

A high separation factor for ^{165}Er from Ho for Meitner-Auger therapy

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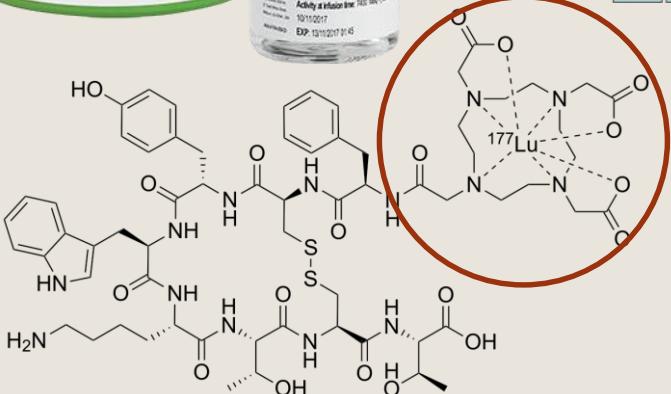
CEMHTI CNRS UPR 3079 University of Orléans (France)

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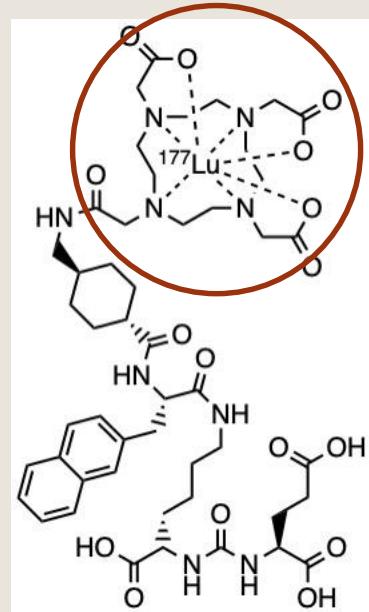
Therapeutic radiolanthanides

LUTATHERA®



1	1A	2	2A	METALS	METALLOIDS	NONMETALS	18	8A	
	H HYDROGEN						He HELIUM		
1	Li LITHIUM	2	Be BERYLLOIUM						
3	Na SODIUM	4	Mg MAGNESIUM	3	4	5	6	7	
11	Al ALUMINUM	12	Si SILICON	13	14	15	16	17	
19	B BORON	20	C CARBON	21	N NITROGEN	O OXYGEN	F FLUORINE	Ne NEON	
29	Ca CALCIUM	30	Sc SCANDIUM	31	P PHOSPHORUS	S SULFUR	Cl CHLORINE	Ar ARGON	
38	Rb RUBIDIUM	39	Y YTTRIUM	40	Ti TITANIUM	V VANADIUM	41	Ne NEON	
55	Cs CESIUM	56	La-Lu LANTHANIDES	57-71	Nb NEONIUM	58	Cr CHROMIUM	59	Lu LUTETIUM
62	Fr FRANCIUM	63	Sr STRONTIUM	64	Hf HAFNIUM	65	Mn MANGANESE	66	Lu LUTETIUM
88	Ra RADON	89-103	Ac-Lr ACTINIDES	90	Ta TANTALUM	91	Mo MOLYBDENUM	92	Lu LUTETIUM
95	Fr FRANCIUM	96-103	Ac-Lr ACTINIDES	97	W TUNGSTEN	98	Tc TECHNETIUM	99	Lu LUTETIUM
104	Rf RUTHENIUM	105	Db DUBNIUM	106	Sg SEABORGIUM	107	Bh BOHRIUM	108	Hs HASSIUM
109	Lu LUTETIUM	109	Os OSMIUM	110	Mt MEITNERIUM	111	Ds DARMSTDENIUM	112	Rg ROENTGENIUM
110	Lu LUTETIUM	110	Re RHENIUM	110	Mt MEITNERIUM	113	Uut UNUNTHRIUM	114	Cn COPERNICIUM
111	Lu LUTETIUM	111	Ir IRIDIUM	111	Ds DARMSTDENIUM	115	Uup UNUNPENTIUM	116	Uuh UNUNHEXIUM
112	Lu LUTETIUM	112	Pd PALLADIUM	112	Rg ROENTGENIUM	117	Uus UNUNHEPTIUM	118	Uuo UNUNOCTIUM
113	Lu LUTETIUM	113	Ag SILVER	113	Gd GADOLINIUM	118	Tm THULIUM	119	Lu LUTETIUM
114	Lu LUTETIUM	114	In INDIUM	114	Tb TERBIUM	120	Lu LUTETIUM	121	Lu LUTETIUM
115	Lu LUTETIUM	115	Sn ZINC	115	Dy DYSPROSIUM	122	Lu LUTETIUM	122	Lu LUTETIUM
116	Lu LUTETIUM	116	Pt PLATINUM	116	Ho HOLMIUM	123	Lu LUTETIUM	123	Lu LUTETIUM
117	Lu LUTETIUM	117	Au GOLD	117	Er ERBIUM	124	Lu LUTETIUM	124	Lu LUTETIUM
118	Lu LUTETIUM	118	Hg MERCURY	118	Tl THALLIUM	125	Lu LUTETIUM	125	Lu LUTETIUM
119	Lu LUTETIUM	119	Pb LEAD	119	Pb LEAD	126	Lu LUTETIUM	126	Lu LUTETIUM
120	Lu LUTETIUM	120	Bi BISMUTH	120	Bi BISMUTH	127	Lu LUTETIUM	127	Lu LUTETIUM
121	Lu LUTETIUM	121	Po POLONIUM	121	Po POLONIUM	128	Lu LUTETIUM	128	Lu LUTETIUM
122	Lu LUTETIUM	122	At ASTATINE	122	At ASTATINE	129	Lu LUTETIUM	129	Lu LUTETIUM
123	Lu LUTETIUM	123	Rn RADON	123	Rn RADON	130	Lu LUTETIUM	130	Lu LUTETIUM

[¹⁷⁷Lu]PSMA-617

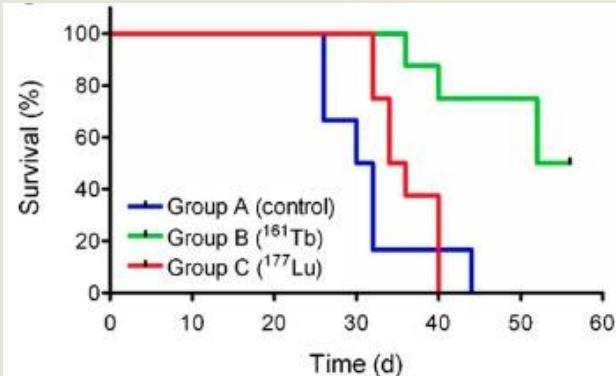


176Yb

¹⁷⁷Lu:
130 keV
(~220 μm)

176Lu

Therapeutic radiolanthanides



1 1A	H HYDROGEN	2 2A	Be BERYLLIUM			18 8A	He HELUM
3 Li LITHIUM	4 Be BERYLLIUM			METALS	METALLOIDS	NONMETALS	
5 Na SODIUM	6 Mg MAGNESIUM	7 B	8 B	9 Al	10 Si	11 P	12 S
11 Na SODIUM	12 Mg MAGNESIUM	3B	4B	5B	6B	7B	8B
19 K POTASSIUM	20 Ca CALCIUM	21 Sc SCANDIUM	22 Ti TITANIUM	23 V VANADIUM	24 Cr CHROMIUM	25 Mn MANGANESE	26 Fe IRON
37 Rb RUBIDIUM	38 Sr STRONTIUM	39 Y YTTRIUM	40 Zr ZIRCONIUM	41 Nb NIOBIUM	42 Mo MOLYBDENUM	43 Tc TECHNETIUM	44 Ru RUTHENIUM
55 Cs CESIUM	56 Ba BARIUM	57-71 La-Lu LANTHANIDES	52 Hf HAFNIUM	73 Ta TANTALUM	74 W TUNGSTEN	75 Re RHENIUM	76 Os OSMIUM
82 Fr FRANCIUM	88 Ra RADON	89-103 Ac-Lr ACTINIDES	104 Rf RUTHERFORDIUM	105 Db DISSIDIUM	106 Sg SEABORIUM	107 Bh BOHRIUM	108 Hs HESSIUM
				109 Mt MEITNERIUM	110 Ds DARMSTIDIUM	111 Rg ROENTGENIUM	112 Cn CGSBERGREN
				113 Uut UNUNTRIUM	114 Uup UNUNQUADRUM	115 Uuh UNUNQUINTIUM	116 Uus UNUNSEPTIUM
				117 Uuo UNUNOCTIUM	118 Uuo UNUNOCTIUM	119 Uuo UNUNOCTIUM	120 Uuo UNUNOCTIUM

165Er:
 $7 \times \text{Ae}^-$
1.1 keV
(~90 nm)

Ho

LANTHANIDES	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
ACTINIDES	Ac	Th	Pa	U	Np	Pu	Am	Cm

Er 164 1.601	Er 165 10.36 h	Er 166 33.503
$\sigma_{13} \sigma_{n,\alpha} < 0.0012$	$\sigma_{n,\gamma}$	$\sigma_{3 + 14} \sigma_{n,\alpha} < 7E-5$
Ho 163 1.09 s	Ho 164 4570 a	Ho 165 100
IT 298	$\sigma_{n,\gamma}$	$\sigma_{3.1 + 58} \sigma_{n,\alpha} < 2E-5$
IT (46), e^- γ 37, 57... e^-	β^- 1.0... γ 91, 73... β^-	

160Gd

161Tb:
154 keV
(~280 μm)
+
11x Ae^-
0.8 keV
(~60 nm)

176Yb

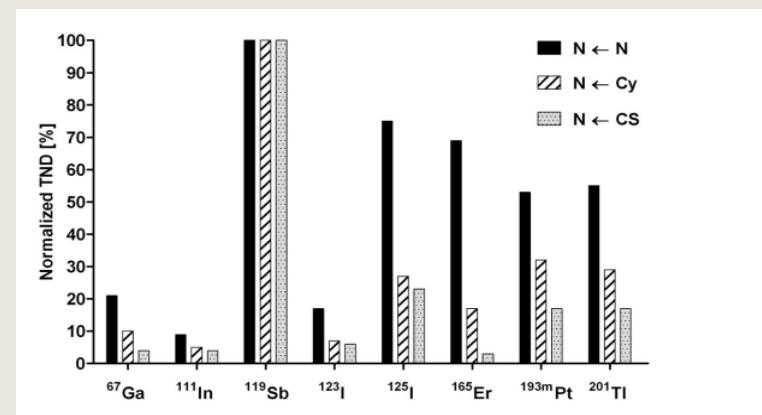
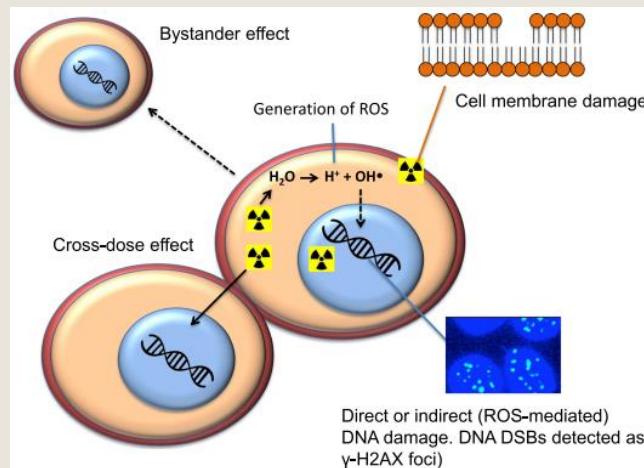
177Lu:
130 keV
(~220 μm)



Dosimetry of ^{165}Er

R.	Half-life (d)	Avg. Aes per decay	Avg. energy per Aes (keV)	Avg. β - per decay	Avg. energy per β -(keV)
^{165}Er	0.43	7.3	11	0	0
^{161}Tb	6.89	11	5,7	1	154
^{177}Lu	6.64	1.1	1	1	133

1. Ku A, Facca VJ, Cai Z, Reilly RM. Auger electrons for cancer therapy – a review. EJNMMI Radiopharm Chem 2019;4:27.



2. Thisgaard, H. (2008). Accelerator based Production of Auger-Electron-emitting Isotopes for Radionuclide Therapy. Risø National Laboratory. Risø-PhD No. 42(EN)



AMA : Apparent Molar Activity

- Unit : Activity of ^{165}Er by μmole of chelator (MBq/nmole or GBq/ μmole)
- Theoretical AMA :

$$MA_{EoB} = \frac{\left(A_{EoB} \cdot 10^6 \frac{Bq}{MBq} \cdot Y_{165\text{Er}} \right)}{\lambda \cdot N_{Av}} + \left(\frac{(m_{Ho} \cdot F_{ErImp} \cdot Y_{165\text{Er}})}{MW_{Er}} \right) + \left(\frac{m_{Ho} \cdot SF_{Ho/Er}}{MW_{Ho} \cdot Y_{165\text{Er}}} \right)$$

The diagram illustrates the theoretical AMA equation. Three terms are circled: the first term (green circle) contains A_{EoB} , $10^6 \frac{Bq}{MBq}$, and $Y_{165\text{Er}}$; the second term (blue circles) contains m_{Ho} , F_{ErImp} , and $Y_{165\text{Er}}$; the third term (red circle) contains m_{Ho} , $SF_{Ho/Er}$, and $Y_{165\text{Er}}$. These circled terms represent different components of the equation: production yield, target purity, and radiochemistry.

- Production : ^{165}Ho (p, n) ^{165}Er
- Parameters :

- 1 : Target : mass (ng), Er impurities (ppm),
- 2 : Targetry : yield (MBq/ $\mu\text{A}/\text{h}$), beam (Energy and particle)
- 3 : Radiochemistry : SF (Separation factor Ho/Er), yield



Radiolabeling for studies : $AMA_{EoS} > 7.4\text{GBq}/\mu\text{mole}$ ($0.2\text{mCi}/\mu\text{mole}$)³

³- Aluicio-Sarduy E, Hernandez R, Valdovinos HF, Kutyreff CJ, Ellison PA, Barnhart TE, et al. Simplified and automatable radiochemical separation strategy for the production of radiopharmaceutical quality ^{86}Y using single column extraction chromatography. Appl Radiat Isot 2018;142:28–31.
<https://doi.org/https://doi.org/10.1016/j.apradiso.2018.09.01>

Parameter 1 : Target Ho foil

□ Er impurity : quality of Ho target

$A_{165\text{Er}} = 1 \text{ GBq}$ and $m(\text{Ho}) = 100 \text{ mg}$, $SF = 10^5$

$\text{AMA(EoB)} \leq 17 \text{ MBq/nmole}$ (100 ppm Er) : commercial Ho foil

$\text{AMA(EoB)} \leq 1100 \text{ MBq/nmole}$ (0,5 ppm Er) : Ames Laboratory)



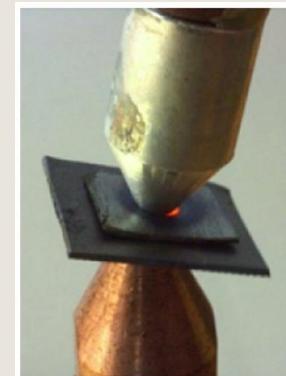
□ Mass Ho foil depends on :

- Thickness foil (μm) → targetry
- Diameter (mm) → targetry and chemistry



→ Easy method to control Ho mass with conditions of targetry : Spot-welding method ⁴

- Ho foil rolled to the desired thickness (from 620 to 150 μm)



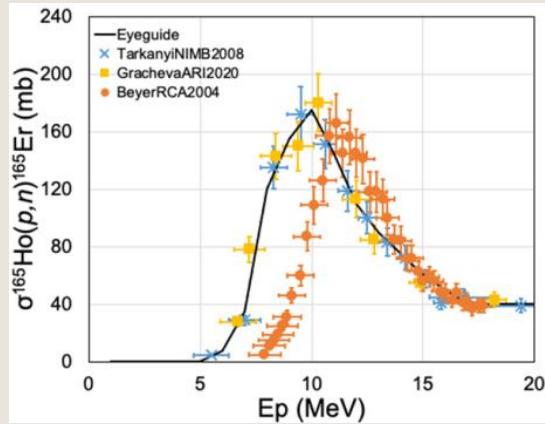
- Punched in various diameter (3.2 to 9.5 mm)

⁴ - Ellison PA, Valdovinos HF, Graves SA, Barnhart TE, Nickles RJ. Spot-welding solid targets for high current cyclotron irradiation. Appl Radiat Isot 2016;118:350–3. <https://doi.org/10.1016/j.apradiso.2016.10.010>.

Parameter 2 : Targetry (Biomedical cyclotron)



GAFChrom : target 3.2, 4.8 and 6 mm Ø
(irradiations on RDS-112)



□ PETtrace or RDS-112 ?



cyclotron	Ho target dimensions			E_{in} (MeV)	E_{out} (MeV)	^{165}Er physical yield		n
	diam. (mm)	thick. (μm)	mass (mg)			($\text{MBq} \cdot \mu\text{A}^{-1} \cdot \text{h}^{-1}$)		
PETtrace	9.5	280	174 ± 6	12.5	7.5	23.7 ± 0.8	2	
PETtrace	9.5	200 – 240	125 ± 6	12.5	$8.4 - 9.1$	18.2 ± 0.5	3	
PETtrace	7.9	270 – 280	108 ± 4	12.5	7.8	13 ± 1	3	
PETtrace	7.9	190	69 ± 1	12.5	9.3	11.5 ± 0.4	4	
RDS-112	7.9	190	75 ± 7	11	7.5	26 ± 2	4	
RDS-112	6.4	320 – 620	121 ± 75	11	< 4.8	29 ± 4	2	

→ More focused beam and low mass with RDS-112 but limited in current 20 μA

Higher activity with PETtrace with higher current and but more Ho mass (Er impurity)

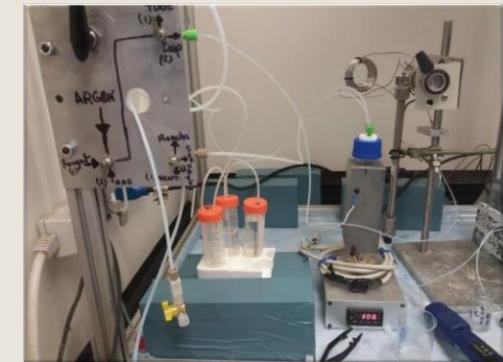
Parameter 3 : Radiochemical separation

AMA (MBq/nmole)



Dissolution of target :

2 ml 10M HCl dry and dissolution reconstituted
in 2 ml of α HIB pH 4.7



Separation in 3 steps :

- S1 : « Pre-column » : rough separation
 - ❖ Cation exchanger AG50W-X8 with α HIBA acid 70 mM pH=4.7
- S2 : « Selective separation » : Ho/Er
 - ❖ Extraction resin LN2 20-50 μ m
- S3 : elimination of transition metals
 - ❖ Extraction DGA-b resin



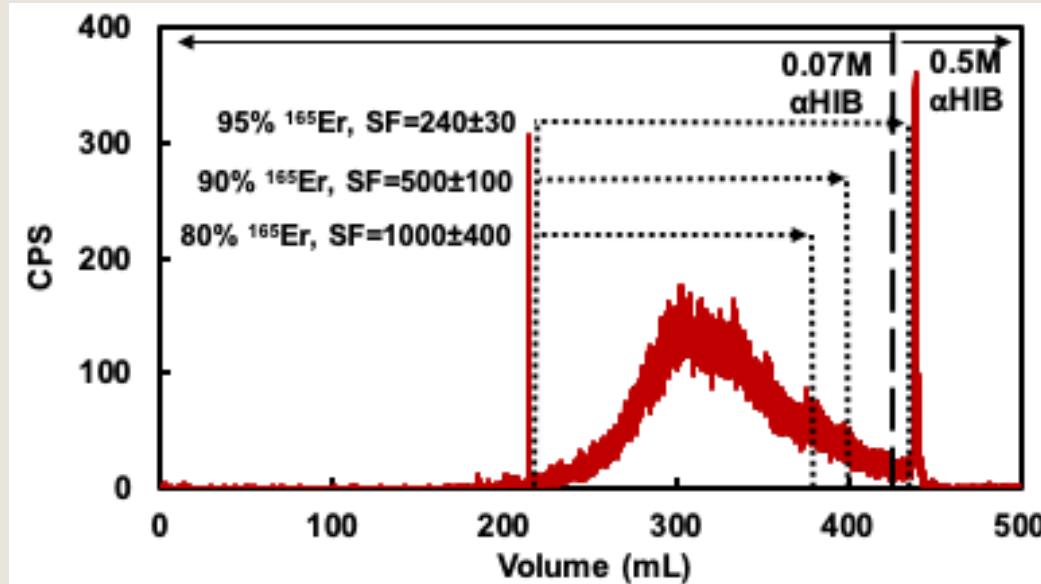
$$SF_{Ho/Er} = \frac{m_{Ho,before}}{A_{165}^{Ho,before}} / \frac{m_{Ho,after}}{A_{165}^{Ho,after}}$$

Assessment:

- ⇒ ^{165}Er : measurement by Capintec number CRC-15R and spectrometry gamma
- ⇒ Ho : MP-AES



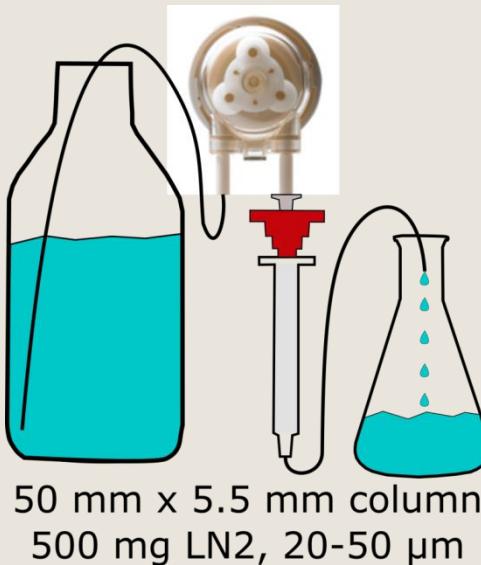
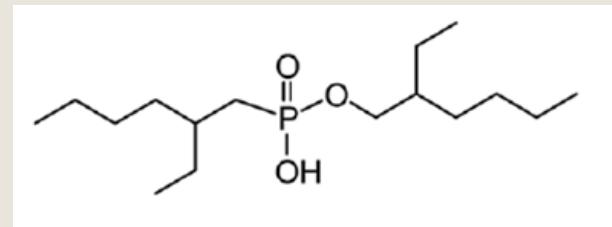
CX / α HIB results



- **110 ± 20 mg** Ho: SF_{Ho/Er} = **280 ± 170** , ^{165}Er recovery **(95 ± 2)%** with (n = 6)
- **174 ± 6 mg** Ho: SF_{Ho/Er} = **280 ± 210** , ^{165}Er recovery **(91 ± 2)%** with (n = 2)

LN2 EXC 20-50μm

1. ^{165}Er in 0.1 M HNO_3 ,
70mM αHIB at 5
 mL/min
2. $49 \pm 6 \text{ mL}$ 0.4 M
 HNO_3 at 1 mL/min
3. 4 – 5 mL 1 M HNO_3 at
1 mL/min



1. No ^{165}Er
2. $(99.91 \pm 0.06)\%$ Ho, $(23 \pm 7)\%$ ^{165}Er
3. $(77 \pm 7)\%$ Er recovery,
 $\text{SF}_{\text{Ho/Er}} = 840 \pm 440$

$530 \pm 480 \mu\text{g Ho}$

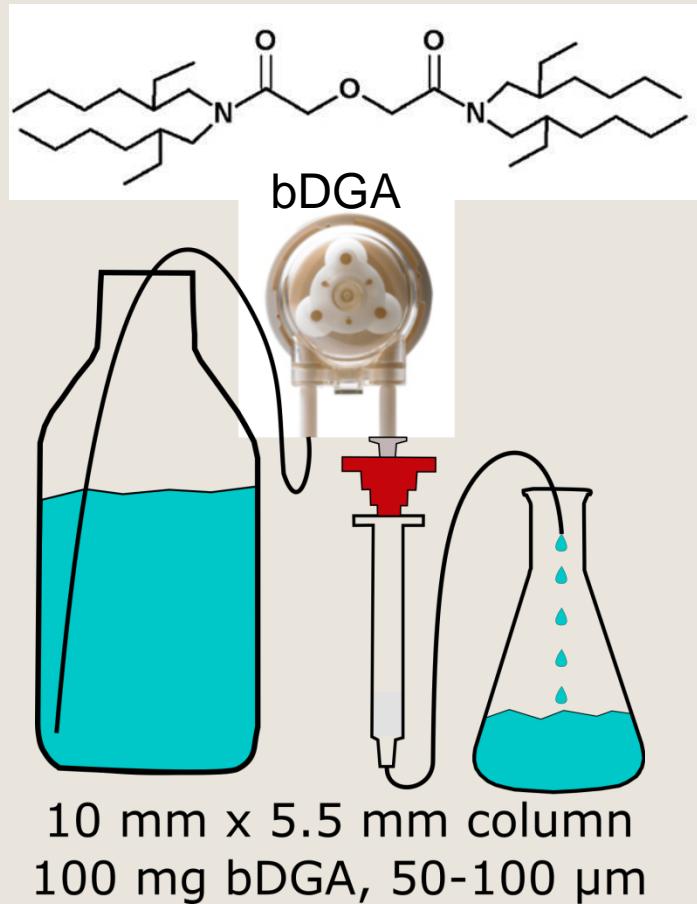
$380 \pm 210 \text{ ng Ho}$ 11



DGA-b 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

4 mL 1 M HNO_3

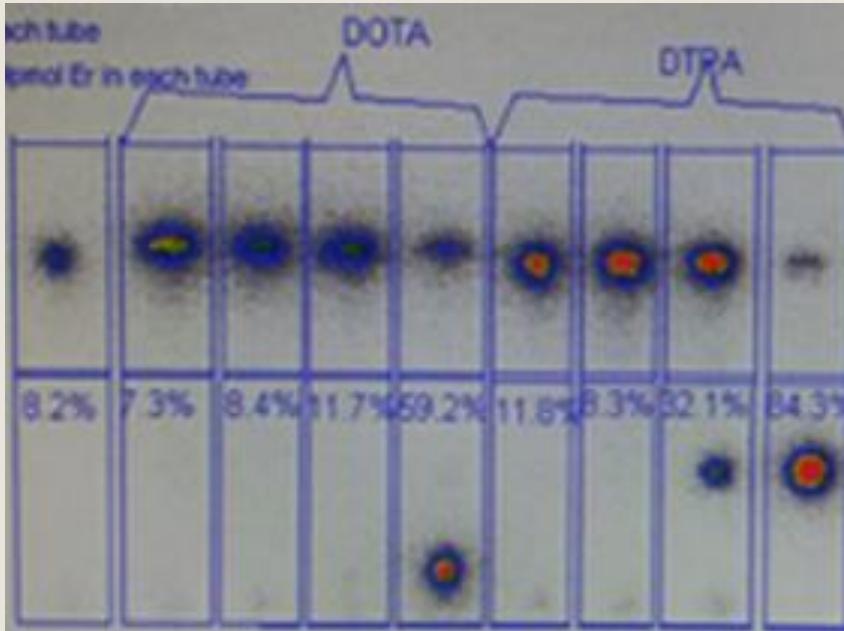


1. No ^{165}Er
2. Trace metal impurities (Fe, Cr, Co, Ni, Cu), no ^{165}Er
3. Lower column acidity, no ^{165}Er
4. $(88 \pm 4)\%$ ^{165}Er recovery, $390 \pm 30 \mu\text{L}$ 0.01 M HCl

0.4 mL 0.01 M HCl



AMA results (Biomedical Cyclotron)



Ho target Er impurity (ppm)	DOTA AMA (MBq/nmol)	DTPA AMA (MBq/nmol)	$^{165}\text{Er}/\text{Er}$ MA (MBq/nmol)	$^{165}\text{Er}/\text{Ho}$ MA (MBq/nmol)	n
<100	8.1 ± 0.2	8.8 ± 0.3	8.6 ± 0.9	105 ± 82	2
0.5	$20 \pm 24^*$	110 ± 100	2300 ± 700	420 ± 190	4

*n = 3 replicates, all molar activities decay corrected to end of bombardment

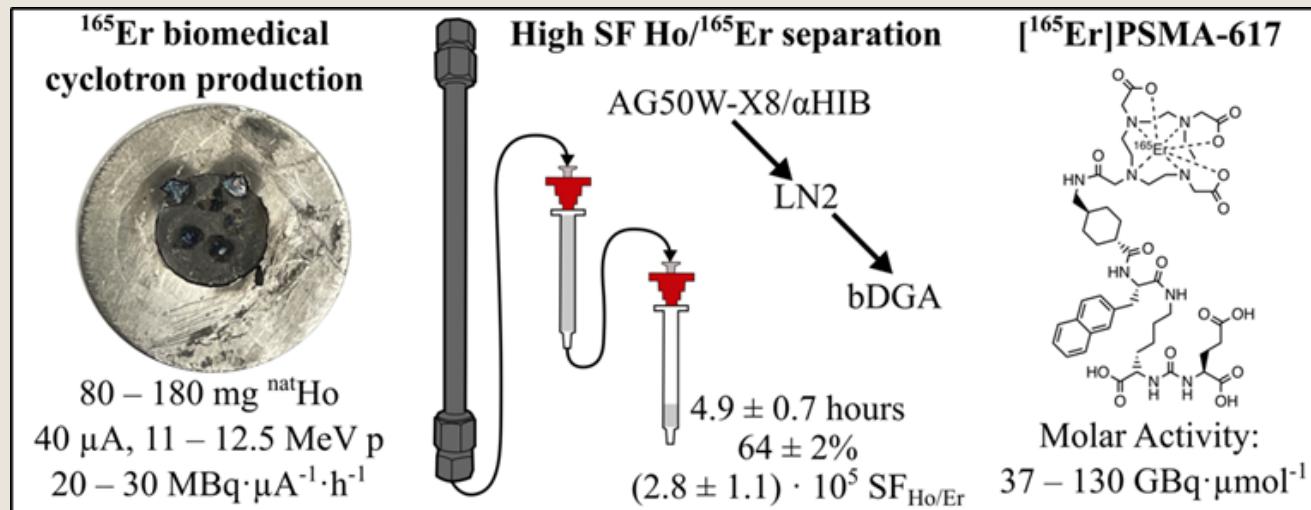


Conclusions

⇒ Batch ^{165}Er with High AMA > 7.4 GBq/ μmole available using :

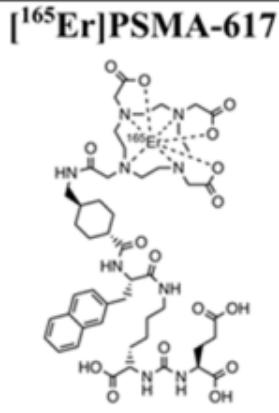
- ❖ proton beam 12.5 MeV on a high purity Ho target (Er impurity : 0.5 ppm)
- ❖ limitation with Ho foil (Er impurity < 100 ppm)

⇒ First radiolabeling of PSMA-617 with ^{165}Er for dosimetry studies⁵ :



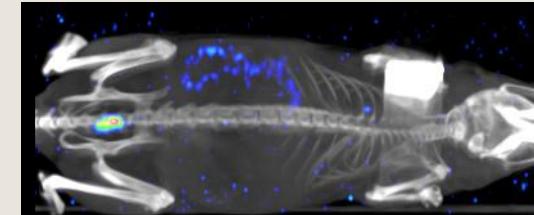
5- I. Da Silva, T. R. Johnson, J. C. Mixdorf, E. Aluicio-Sarduy, T. E. Barnhart, R. J. Nickles, J. W. Engle, P. A. Ellison. A high separation factor for ^{165}Er from Ho for targeted radionuclide therapy, in press in Molecules.

Outlooks



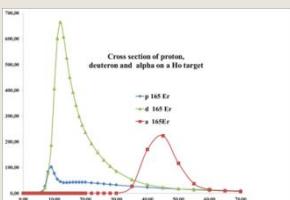
⇒ Radiolabeling molecules with ¹⁶⁵Er for targeted receptor :

- ⇒ Dosimetry studies for targeted radionuclide therapy
- ⇒ Bimodality MRI/SPECT for preclinical use



⇒ Developments with commercial Ho foil to high AMA :

- ⇒ Deuteron beam : higher activity (CEMHTI, Orléans)
- ⇒ Alpha beam : generator of ¹⁶⁵Er by decay of ¹⁶⁵Tm
- ⇒ Radiochemistry : nanoporous use and μseparation



6- L. Frealle, J. Vaudon , G. Audiger , E. Dutilly, M. Gervais, E. Sursin, C. Ruggeri, F. Duval, M.-L. Bouchetou, A. Bombard, I. Da Silva, "First steps at the Cyclotron of Orleans in the radiochemistry of radiometals : 52Mn and 165Er, Instruments, 2018, 2(3) 15.

7. Gracheva N, Carzaniga TS, Schibli R, Braccini S, van der Meulen NP. 165Er: A new candidate for Auger electron therapy and its possible cyclotron production from natural holmium targets. Appl Radiat Isot 2020;159:109079.

Acknowledgements



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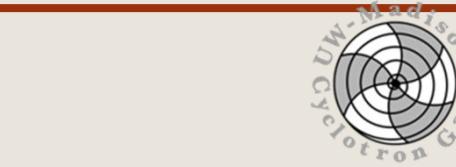
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Jerry Nickles



Paul Ellison



Taylor
Johnson



Jason
Mixdorf



Tara
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Jennifer
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(Hunter College)



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