

**High specific activities  
of therapeutic radiolanthanides  
following neutron capture nuclear reactions**

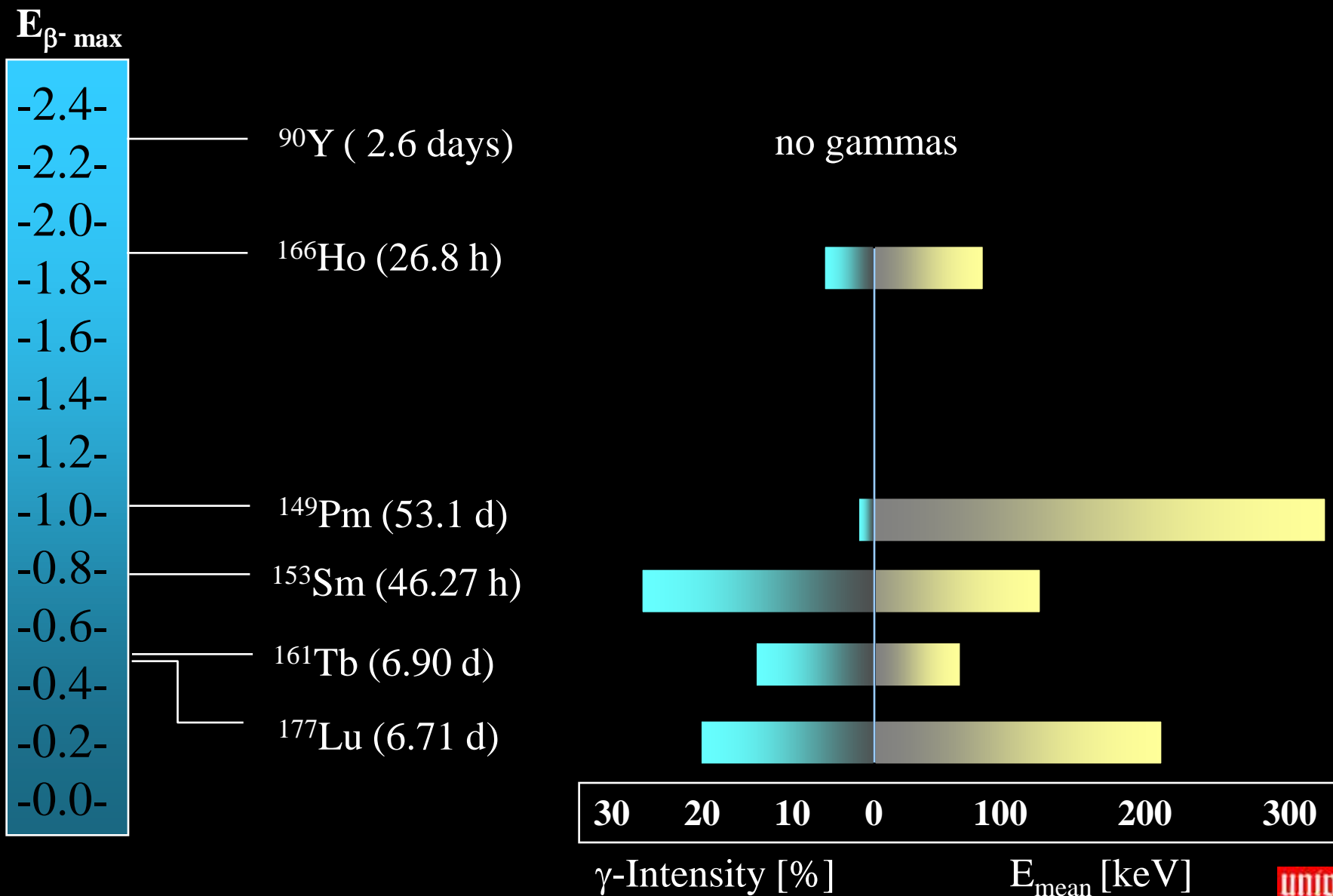
F Roesch<sup>1</sup>, KP Zhernosekov<sup>1</sup>, DV Filosofov<sup>2</sup>

<sup>1</sup>Institute of Nuclear Chemistry, University of Mainz, D-55128 Mainz, Germany

<sup>2</sup>Joint Institute of Nuclear Research, LJAP, RUS-141980 Dubna, Russian Federation



# Radiolanthanides for Therapy



# Specific activities

specific activity SA:

radioactivity [Ci] or [GBq] related to the mass [g] or [ $\mu\text{mol}$ ] of the element  
for molecular targeting vectors: max. SA

For radiolanthanides produced by (n, $\gamma$ ) processes ( $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ , ...),



SA depends on

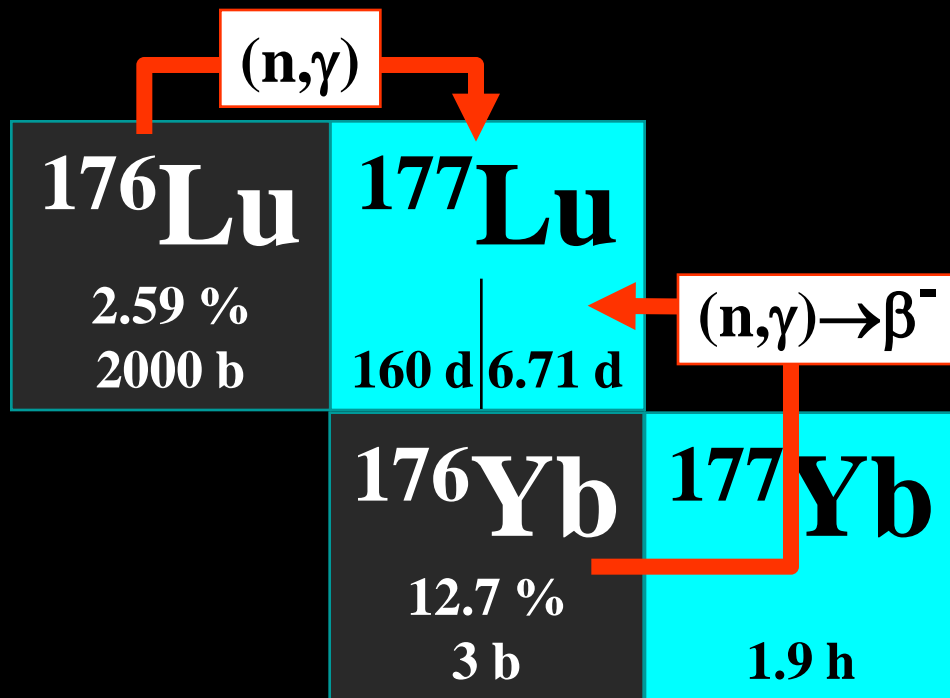
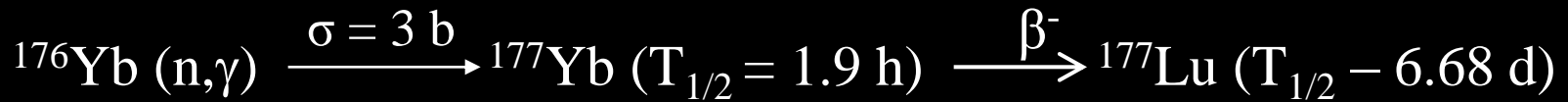
- neutron flux,
- neutron capture cross section,
- isotopic enrichment of the target lanthanide isotope,
- irradiation periods,

..... and is thus a pure physical parameter.....

..... but chemistry is able to contribute (i) ....

# $^{177}\text{Lu}$ : nca vs. ca

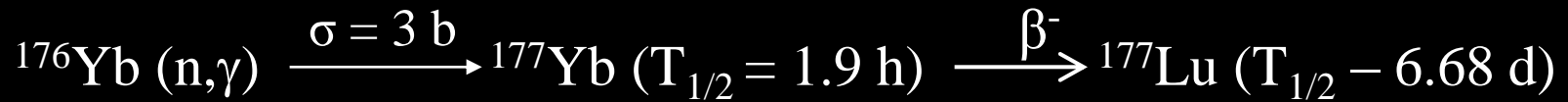
specific activity of  $^{177}\text{Lu}$  labeled peptides for tumor receptors:  
high specific activity vs. nca status



..... but chemistry is able to contribute (i) ....

# $^{177}\text{Lu}$ : nca vs. ca

specific activity of  $^{177}\text{Lu}$  labeled peptides for tumor receptors:  
high specific activity vs. nca status



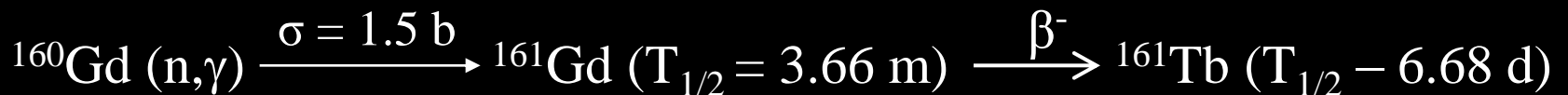
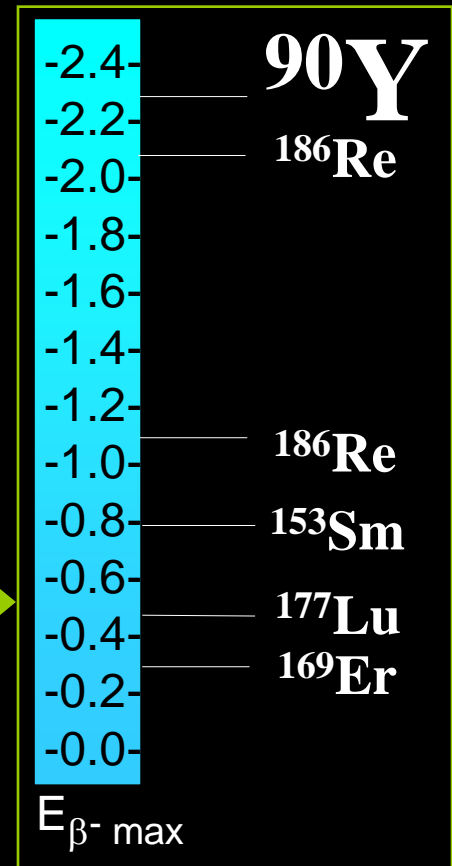
$^{177}\text{Lu}$
160 d   6.71 d
$^{176}\text{Yb}$
12.7 %
3 b

## Problem:

Radiochemical separation of type:  
macroscopic target (10 – 100 mg)  
vs.  
irradiation product (nca)

# Analogue strategy for:

target	product	$T_{1/2}$ [d]	$E_{\beta^- \text{ max}}$
$^{142}\text{Ce}$	$^{143}\text{Pr}$	13.58	0.9
$^{148}\text{Nd}$	$^{149}\text{Pm}$	2.212	1.1
$^{160}\text{Gd}$	$^{161}\text{Tb}$	6.91	0.5, 0.6
$^{164}\text{Dy}$	$^{166}\text{Ho}$	1.117	1.9
$^{176}\text{Yb}$	$^{177}\text{Lu}$	6.71	0.5



other radiochemical separation

more relevant to routine and large-scale activity processing ?

# High Specific Activity vs. Radiochemistry

types of reaction	parameters	$A_s$
nuclear reactors (n, $\gamma$ )		low
nuclear reactors (n, $\gamma$ )	High $\sigma$	medium
nuclear reactors (n, $\gamma$ )	High flux + high $\sigma$	high
nuclear reactors (n, $\gamma$ ) $\rightarrow\beta^-$	+ chemistry	$\rightarrow$ nca

# High Specific Activity vs. Radiochemistry

types of reaction	parameters	$A_s$
nuclear reactors (n, $\gamma$ )		low
nuclear reactors (n, $\gamma$ )	High $\sigma$	medium
nuclear reactors (n, $\gamma$ )	High flux + high $\sigma$	high
nuclear reactors (n, $\gamma$ ) $\rightarrow\beta^-$	+ chemistry	$\rightarrow$ nca

..... but chemistry is able to contribute (ii) ....

## Szilard-Chalmers effect

“The rapture of the chemical bond between an atom and the molecule of which the atom is part, as a result of a nuclear reaction of that atom”

IUPAC compendium of Chem Terminology

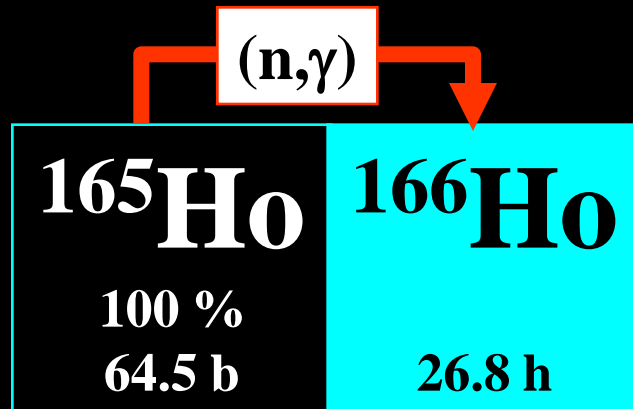
2nd Edition (1997)

combine

unique thermodynamic and **kinetic** parameters of Ln(III)-DOTA complexes and the **hot atom chemistry** of radionuclides *following nuclear reactions*

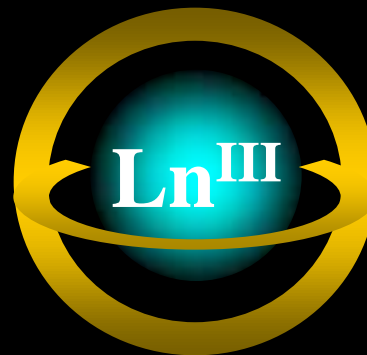
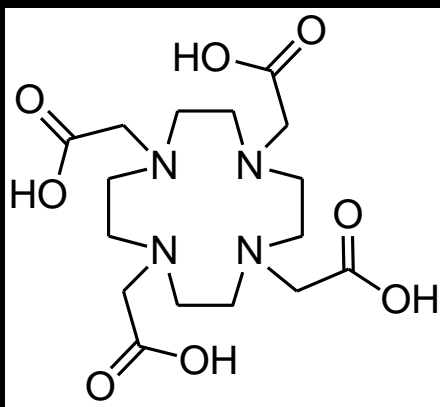
# Example

- prepare and irradiate  $^{165}\text{Ho}$ -DOTA
- $^{166}\text{Ho}$  is produced *in situ* by the  $^{165}\text{Ho}(n,\gamma)^{166}\text{Ho}$  process



## macrocyclic DOTA:

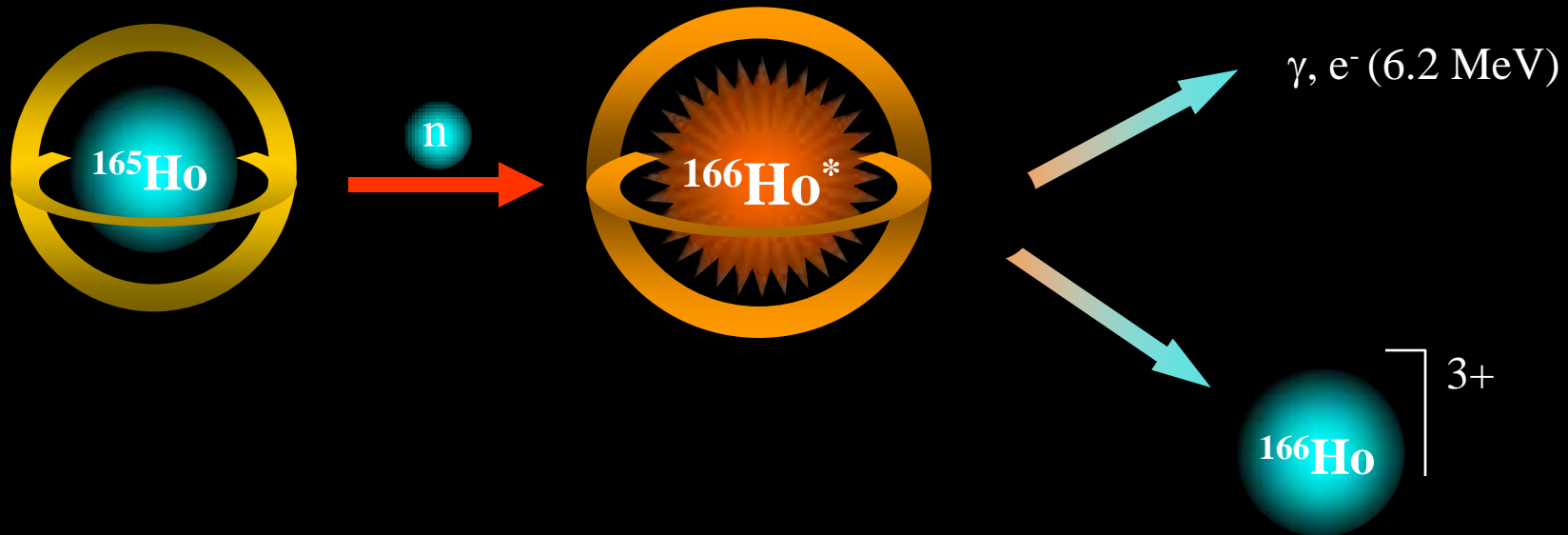
known to offer excellent thermodynamic and kinetic parameters relevant to the formation of complexes with tri-valent metals, mainly represented by rare earth elements and in particular lanthanides.



1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid

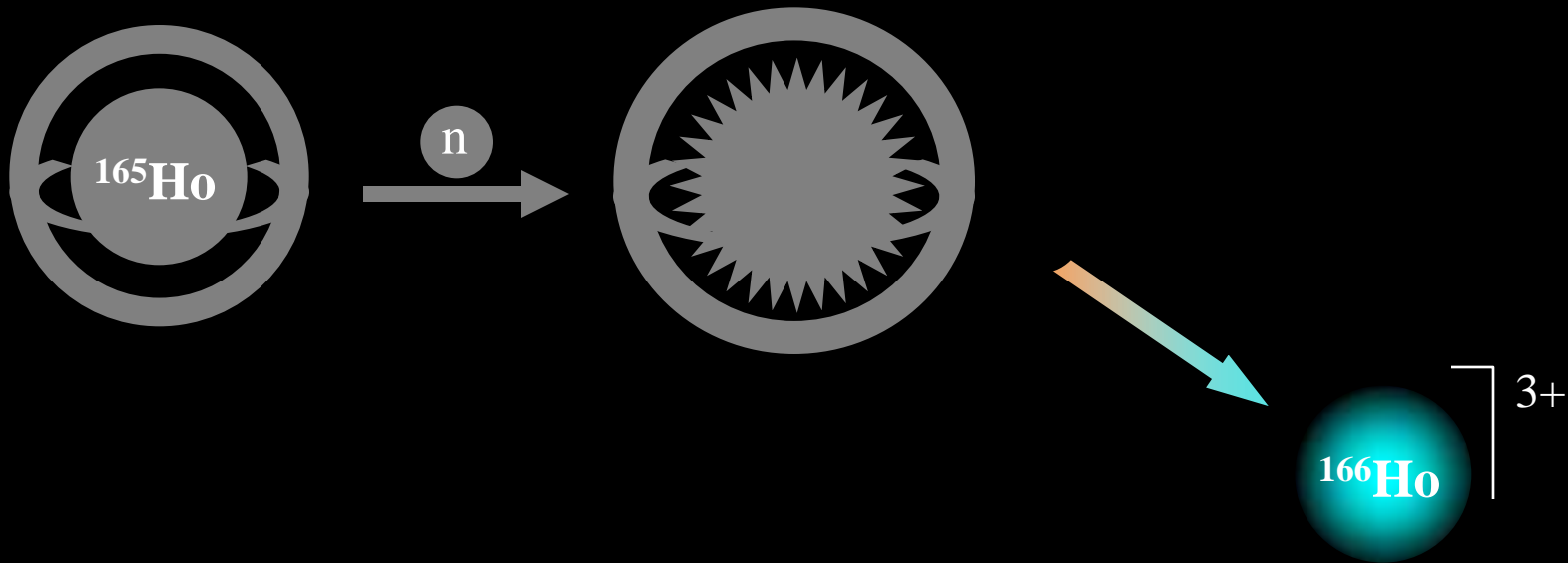
# Experiment

- prepare and irradiate  $^{165}\text{Ho}$ -DOTA
- $^{166}\text{Ho}$  is produced *in situ*  
 $^{165}\text{Ho}(n,\gamma)^{166}\text{Ho}$  process
- **and released from DOTA**



# Experiment

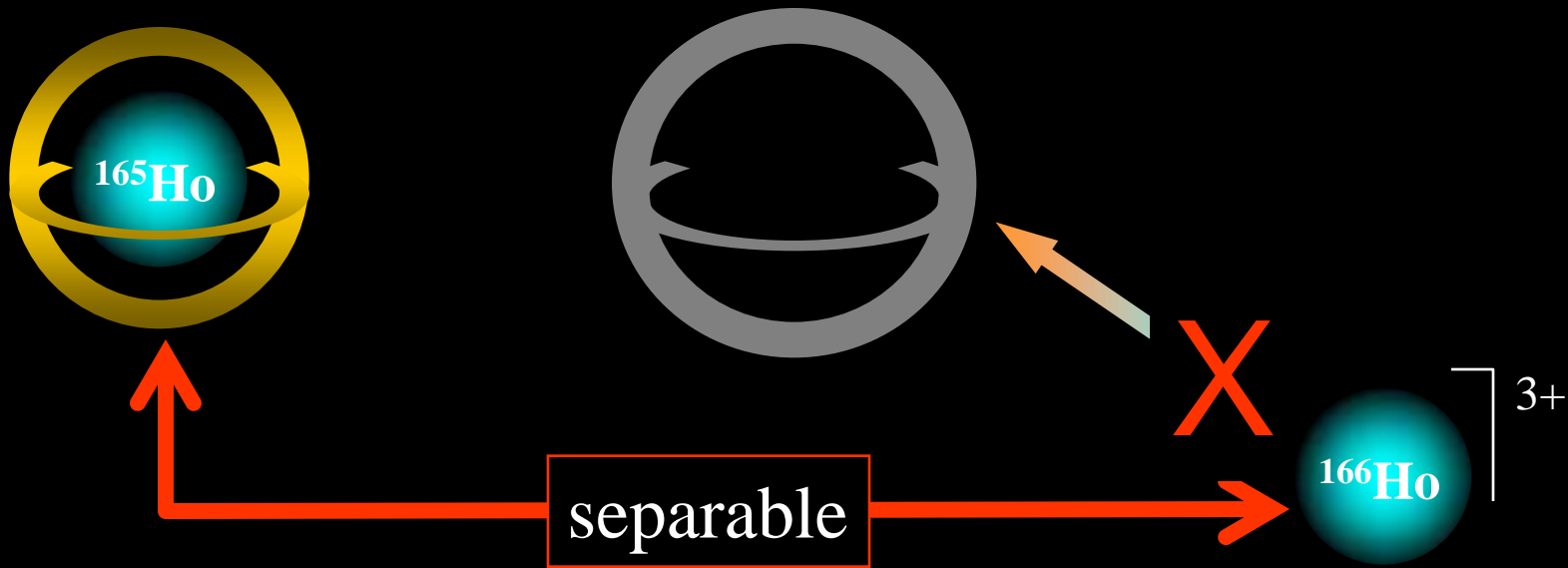
- prepare and irradiate  $^{165}\text{Ho}$ -DOTA
- $^{166}\text{Ho}$  is produced *in situ*
- released from DOTA



- not forming  $^{166}\text{Ho}$ -DOTA

# Experiment

- prepare and irradiate  $^{165}\text{Ho}$ -DOTA
- $^{166}\text{Ho}$  is produced *in situ*
- released from DOTA



- not forming  $^{166}\text{Ho}$ -DOTA
- **separate  $^{166}\text{Ho}^{3+}$  from inactive  $^{165}\text{Ho}$ -DOTA**

### Ho-DOTA:

Separation of [Ho-DOTA]<sup>-</sup> from uncomplexed Ho(III)

on a chromatography column 8 × 140 mm, AG 50W-X8, 200 - 400 mesh cation-exchanger K<sup>+</sup>-form.

Free <sup>166/165</sup>Ho(III) quantitatively absorbed on the resin

while <sup>165</sup>Ho-DOTA complex (1:1 stoichiometry) obtained in the eluate.

<sup>166/165</sup>Ho(III) washed out with 4 M HCl.

### Irradiations:

aqueous solution of K[<sup>165</sup>Ho-DOTA] (1 mg Ho) evaporated in a polyethylene capsule at < 100° C.

Remained activity of <sup>166</sup>Ho negligible.

irradiations at TRIGA II Mainz nuclear reactor at the neutron flux of  $4 \cdot 10^{12} \text{ n cm}^{-2} \text{ s}^{-1}$ ,

external temp ~ 21° C, within different periods of 0.5 – 6 hours, resulting in 10 – 120 MBq <sup>166</sup>Ho.

### Separation:

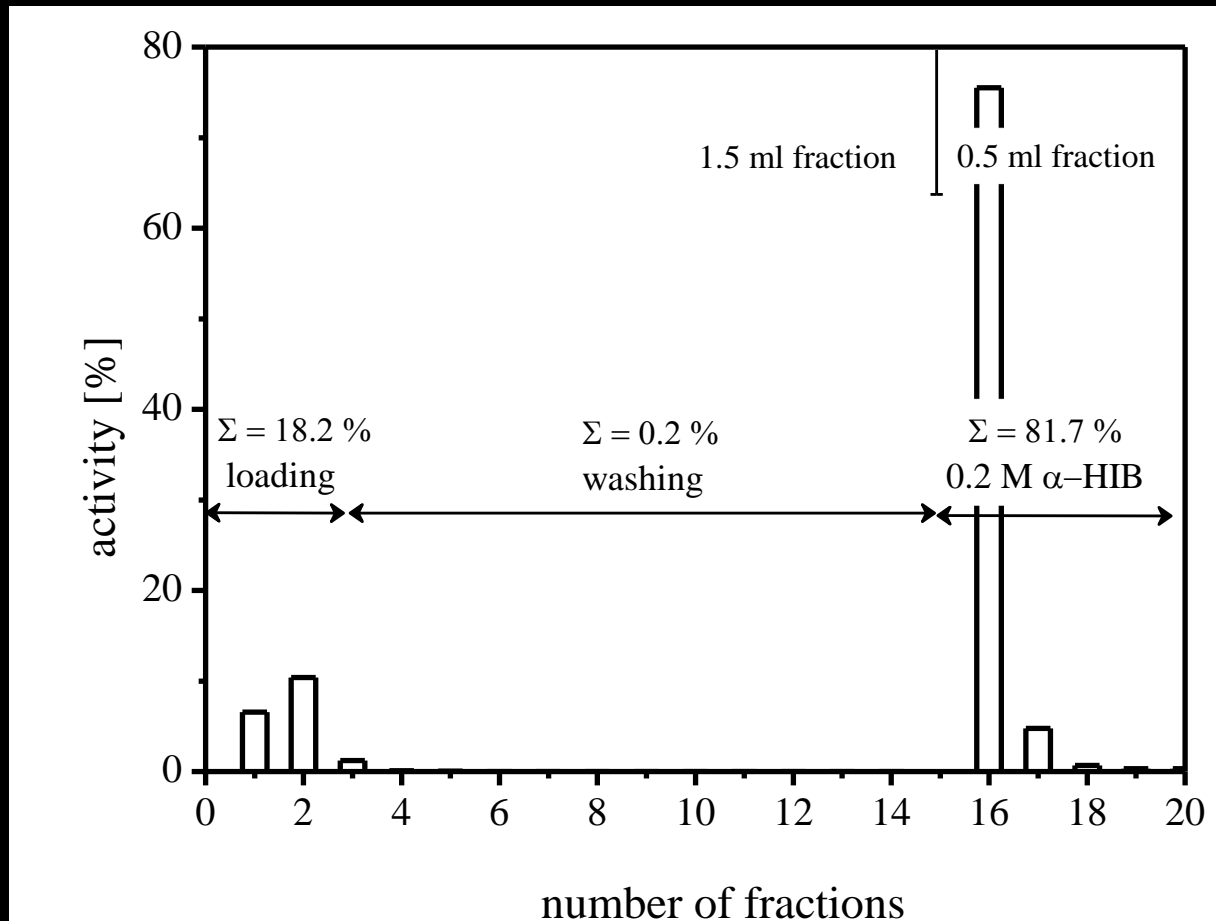
sample dissolved in 3 ml of water and loaded on a column 4 × 50 mm, AG 50W-X8, minus 400 mesh cation-exchanger in NH<sub>4</sub><sup>+</sup> -form.

target material [ <sup>165</sup>Ho-DOTA ]<sup>-</sup> removed by washing of the column with water.

enriched <sup>166</sup>Ho(III) eluted with 0.20 M α-HIBA

In order to determine the amount of stable <sup>165</sup>Ho, remained in the obtained <sup>166</sup>Ho, fractions of maximum <sup>166</sup>Ho activity in α-HIBA solutions evaporated after 10 half-lives of the radionuclide irradiated at the same neutron flux.

# Separation $^{165/166}\text{Ho-DOXA} / ^{166}\text{Ho}^{3+}$



Elution profile at a processing of the irradiated target material chromatography column  $4 \times 50$  mm Bio-Rad AG 50W-X8, minus 400 mesh,  $\text{NH}_4^+$ -form

# enrichment factor $\xi$ and retention value R

of  $^{166}\text{Ho(III)}$  for different irradiation periods of Ho-DOTA complex  
(TRIGA II Mainz -  $4 \cdot 10^{12} \text{ n cm}^{-2} \text{ s}^{-1}$ )

Time of irradiation [h]	Integral flux [neutron/cm <sup>2</sup> ]	$\xi$ Enrichment factor	R Retention “in target” [%]
0.5	$7.2 \cdot 10^{15}$	90.0	13.2
1	$1.44 \cdot 10^{16}$	50.6	24.5
2	$2.88 \cdot 10^{16}$	31.1	11.3
4	$5.75 \cdot 10^{16}$	21.5	18.0
6	$8.64 \cdot 10^{16}$	7.3	10.3

# Szilard-Chalmers effect to increasing SA

effective if

radiolytical decomposition of target material is lower

compared to the radioactive decay of produced radionuclide:

$$\phi_0 k < \lambda$$

$^{165}\text{Ho}$ -DOTA:

TRIGA II Mainz  $4 \cdot 10^{12} \text{ n cm}^{-2} \text{ s}^{-1}$ :

$k = 750,000$  barns

Target material	$^{166}\text{Ho}$ experimental SA 6 h irradiation [MBq/mg]	$^{166}\text{Ho}$ max. specific activity [MBq/mg] for TRIGA II Mainz
$\text{Ho}_2\text{O}_3$	135	886
Ho-DOTA	~ 2000	~ 2200

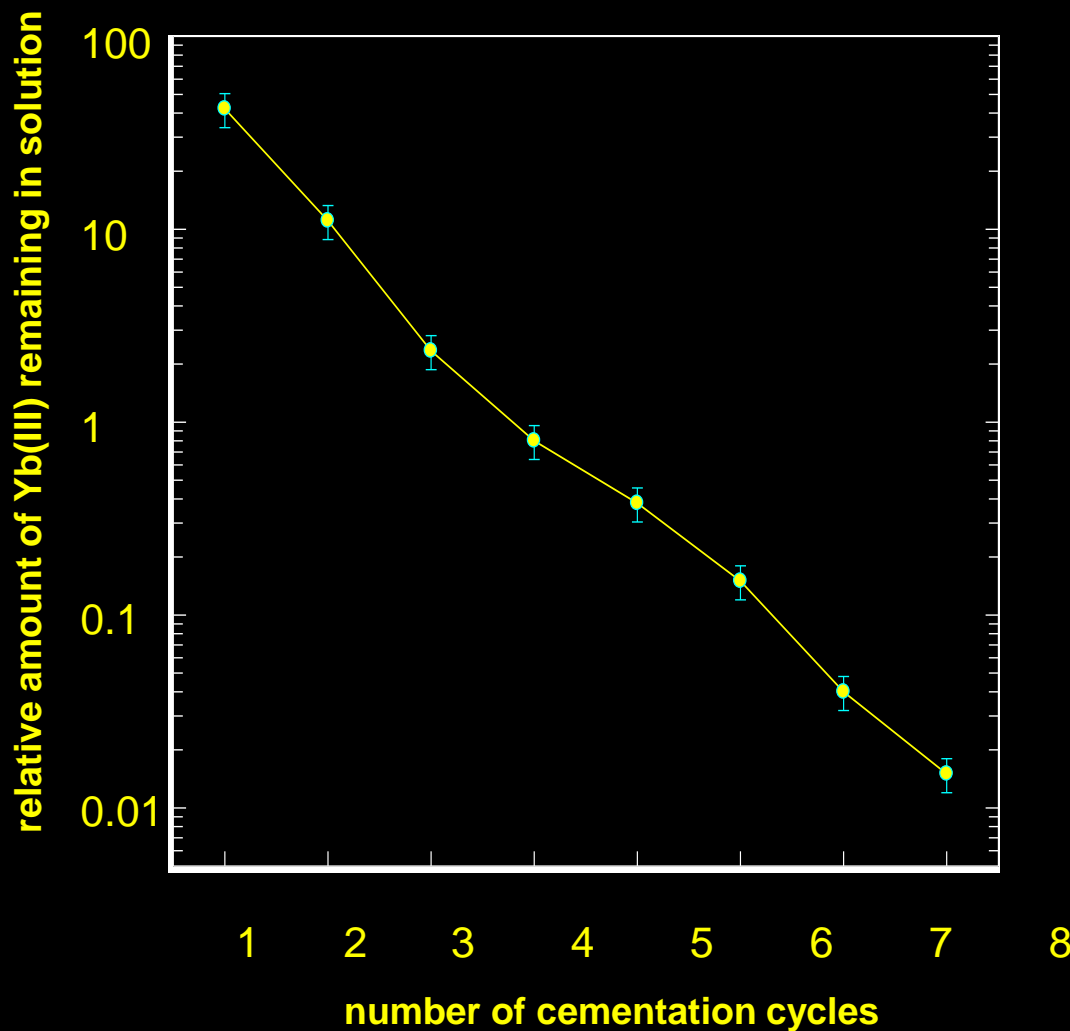
# Summary

New approaches to increased specific activities  
of trivalent therapeutic radiolanthanides following  $(n,\gamma)$  processes

1.  $(n,\gamma) \rightarrow \beta^-$  plus chemistry
2.  $(n,\gamma)$  of Ln-DOTA complexes plus (Szillard-Chalmers) chemistry

An option for research reactors !

# radiochemical separation of no-carrier-added $^{177}\text{Lu}$ as produced via the $^{176}\text{Yb}(n,\gamma)^{177}\text{Yb} \xrightarrow{1.9\text{h}, \beta^-} ^{177}\text{Lu}$ process



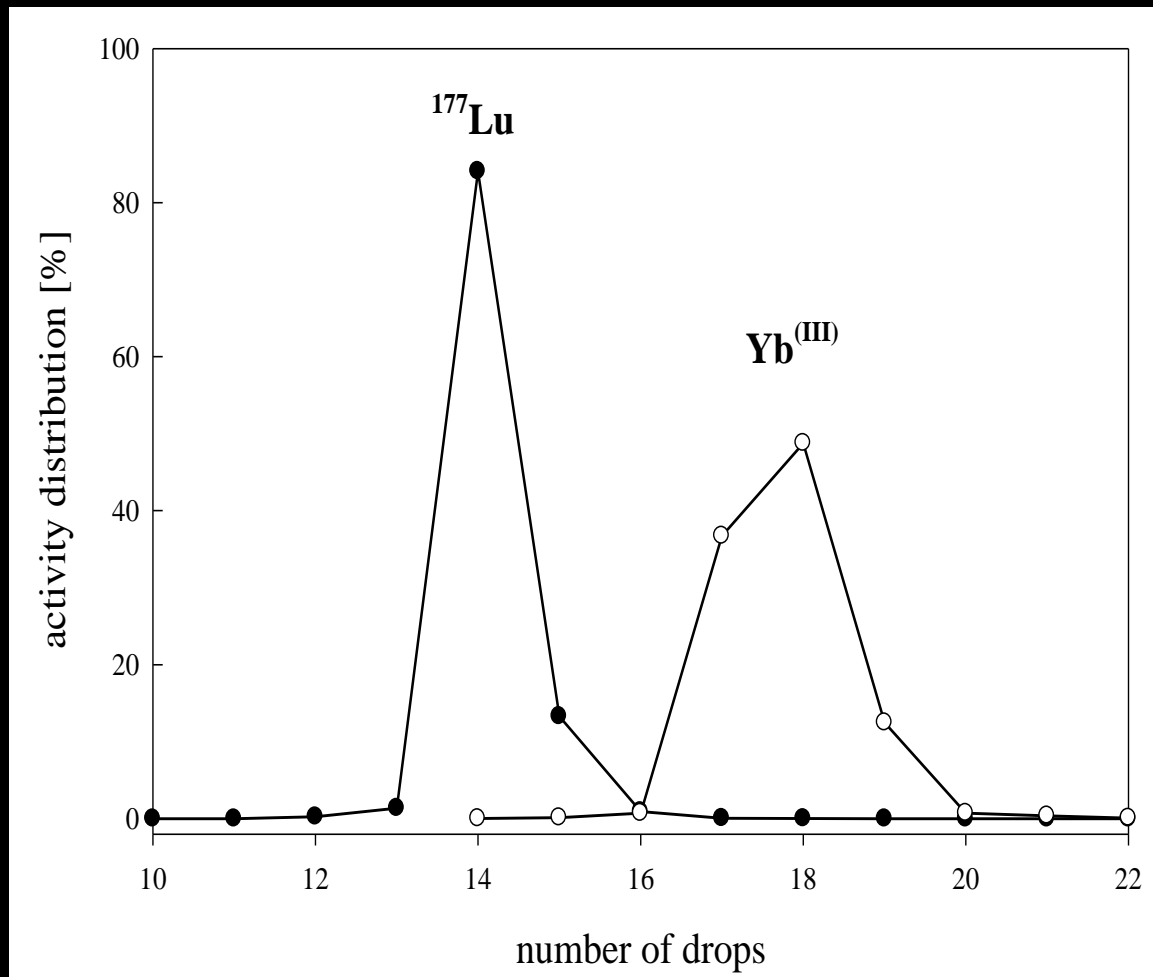
## 1. Production

94.72% enriched  $^{176}\text{Yb}$   
100 mg of  $^{176}\text{Yb}_2\text{O}_3$   
 $F_{\text{th}}$  of  $1 \cdot 10^{14} \text{ cm}^{-2}\text{s}^{-1}$ ,  
> 370 MBq per hour  
batch yields > 10 GBq

## 2. Separation (bulk)

Na(Hg) reductive cementation  
of Yb(III) via extraction  
 $^{177}\text{Lu}$  remaining in solution  
(100 mg  $\rightarrow$  20  $\mu\text{g}$ )

# radiochemical separation of no-carrier-added $^{177}\text{Lu}$ as produced via the $^{176}\text{Yb}(n,\gamma)^{177}\text{Yb} \xrightarrow{1.9\text{h}, \beta^-} ^{177}\text{Lu}$ process



## 1. Production

94.72% enriched  $^{176}\text{Yb}$

100 mg of  $^{176}\text{Yb}_2\text{O}_3$

$F_{\text{th}}$  of  $1 \cdot 10^{14} \text{ cm}^{-2}\text{s}^{-1}$ ,

> 370 MBq per hour

batch yields > 10 GBq

## 2. Separation (bulk)

$\text{Na}(\text{Hg})$  reductive cementation  
of  $\text{Yb}(\text{III})$  via extraction

$^{177}\text{Lu}$  remaining in solution

(100 mg  $\rightarrow$  20  $\mu\text{g}$ )

## 3. Purification

Cation exchange purification

(Aminex A6 2 mm x 80 mm,

0.07 M  $\alpha$ -HIB, pH 4.7)

75% yield, 5 h

# Production of radiolanthanides at nuclear reactors: other processes ?

