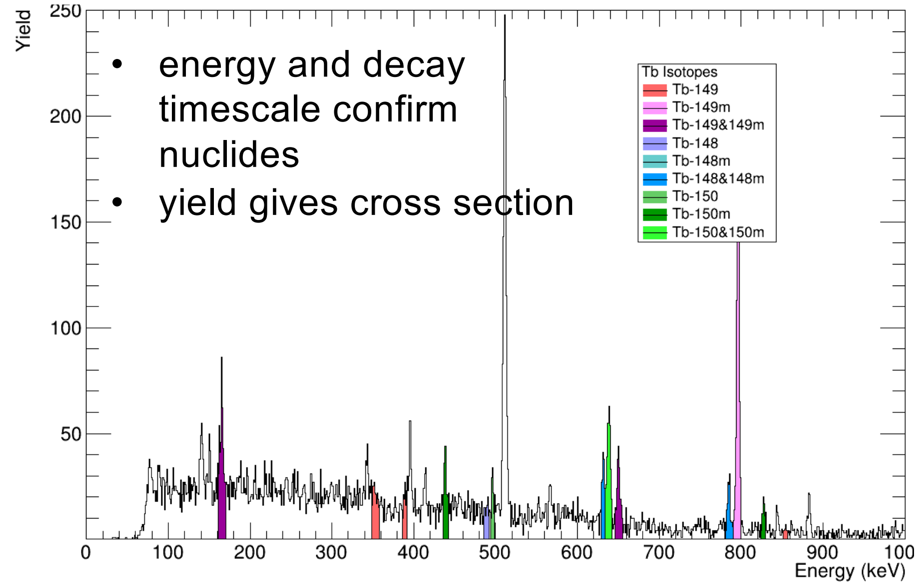
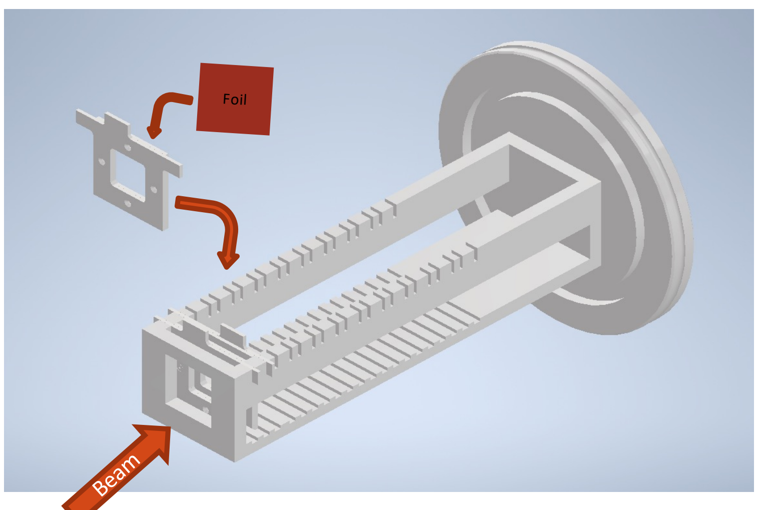
Terbium-149 @ Texas A&M University Cyclotron Institute

- Theragnostic: decay by α and β+ (TAT and PET)
- $t_{1/2}$ = 4.1 hours
- Cross section measurements
  - ^{6}Li, ^{7}Li, ^{1}H beams
  - Sm, Eu, Gd targets
  - 22 isotope cross sections measured
  - including 3 metastable states
- Hyperion (LLNL) allows ^{148m}Tb, ^{149m}Tb, ^{150m}Tb cross sections, thus ratio of metastable state to ground
- Future foil stack measurements → excitation function





“Cross sections for $^{147-149}$Sm(^{6}Li,x) for the Production of ^{149}Tb for Targeted Alpha Therapy” Bills, L.A. *et al.*, Manuscript in preparation.

Laura Bills (McCann) – Graduate Student
lamccan@tamu.edu

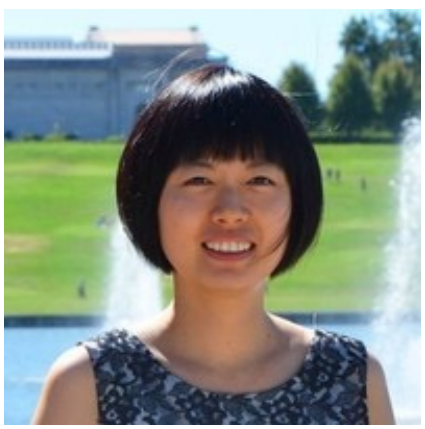
Alan McIntosh – Research Scientist
alanmcintosh@tamu.edu

Sherry Yennello – Professor

Universities of Missouri / Washington Tb collaboration

University of Washington Clinical Cyclotron

- Multiparticle (p, d, α)
- Up to 50 MeV p, α, 70 μA

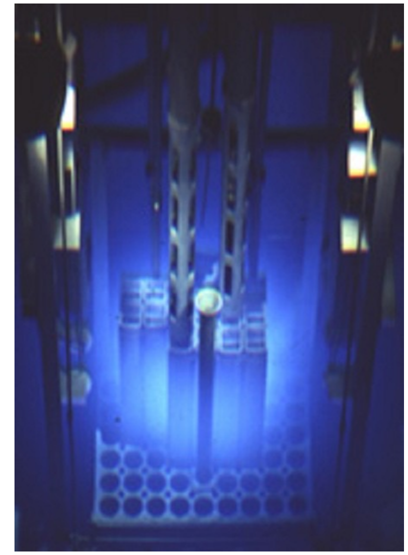


Professor Yawen Li

Anster Charles

University of Missouri Research Reactor

- 10 MW
- thermal flux: ~$4 \cdot 10^{14}$ $cm^{-2} \cdot s^{-1}$

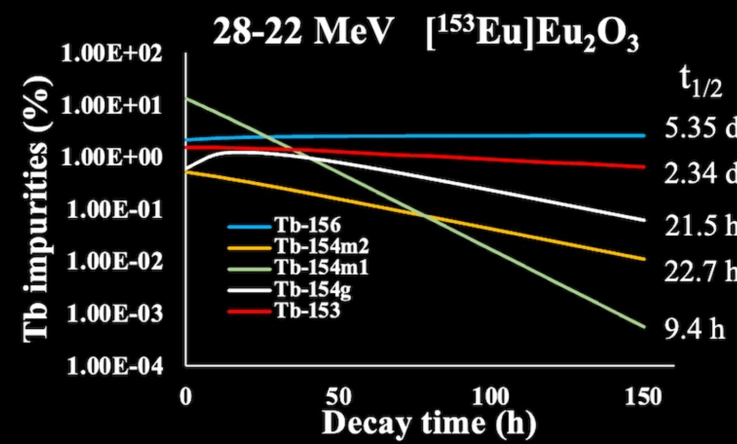


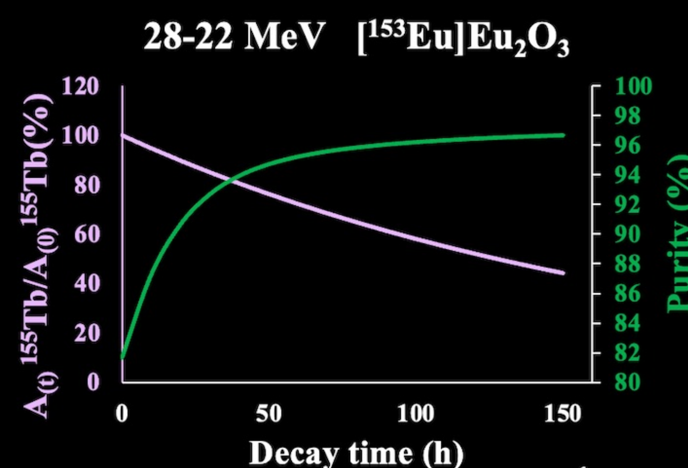
Professor Heather Hennkens

Madhushan Serasinghe

$^{153}Eu(\alpha,2n)^{155}Tb$

Energy window (MeV)	Production rate (MBq/µAh)	^{155}Tb Purity, 100 h (%)
26-20	1.9, EOB	93.1
28-22	3.5, EOB	96.2
30-24	2.6, EOB	93.9





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Slide provided courtesy of Anster Charles and Yawen Li (UWash)

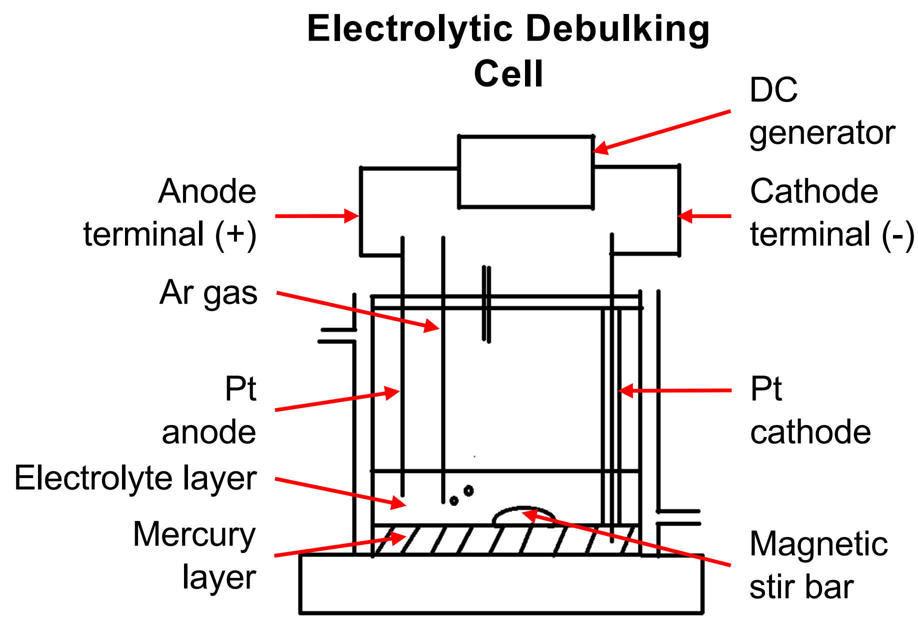
Eu debulking for Eu/Tb separation

- Eu to Tb mass ratio is significantly large (1 g : 0.5 µg)
- Debulking is desirable to reduce and recover ^{153}Eu excess mass
- Eu, Sm, Yb – only lanthanides with accessible +2 oxidation states

$$Eu^{3+} + e^{-} \rightarrow Eu^{2+} \; (-0.43V)$$

$$Tb^{3+} + 3e^{-} \rightarrow Tb \; (-2.28V) \quad \times$$

- Since Eu^{3+} can be easily reduced to its +2 state, an electro-amalgamation approach was used for debulking
- 90-95% Eu^{3+} debulking observed in 25-min run (86 mg Eu, 300 MBq of ^{161}Tb as ^{155}Tb surrogate)



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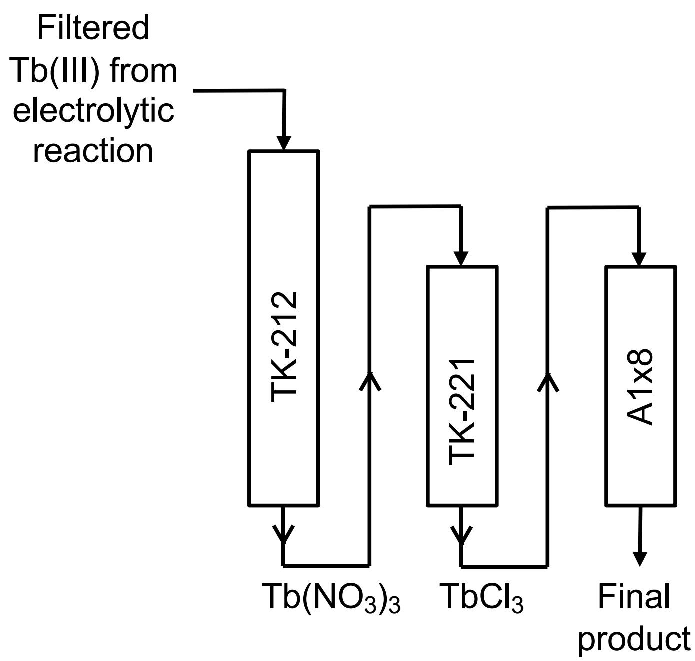
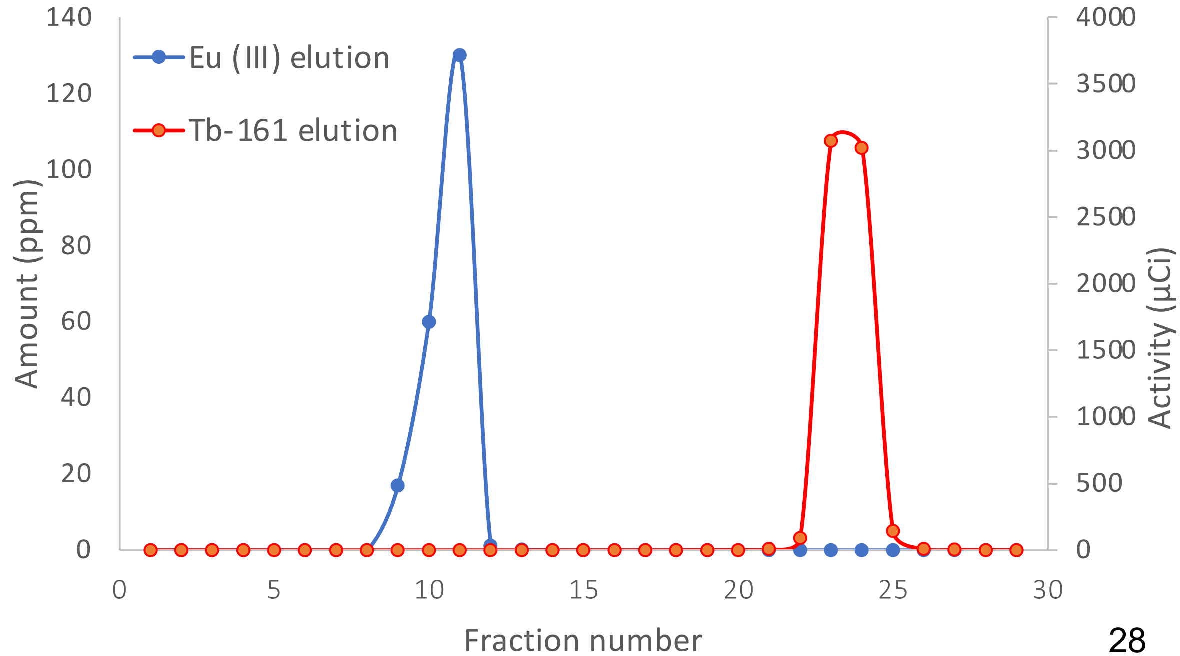
University of Missouri
M. Serasinghe (Hennkens research group)

Slide provided courtesy of Madhushan Serasinghe and Heather Hennkens (University Missouri)

Chromatographic polishing separation

- TrisKem columns used to isolate Tb from remaining Eu and formulate Tb product
- 84-90% overall recovery of Tb as $TbCl_3$ in 0.05 M HCl with RCP >95%
    - labels DOTA at 4 MBq/nmol at ~0.07 MBq/µL
- 82% recovery of Eu as Eu_2O_3 (from processing of Hg layer following electrolytic reaction)





Elution profile observed in TK-212 column

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University of Missouri
M. Serasinghe (Hennkens research group)

Slide provided courtesy of Madhushan Serasinghe and Heather Hennkens (University Missouri)

MURR production of ^{161}Tb

- MURR is the University of Missouri Research Reactor, located in Columbia, Missouri, USA
- Highest power university-operated research reactor in the USA (10 MW)
- Produces various radiolanthanides via neutron irradiation
- High thermal neutron flux is desirable for indirect ^{161}Tb production from enriched ^{160}Gd

Lanthanide Series	^{57}La	^{58}Ce	^{59}Pr	^{60}Nd	^{61}Pm	^{62}Sm	^{63}Eu	^{64}Gd	^{65}Tb	^{66}Dy	^{67}Ho	^{68}Er	^{69}Tm	^{70}Yb	^{71}Lu
	Lanthanum	Cerium	Lanthanum	Neodymium	Promethium	Samarium	Europium	Gadolinium	Terbium	Dysprosium	Holmium	Erbium	Thulium	Ytterbium	Lutetium
	138.905	140.116	140.908	144.243	144.913	150.36	151.964	157.26	158.925	162.500	164.930	167.259	168.934	173.055	174.967

$$^{160}\mathrm{Gd} \xrightarrow[\sigma_{th} = 1.4\ \mathrm{b}]{(n,\gamma)} {}^{161}\mathrm{Gd} \xrightarrow[t_{1/2} = 3.66\ \mathrm{min}]{\beta^-\ \mathrm{decay}} {}^{161}\mathrm{Tb}$$

Prepare $[^{160}Gd]Gd(NO_3)_3$ or $[^{160}Gd]Gd_2O_3$ target, 98.2% or 99.96% enrichment, respectively (0.9-1.4 mg ^{160}Gd) → Irradiate in flux trap for ~6.5 d, high flux position (1.8-3.9 × 10^{14} n·cm^{-2}·s^{-1}, 0.7-1.4 GBq @ EOI) → Separate Gd* and Tb following decay of short-lived ^{161}Gd radionuclide intermediate

*To simulate processing of large target masses, 200 mg of ^{nat}Gd is added prior to Gd/Tb separation

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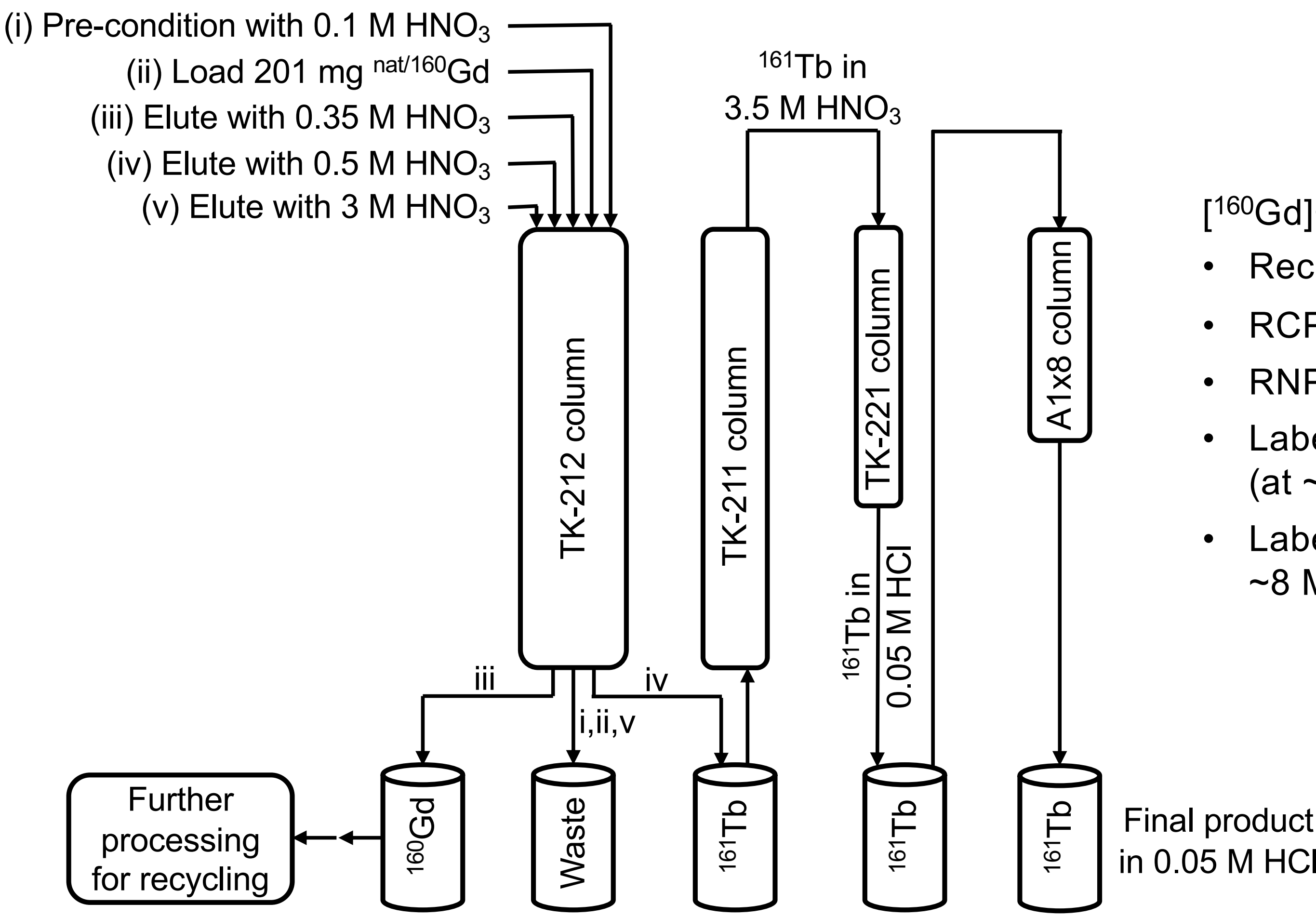
University of Missouri
P. Bokolo (Hennkens research group)

Slide provided courtesy of Patrick Bokolo and Heather Hennkens (University Missouri)


MURR processing of ^{161}Tb



[^{160}Gd]Gd_2O_3 target data:

- Recovery 89 ± 4%
- RCP >99%
- RNP >99.99%
- Labels DOTA at ~50 MBq/nmol (at ~0.13 MBq/µL)
- Labels DOTA-TATE at ~8 MBq/nmol (at ~0.13 MBq/µL)

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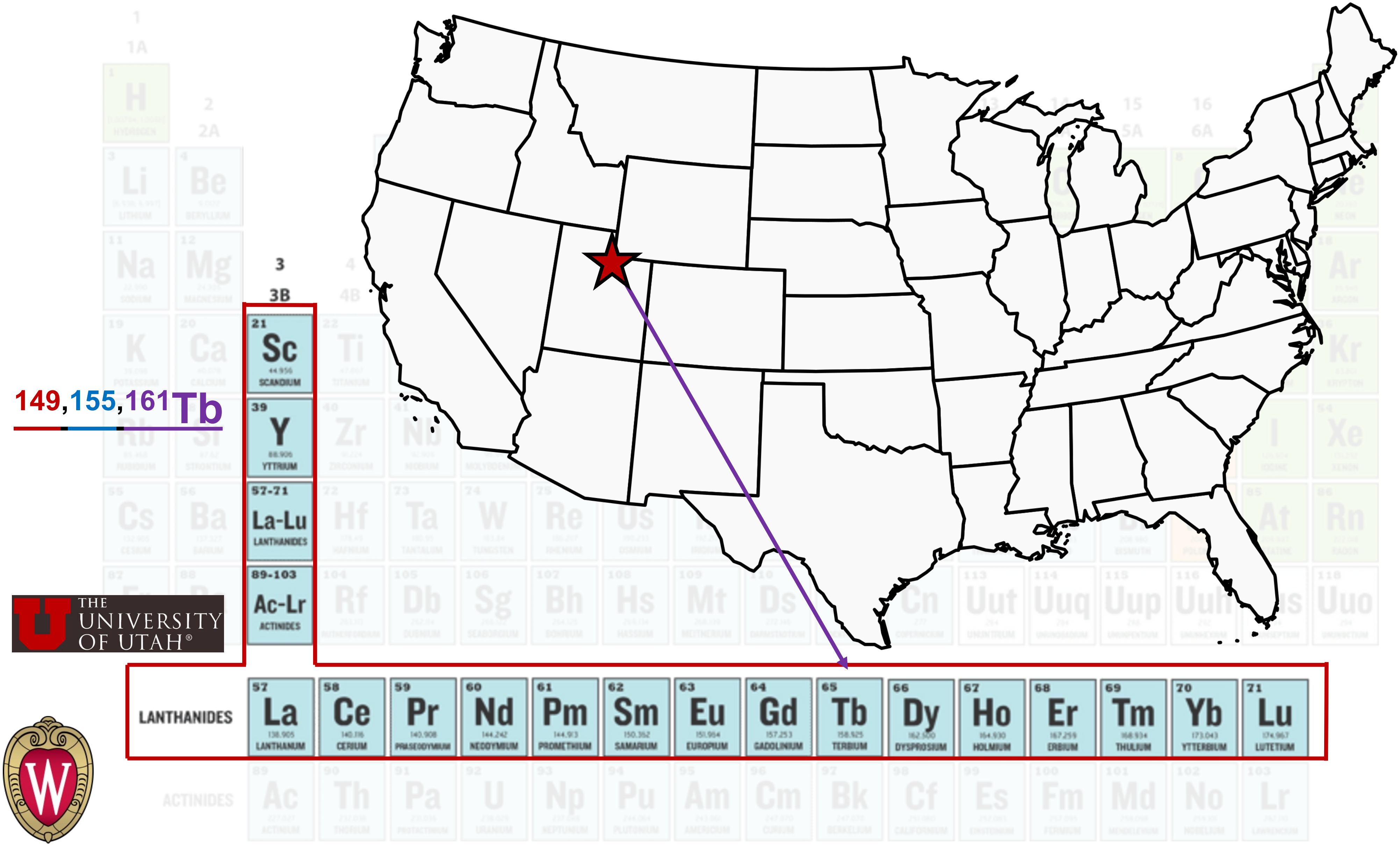
University of Missouri
P. Bokolo (Hennkens research group)

Slide provided courtesy of Patrick Bokolo and Heather Hennkens (University Missouri)

Radiolanthanides across the United States



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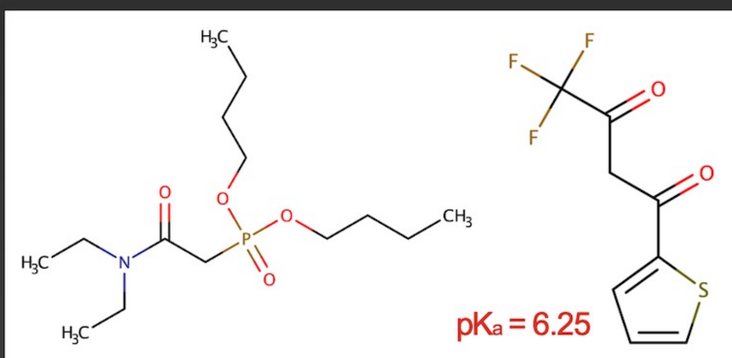
Synergistic Solvent Extraction

1. Solvent Extraction Studies

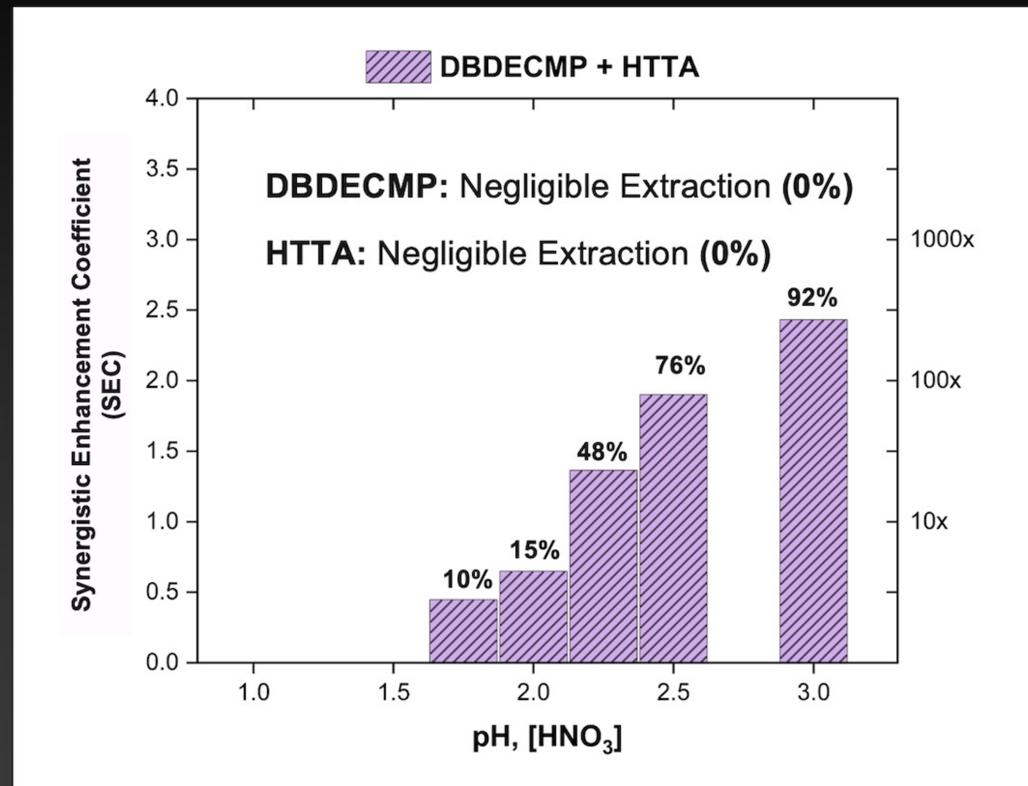
(Measure K_d, Synergism, Separation Factors)

- ✓ Dibutyl N,N-Diethylcarbamyl-methylenephosphonate **(DBDECMP)**
- ✓ 2-Thenoyltrifluoroacetone **(HTTA)**

- **0.05 M DBDECMP and 0.05 M HTTA extractant in 1,2-Dichloroethane**
- **Maximum K_d Ratio of 3.5 – 3.7**



DBDECMP **HTTA**



$$SEC = Log_{10}\left[\frac{K_{d\,(1,2)}}{\left(K_{d\,(1)} + K_{d\,(2)}\right)}\right]$$

SEC = 1 = 10x increase in K_d

SEC = 2 = 100x increase in K_d

SEC = 3 = 1000x increase in K_d

Connor K. Holiski et al. **The Investigation of the Synergistic Effect of Neutral Organophosphorus Ligands Combined with Acidic β-Diketones for the Extraction and Separation of Lanthanides.** *Under review with the Solvent Extraction and Ion Exchange.*

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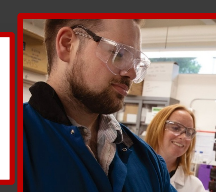


Novel Synergistic EXC Resins for Gd/Tb Separations

2. EXC Extraction Studies

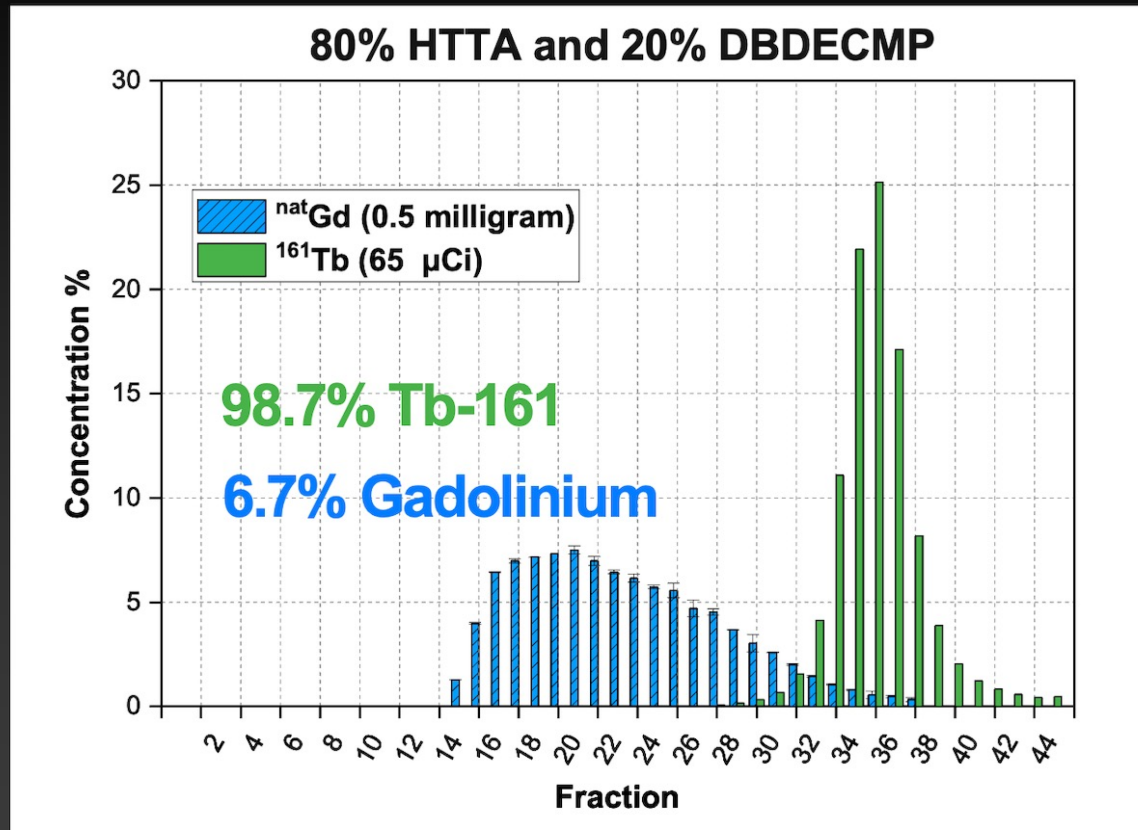
(EXC Resin Preparation, Evaluate D_w, Thermodynamics, Synergism, and Separation Factors)

- ✓ Prepare numerous EXC resins with differing wt. % of each ligand
- ✓ **Synergism retained**
- ✓ D_w are functions of pH and ligand wt. %

3. Column Experiments

(Study feasibility of Gd/Tb column separations)

- ✓ D_w Ratio of 1.5 at pH 2 HNO_3
- ✓ Load at pH 3 HNO_3
- ✓ Separate at pH 2 HNO_3
- ✓ **Proof-of-concept to design new EXC materials with multiple ligands to improve extraction and separation.**



Flow Rate: ≈ 0.22 mL/min (Peristaltic pump) & **Fraction Volume:** ≈ 2000 μL

Column Type: 3 mL (⌀ = 5 mm, ℓ = 150 mm BIORAD 7370517)

Connor K. Holiski et al. Novel Synergistic Extraction Chromatographic Materials for the Separation of ^{161}Tb from Enriched ^{160}Gd Targets. *Submitted to Separation and Purification Technology.*

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Slide provided courtesy of Connor Holiski and Tara Mastren (UUtah)

Radiolanthanides across the United States

^{165}Er, ^{86}Y

WISCONSIN
UNIVERSITY OF WISCONSIN–MADISON

^{134}Ce/ ^{134}La

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149,155,161Tb

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Mizzou
University of Missouri

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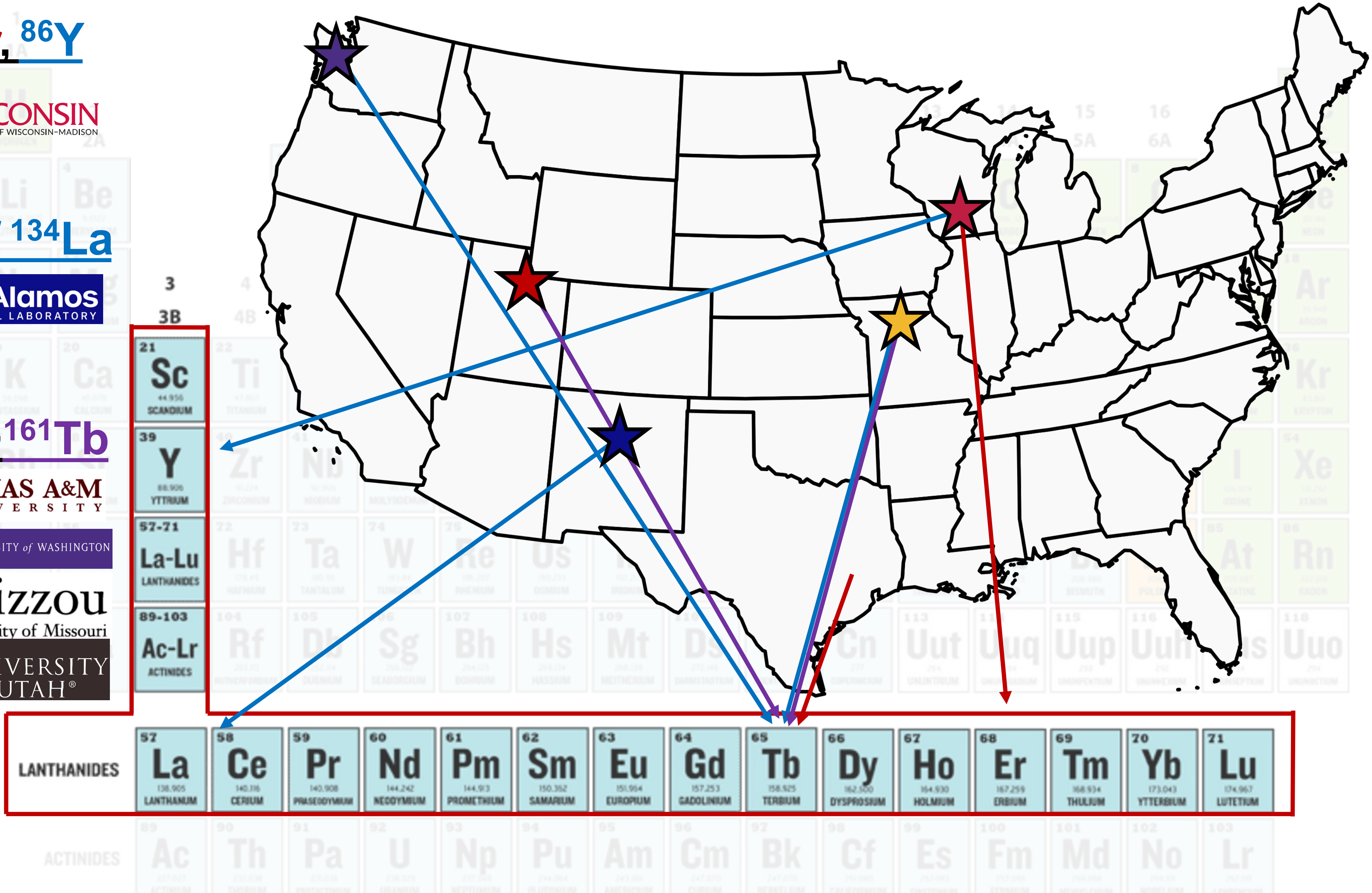

Acknowledgements

Jonathan Engle

Eduardo Aluicio-Sarduy

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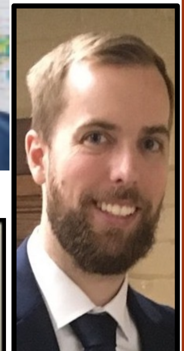
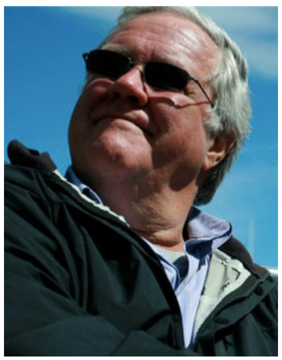


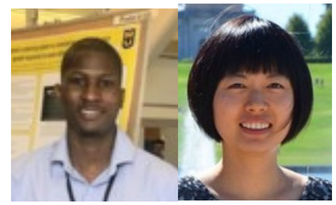
Jason Mixdorf

Todd Barnhart



Jerry Nickles

Taylor Johnson



Anster Charles and Yawen Li (U. Washington)

V. Mocko (LANL)

L. Bills (McCann), A. McIntosch, S. Yennello (TAMU)

M. Serasinghe, P. Bokolo and H. Hennkens (Mizzou)

Connor Holiski and Tara Mastren (UUtah)

Isotope Program
U.S. Department of Energy

- Department of Energy Isotope Program, managed by the Office of Science for Isotope R&D and Production grant DE-SC0020955 (Mastren), DE-SC0022550 (Engle/Ellison), DE-SC0022235 (Hennkens).

Thank you for your attention

$Ho_{(m)}$ target material selection

- Alfa Aesar 99.9% $Ho_{(m)}$ foils
  - ~100 ppm Er impurity
  - With 1 GBq in 100 mg $Ho_{(m)}$
    - 10 µg = 60 nmol Er
    - **AMA limit ≤ 17 MBq/nmol**

- US DOE Ames Laboratory Materials Preparation Center discs
  - 0.5 ppm Er impurity
  - With 1 GBq in 100 mg $Ho_{(m)}$
    - 50 ng = 0.30 nmol Er
    - **AMA limit ≤ 3,300 MBq/nmol**

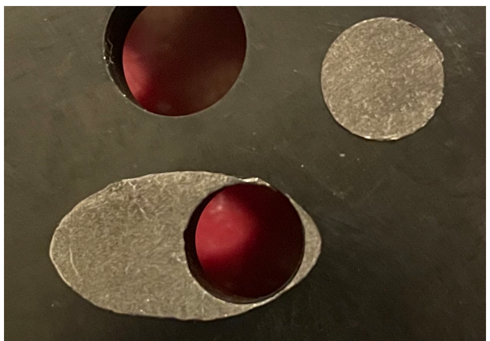
AMES LABORATORY
U.S. DEPARTMENT OF ENERGY

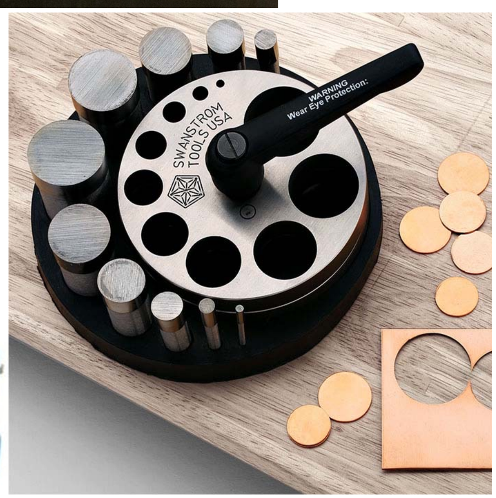
$Ho_{(m)}$ cyclotron target fabrication

AMES LABORATORY
U.S. DEPARTMENT OF ENERGY
Materials Preparation Center

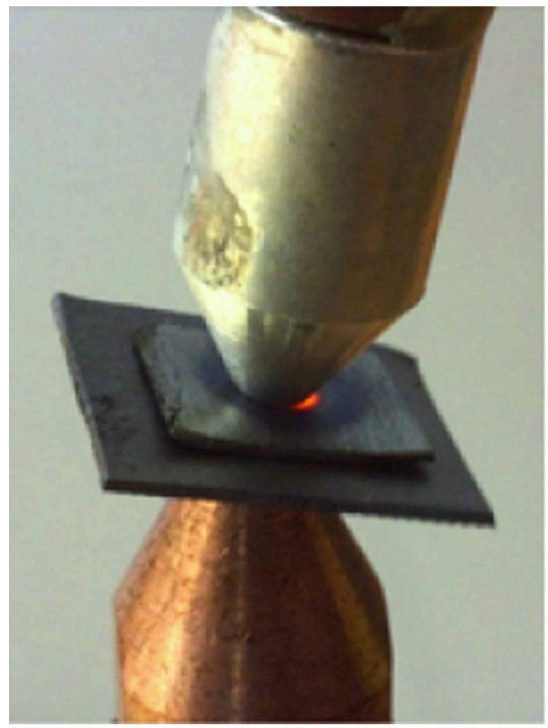
$^{nat}Ho_{(m)}$ 99.99995% purity from ^{nat}Er (0.5 ppm)

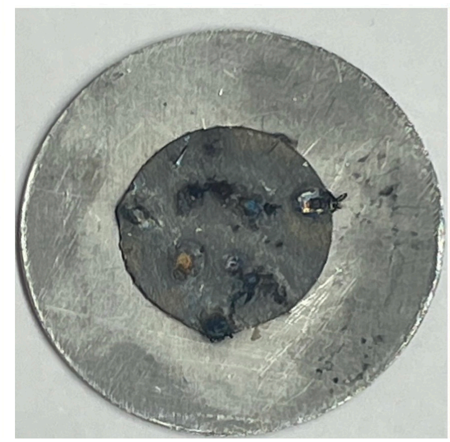
Rolled and punched





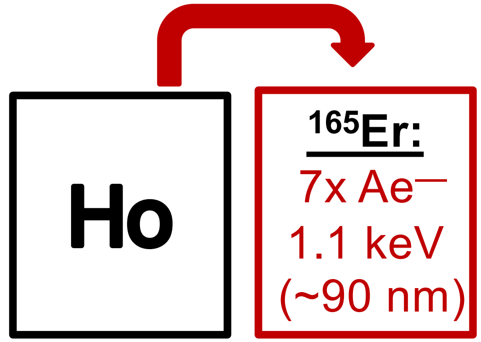
Spot welded to 19 mm ø, 0.5 mm Ta

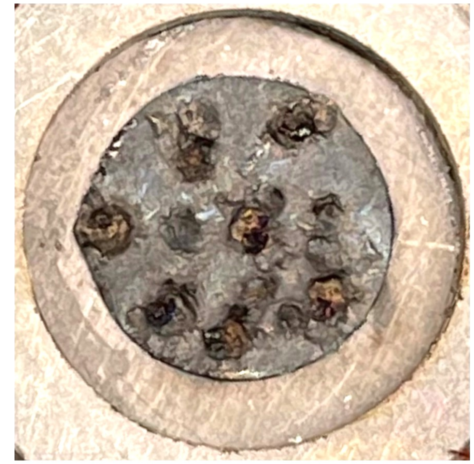




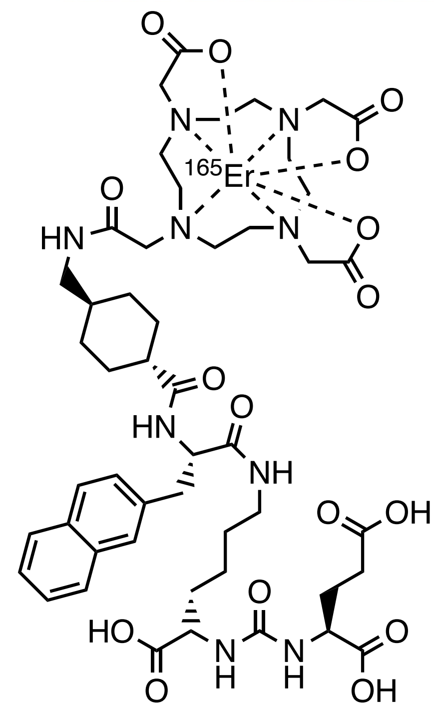
Ellison *et al.*, *Appl Radiat Isot* **118:** 350-353 (2016).

Radiotherapeutic quality ^{165}Er in preclinical quantities





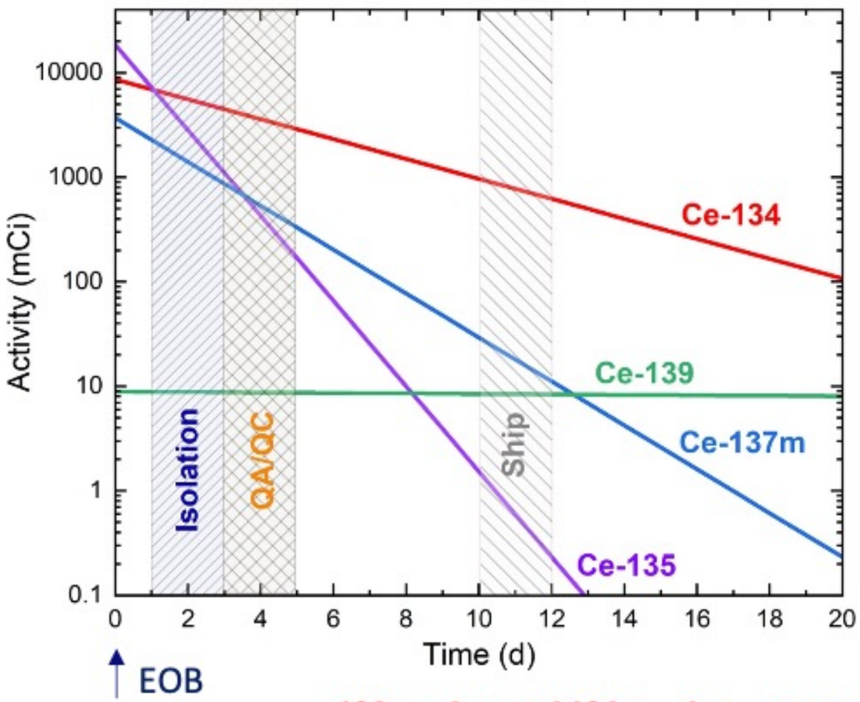
- **1 GBq ^{165}Er** per hour irradiation
- Isolation from up to **180 mg** Ho
  - **(64 ± 2)%** ^{165}Er recovery into ≤1 mL 0.01 M HCl
  - Ho/Er separation factor **(2.8 ± 1.1)·10^5**
  - **4.9 ± 0.7 hour** chemical processing time
- Successful ~50 MBq-scale DOTA-based radiopharmaceutical labelings performed at **10 – 50 MBq/nmol**

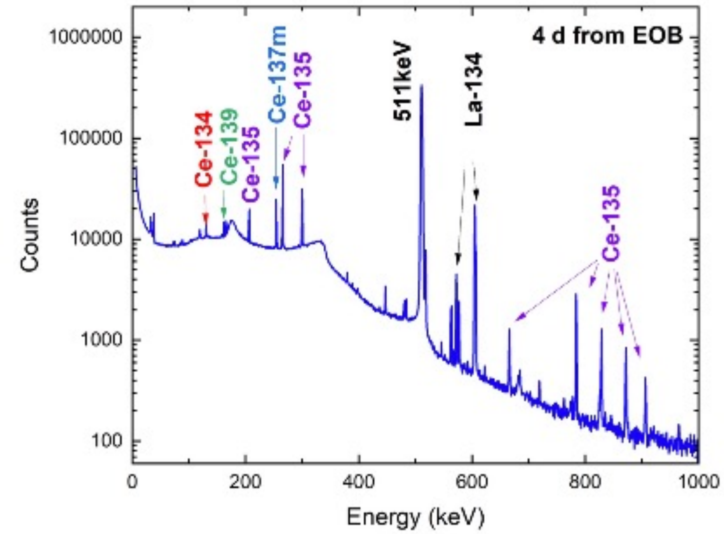


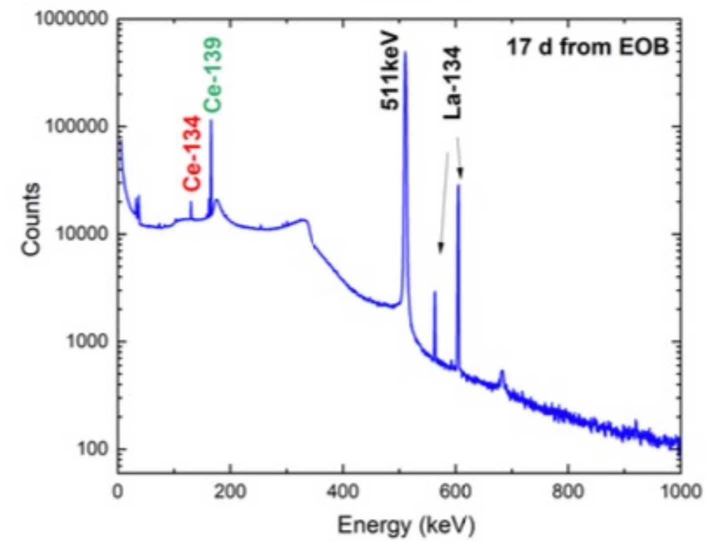
Da Silva *et al*., *Molecules* **26:** 7513 (2021).

Positron-emitting ^{134}Ce/^{134}La

^{134}Ce radiochemical purity







^{139}La (p,6n)^{134}Ce ($T_{1/2}$ 3.16 d)

^{139}La (p,5n)^{135}Ce ($T_{1/2}$ 0.74 d)

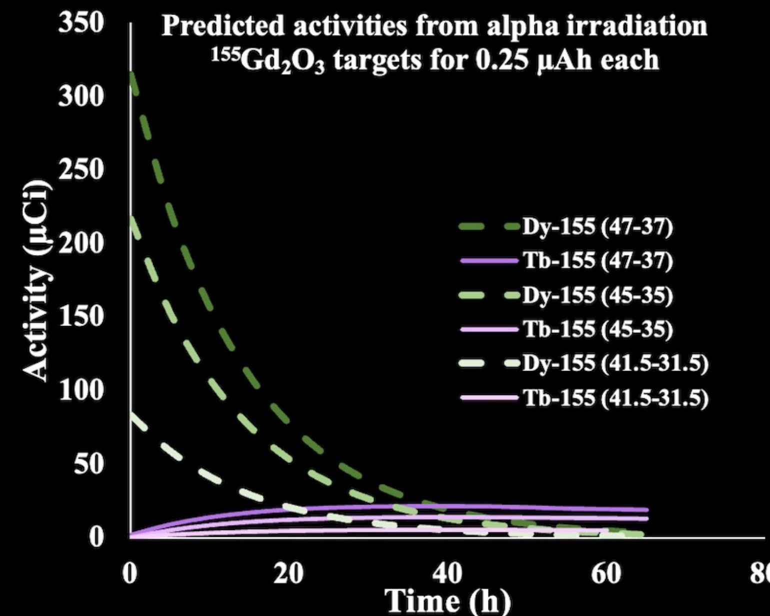
^{139}La (p,3n)^{137m}Ce ($T_{1/2}$ 1.43 d)

^{139}La (p,n)^{139}Ce ($T^{1/2}$ 137.64 d)

Slide provided courtesy of Veronika Mocko (LANL) – full presentation available at:
https://www.isotopes.gov/sites/default/files/2023-11/DOE_IP_virtual-seminar-series_Ce-134.pdf

$^{155}Gd(\alpha,4n)^{155}Dy \rightarrow {}^{155}Tb$

Energy window (MeV)	Production rate (MBq/µAh)		^{155}Tb Purity, 100 h (%)
	^{155}Dy, EOB	^{155}Tb, ~50 h post EOB	
47-37	37.7	2.7	88.8*, ^{157}Dy main impurity
45-35	22.3	1.9	88.8*, ^{157}Dy main impurity
41.5-31.5	8.0	0.5	75.0*, ^{157}Dy main impurity



*Before chemical separation

Slide provided courtesy of Anster Charles and Yawen Li (UWash)