

# IS528-ADD1

## Novel diagnostic and therapeutic radionuclides for the development of innovative radiopharmaceuticals

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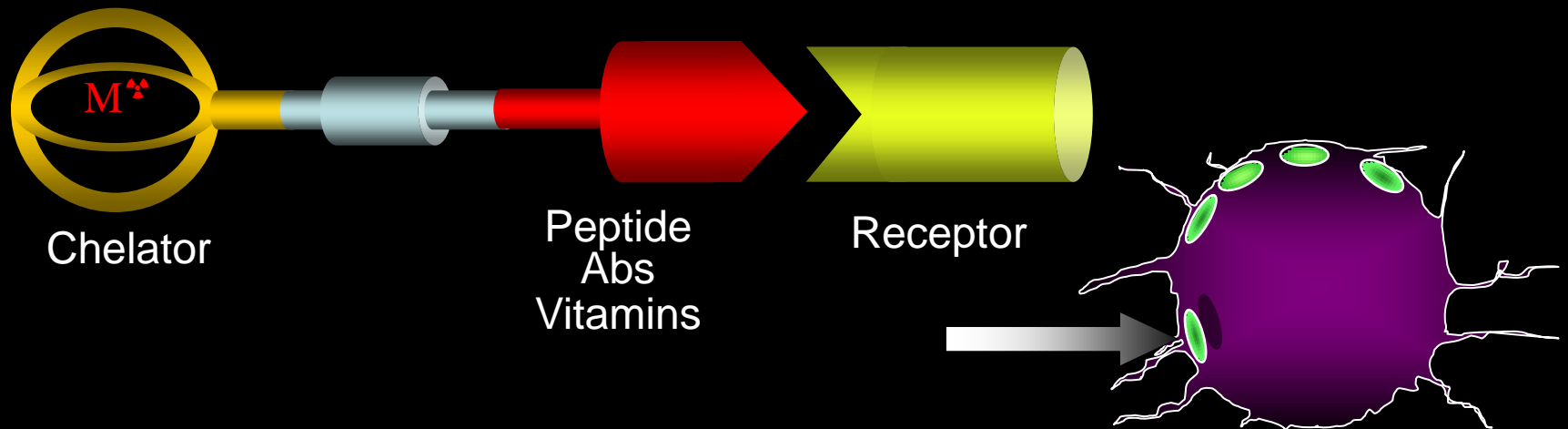
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<sup>7</sup> Institut de Recherche en Cancérologie de Montpellier, France



# Radiometals for diagnostic imaging and therapy

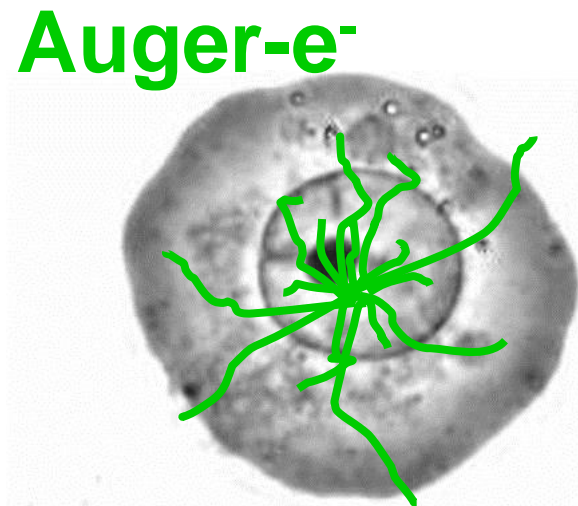
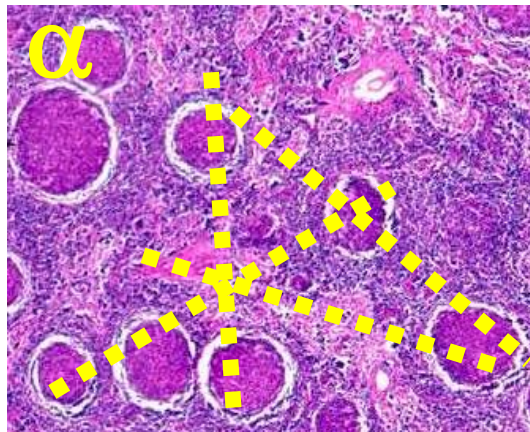
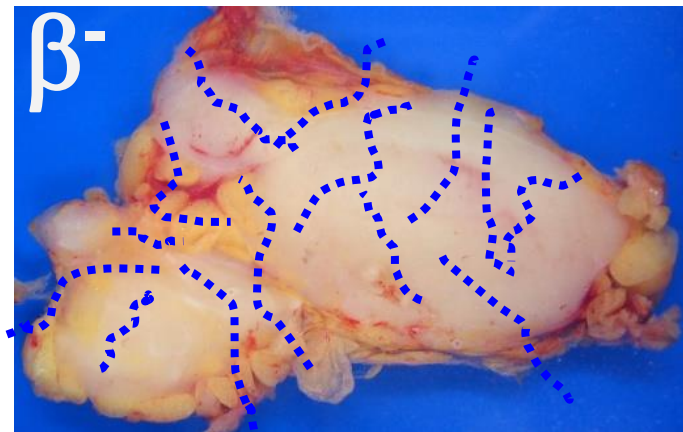
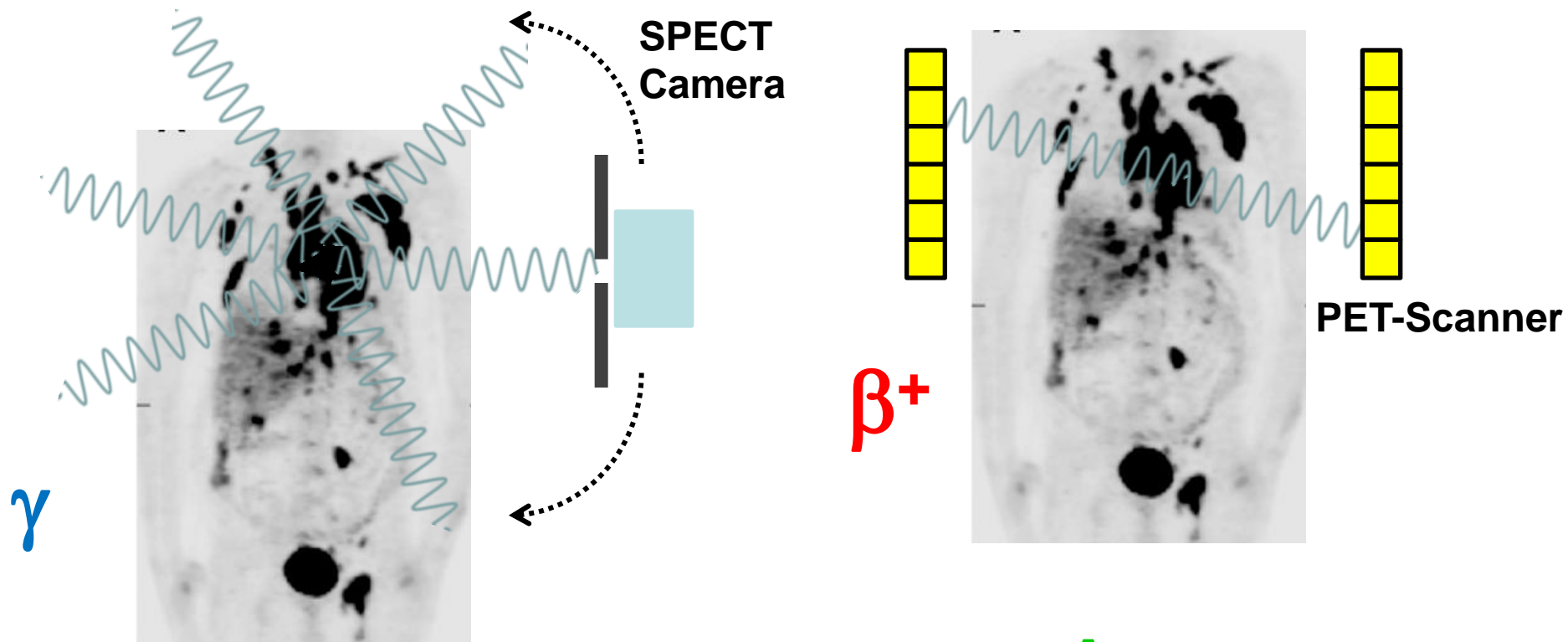


Photon or positron emitters  $^{99m}\text{Tc}$ ,  $^{68}\text{Ga}$ , ... for imaging

Particle emitters  $^{90}\text{Y}$ ,  $^{177}\text{Lu}$ , ... for radionuclide therapy

*applicable only  
with high specific activity and chemical purity*

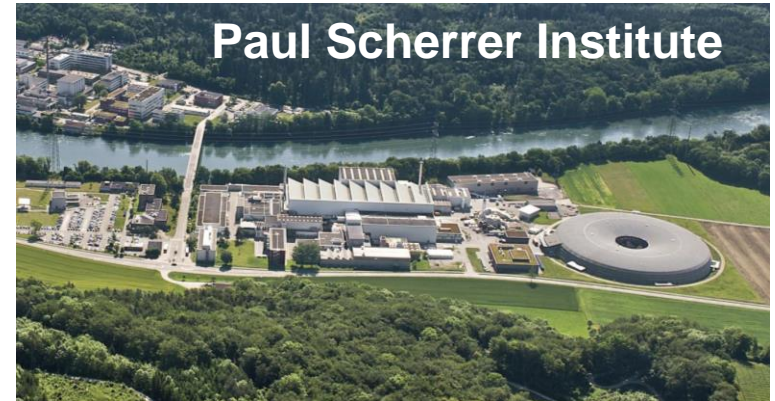
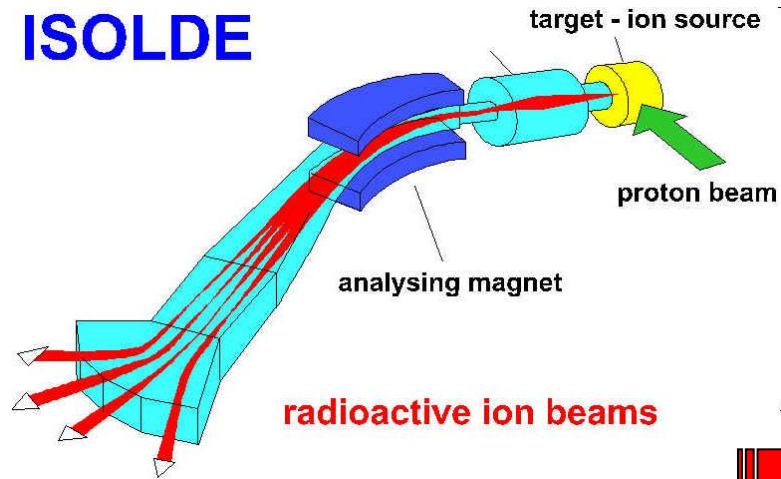
# The Nuclear Medicine Alphabet



# Production of n.c.a. [ $^{149/152/155}\text{Tb}$ ]-Terbium

## ISOLDE CERN and PSI

**ISOLDE**



Separation by means of cation exchange chromatography

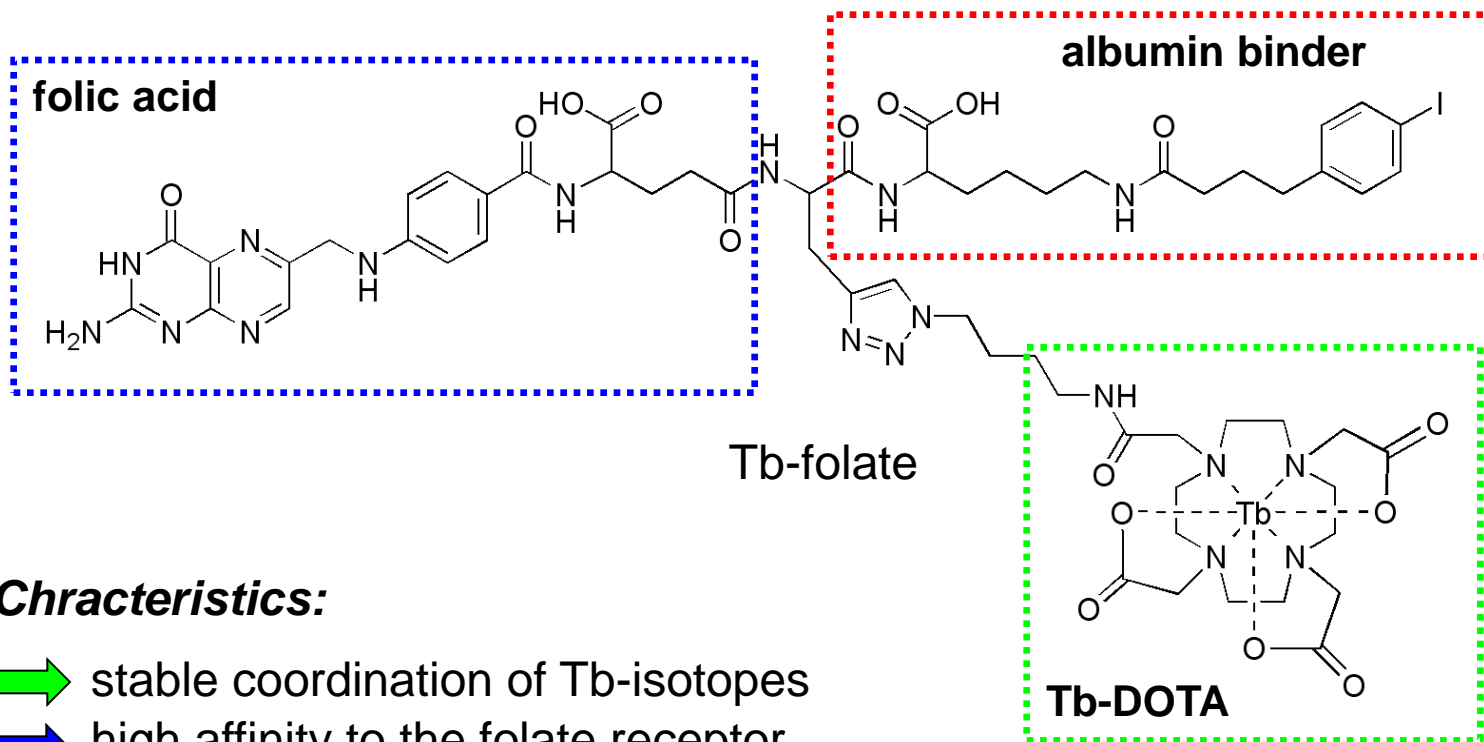
Spallation of tantalum targets followed by resonant laser ionization of Dy precursor and mass separation

⇒  $^{149,152,155}\text{Tb}$  with some oxide sidebands






# Tumor Targeting Agent for Tb-Coordination

## Chemical Structure with 3 Functionalities



### **Characteristics:**

-  stable coordination of Tb-isotopes
-  high affinity to the folate receptor
-  prolonged blood circulation time

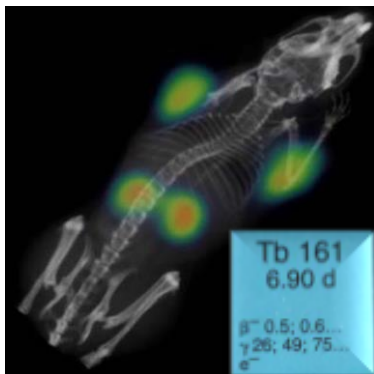


# Terbium: the Swiss Army knife of Nuclear Medicine

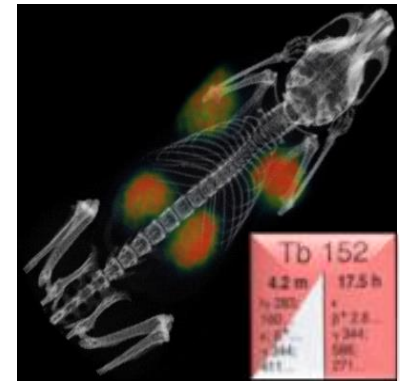
## $^{149}\text{Tb}$ -therapy



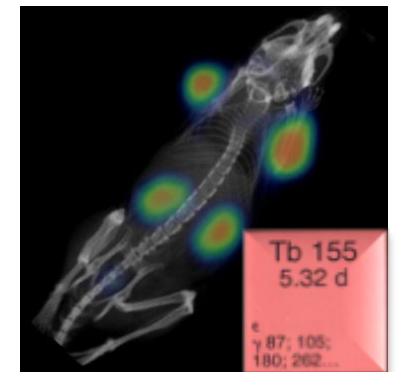
## $^{161}\text{Tb}$ -therapy & SPECT



## $^{152}\text{Tb}$ -PET



## $^{155}\text{Tb}$ -SPECT





# The Biologist

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## TOUCH WOOD

How arboreta can protect the UK's forests

### PHARMACOLOGY

#### RADIOACTIVE REMEDIES

Fighting cancer with rare radioisotopes



### RESEARCH

#### GET INVOLVED

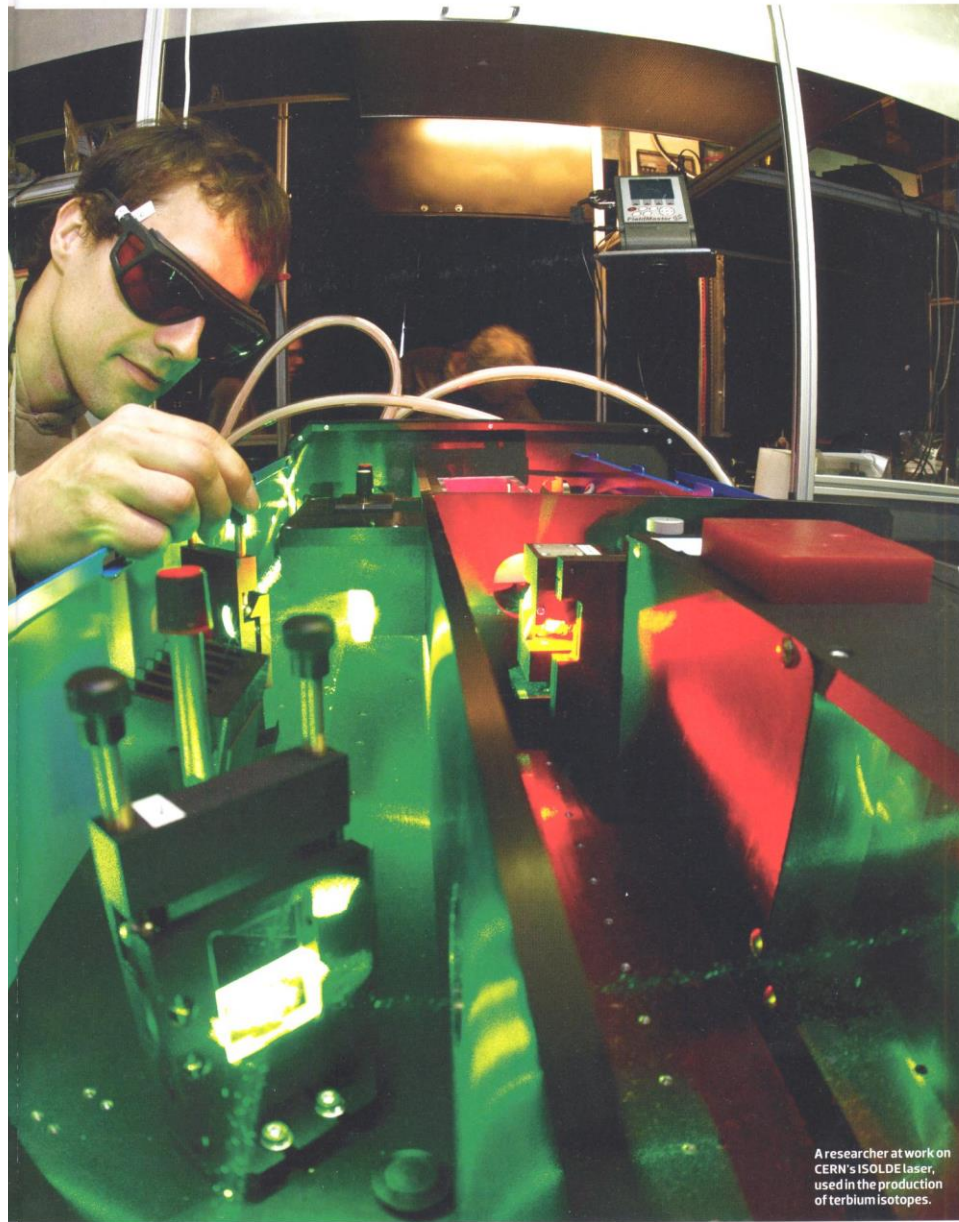
The 10 best citizen science biology projects



### INTERVIEW

#### BRUCE HOOD

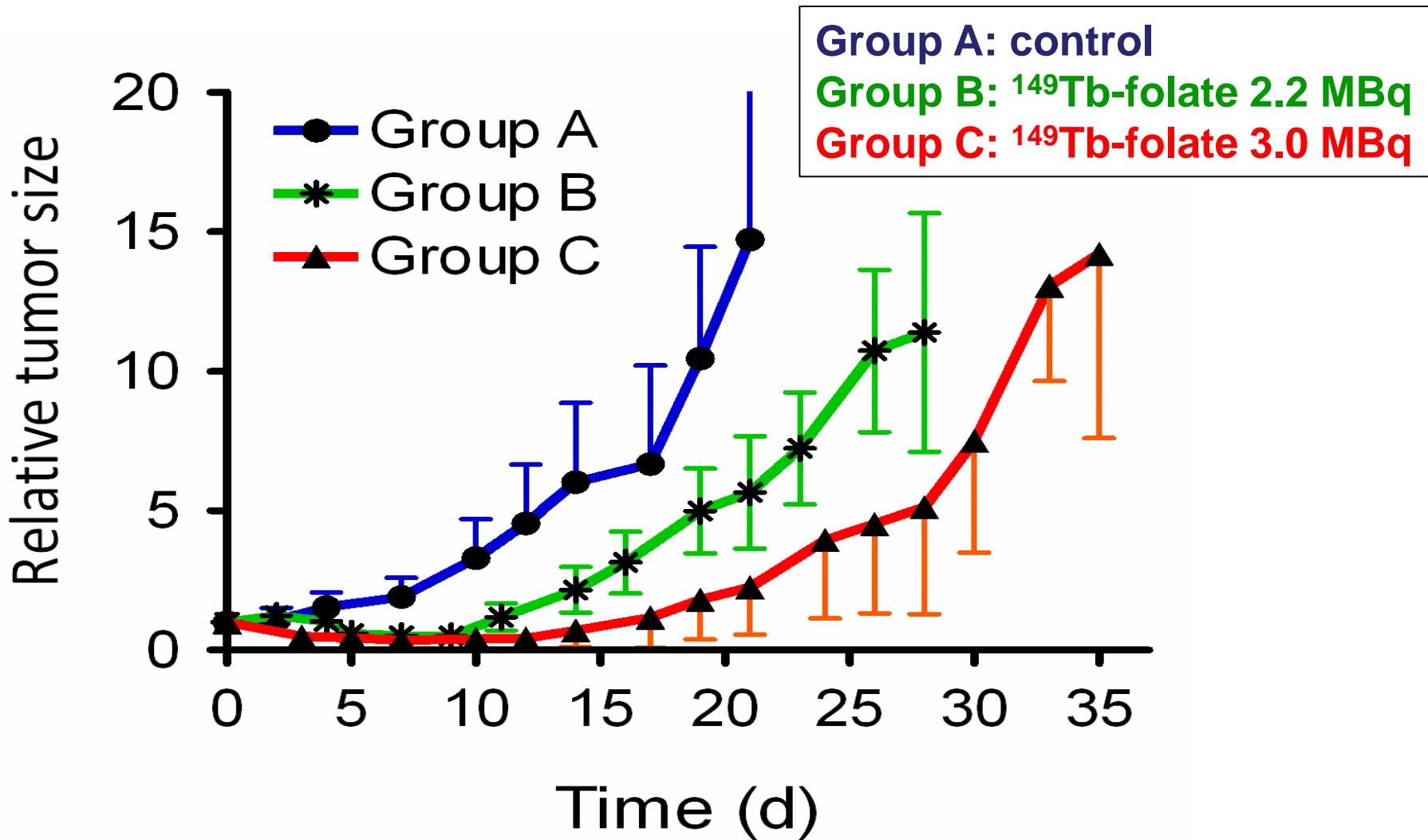
Psychology, neuroscience and our sense of self



A researcher at work on CERN's ISOLDE laser, used in the production of terbium isotopes.

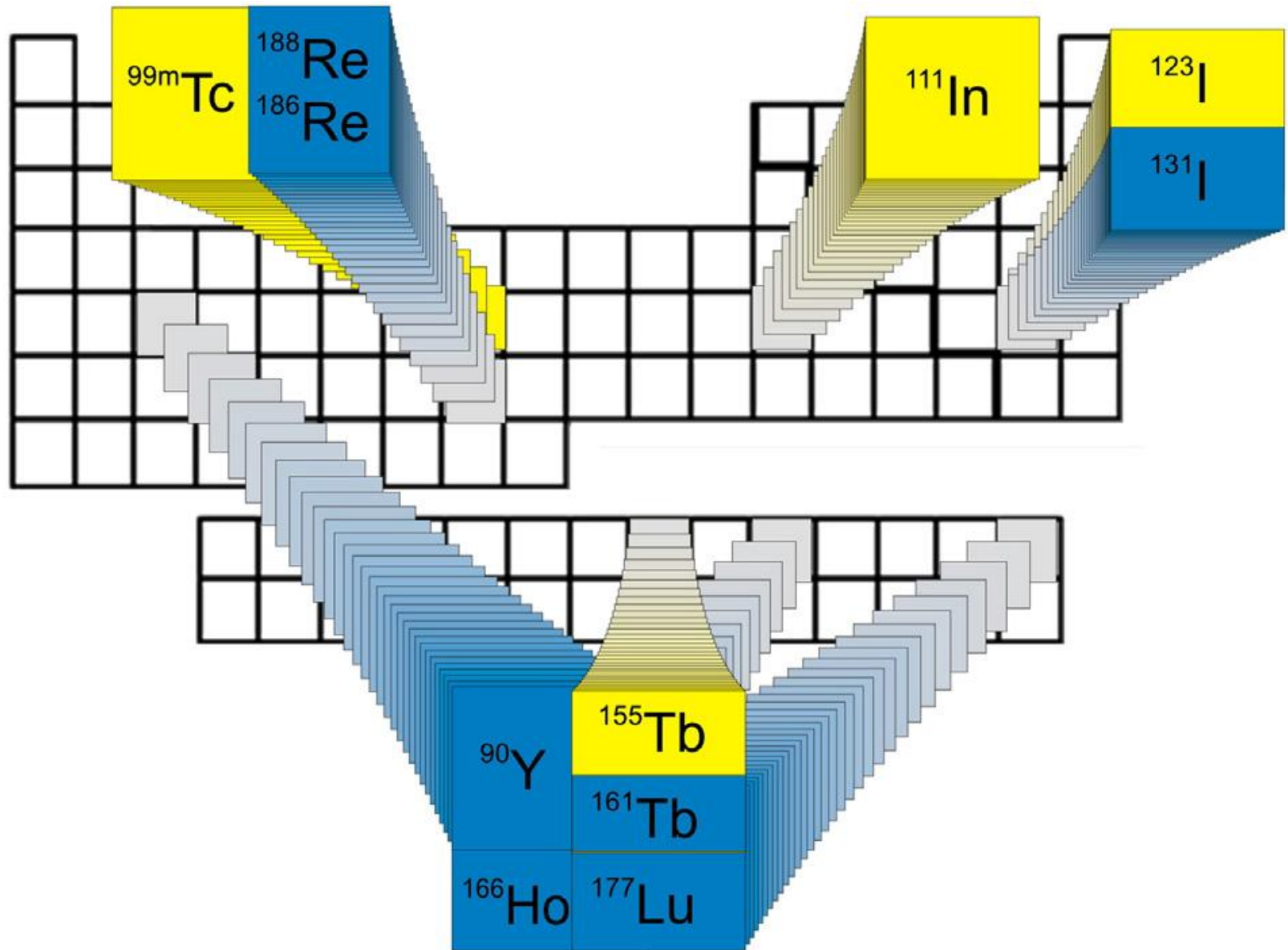
# Terbium-149: alpha-Emitter

## Folate Receptor Targeted $\alpha$ -Radionuclide Therapy

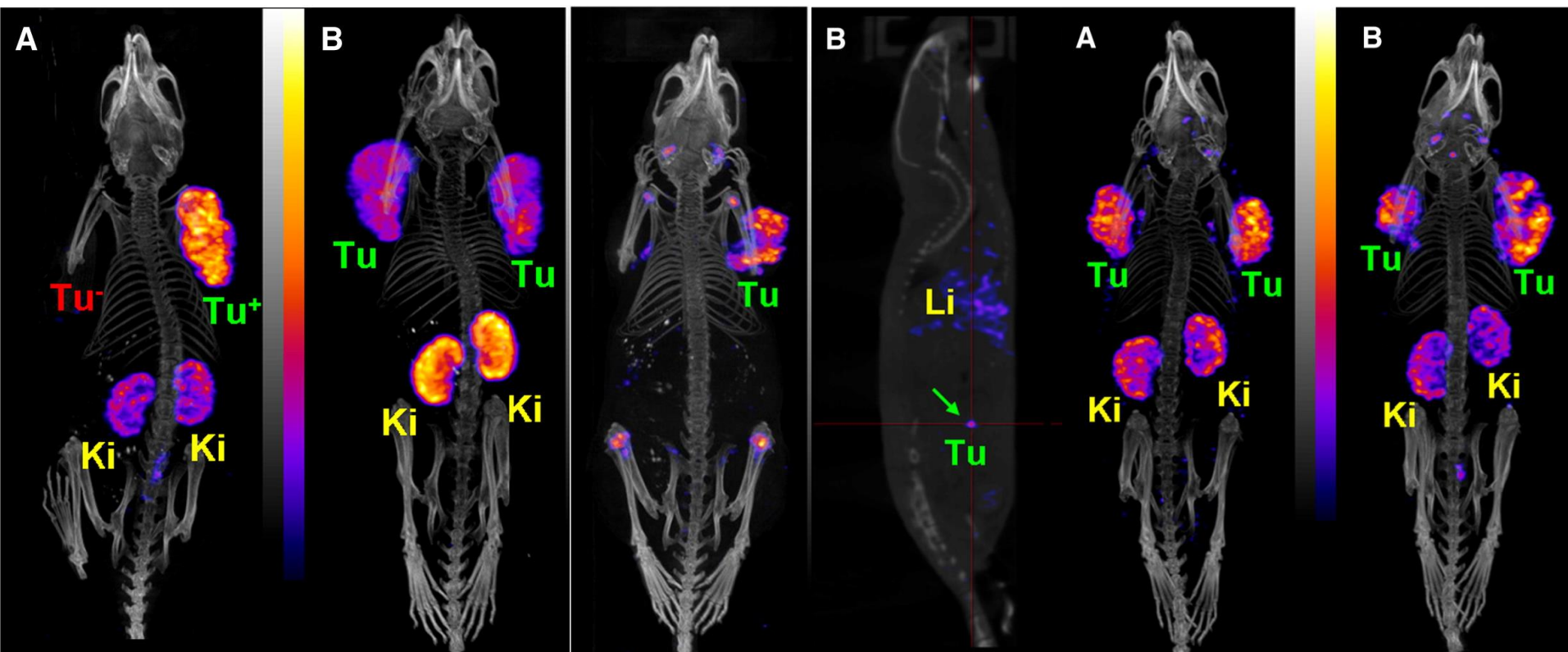




# $^{155}\text{Tb}$ : low-dose SPECT prior to therapy



# *in vivo* validation with peptides, mAbs and vitamins



Peptides  
MD DOTATATE  
monoclonal antibody  
chCE7 chCE7  
folate  
cm09 cm09



# Efficient parallel operation

GPS MAIN  
HRS MAIN CENTRAL MASS  
HRS USER LOW MASS  
HIGH MASS

152Tb

149Tb

155Tb

HRS setup



# $^{140}\text{Nd}/^{140}\text{Pr}$ : an *in vivo* PET generator

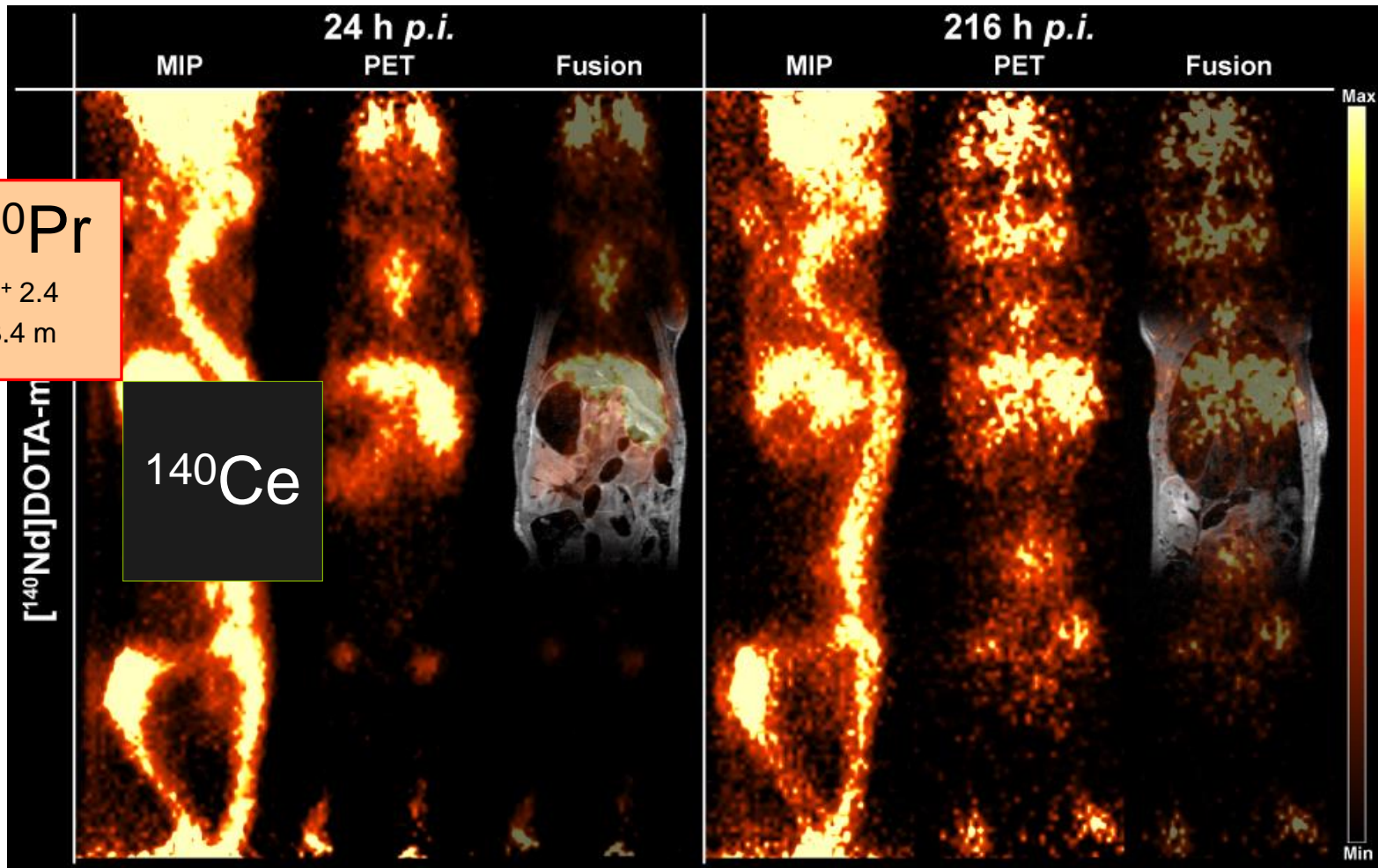
$^{140}\text{Nd}$

$\epsilon$   
3.37 d

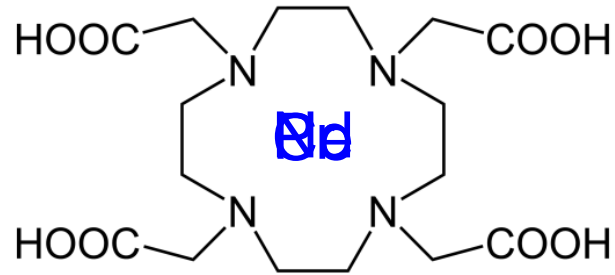
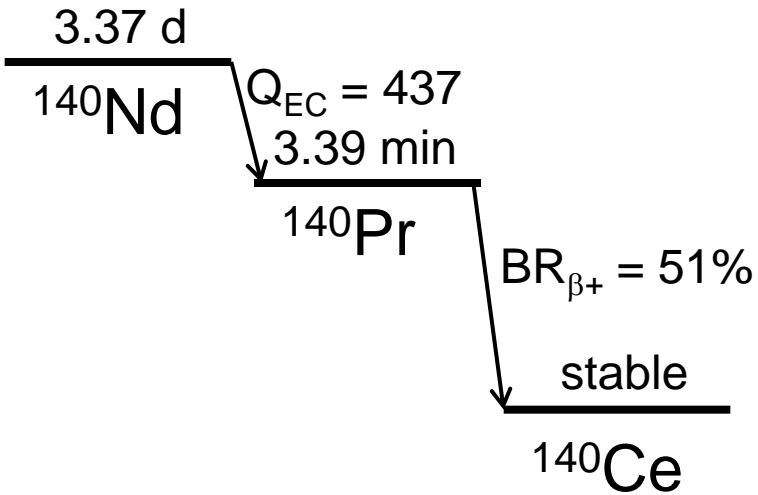
$^{140}\text{Pr}$

$\beta^+$  2.4  
3.4 m

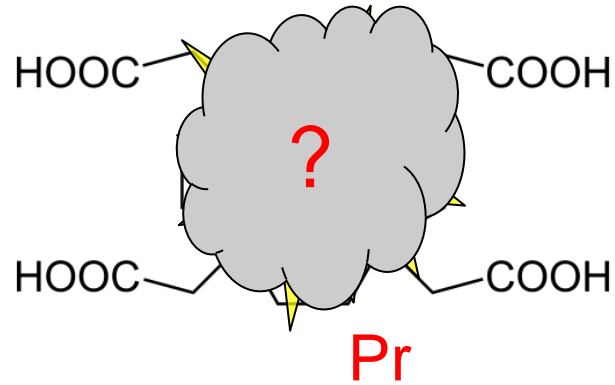
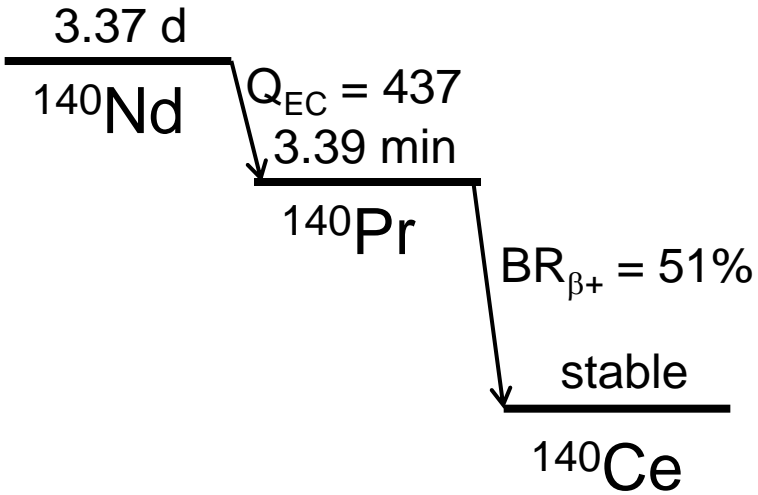
$^{140}\text{Ce}$



# Understanding the Auger release from chelators

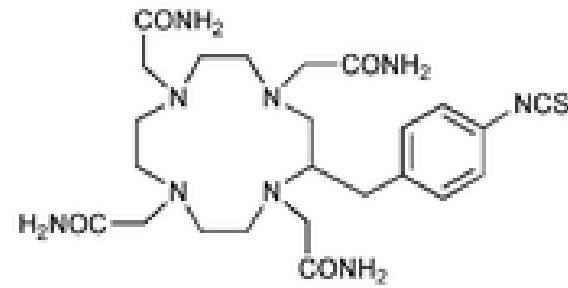
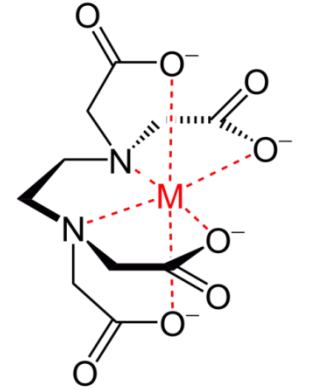
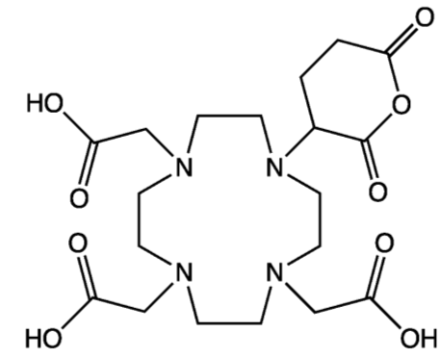
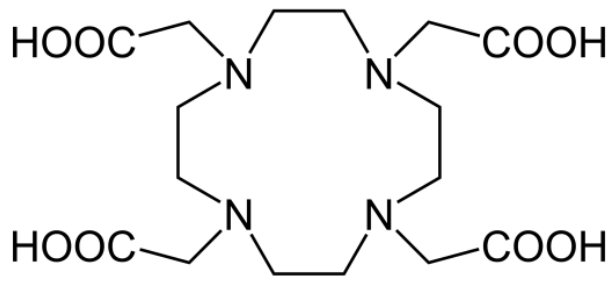
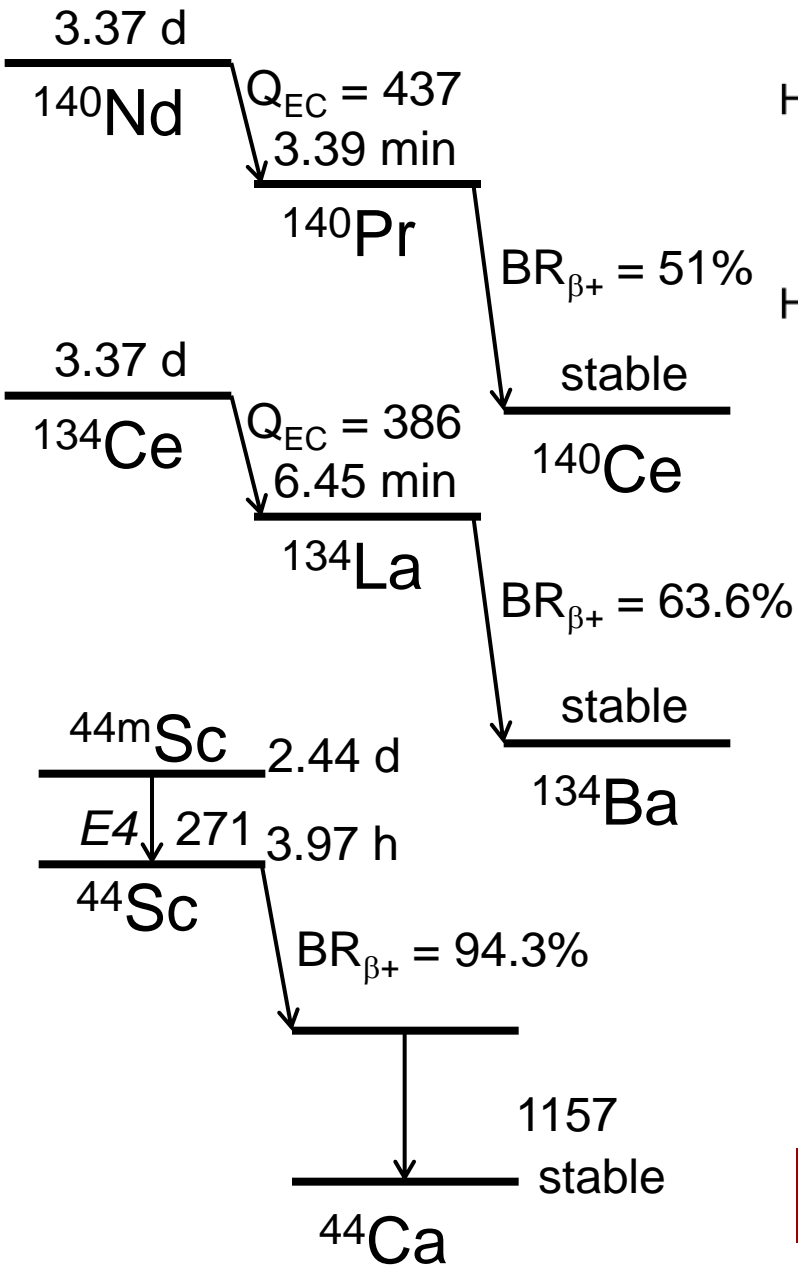


# Understanding the Auger release from chelators





# Understanding the Auger release from chelators



# Theranostic of Invasive Aspergillosis and Echinococcus Multilocularis



New Molecular-Functional Imaging Technologies and Therapeutic Strategies for Theranostic of Invasive Aspergillosis



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PUBLICATIONS

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## Welcome to the MATHIAS project

The MATHIAS project is funded by the European Union in the 7<sup>th</sup> Framework Programme under the theme: HEALTH.2013.12-1 - Development of imaging technologies for therapeutic interventions in rare diseases.

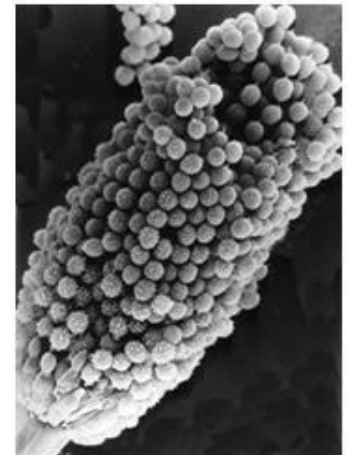
The project started on 1<sup>st</sup> October 2013, the project duration is five years.

## Scope of the project

The development of novel technologies to diagnose and clinically treat invasive *Aspergillus fumigatus* infections is the scope of this research consortium.

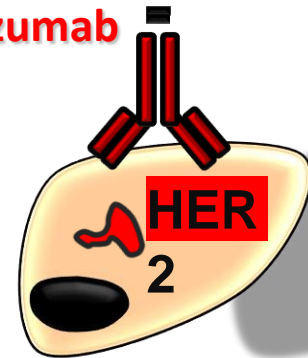
*A. fumigatus* is a ubiquitous mould whose spores are airborne and thus frequently inhaled. Humans with impaired immunity, e.g. those with haematological malignancies or bone marrow transplant recipients, are at a dramatically increased risk of severe, invasive *A. fumigatus* infection known as invasive aspergillosis (IA). IA is a rare disease in Europe but causes tremendous costs to the public health sector.

Currently definitive diagnosis of IA is only obtained at autopsy or relies on invasive biopsy, an extremely unpleasant procedure which is not always applicable in suffering patients. Thus, a convenient, fast and specific diagnosis of IA is not available forcing clinicians to administer antifungal drugs, if a standard antibiotic treatment failed to reduce fever in risk patients. It would be of high financial benefit for clinics and has the potential to increase the survival rates of immuno-compromised patients, if a definitive diagnosis of IA could be obtained early and its response to treatment be monitored. This would allow applying the correct therapy at a dose and duration exactly tailored to patient needs. Equally important is the development of new treatment

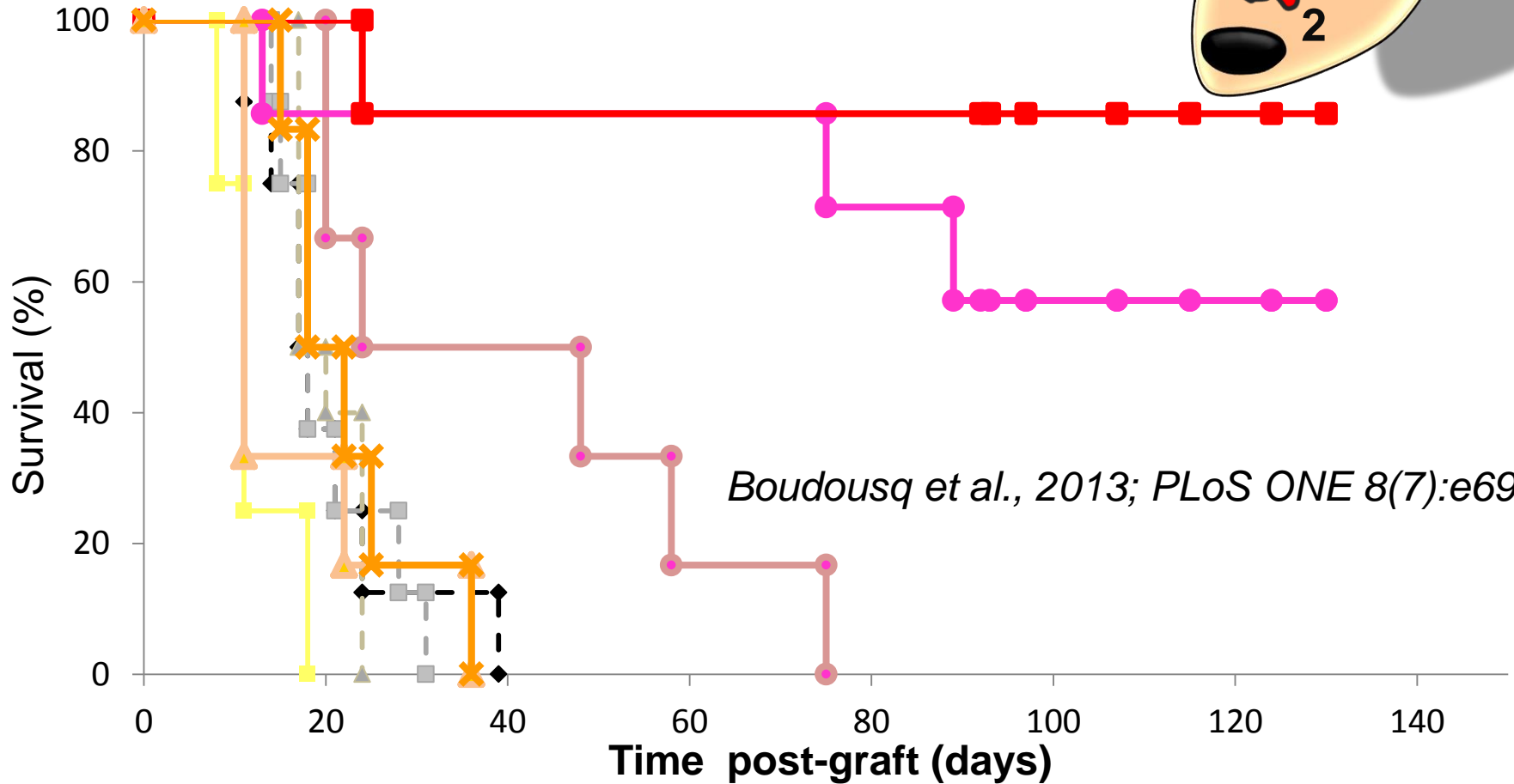


# Survival with anti-HER2 $^{212}\text{Pb}$ -mABS

$^{212}\text{Pb}$ -Trastuzumab

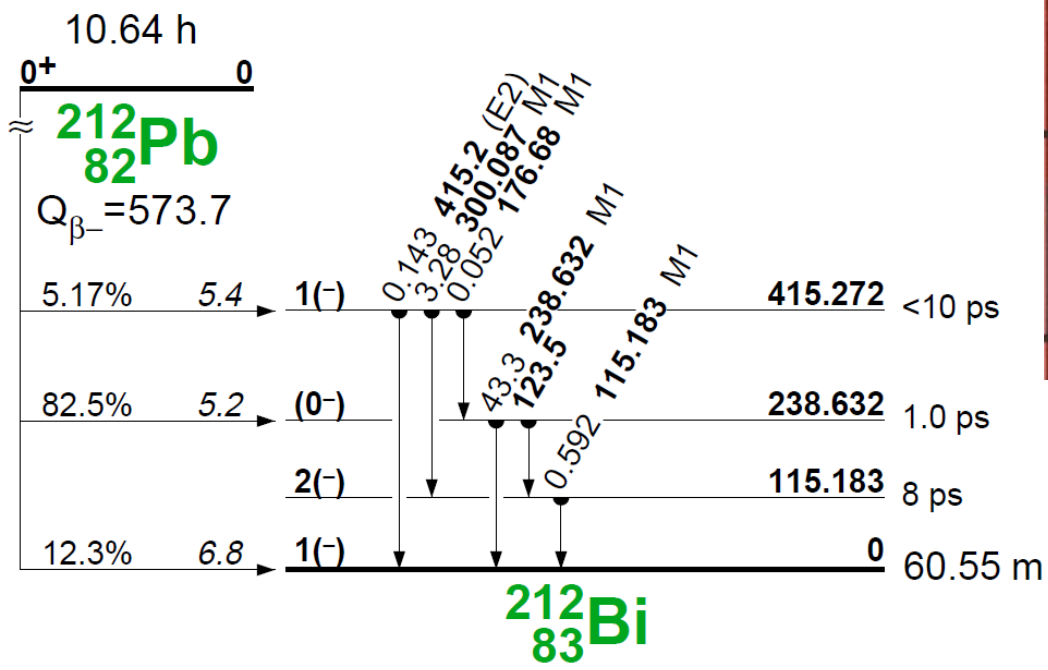
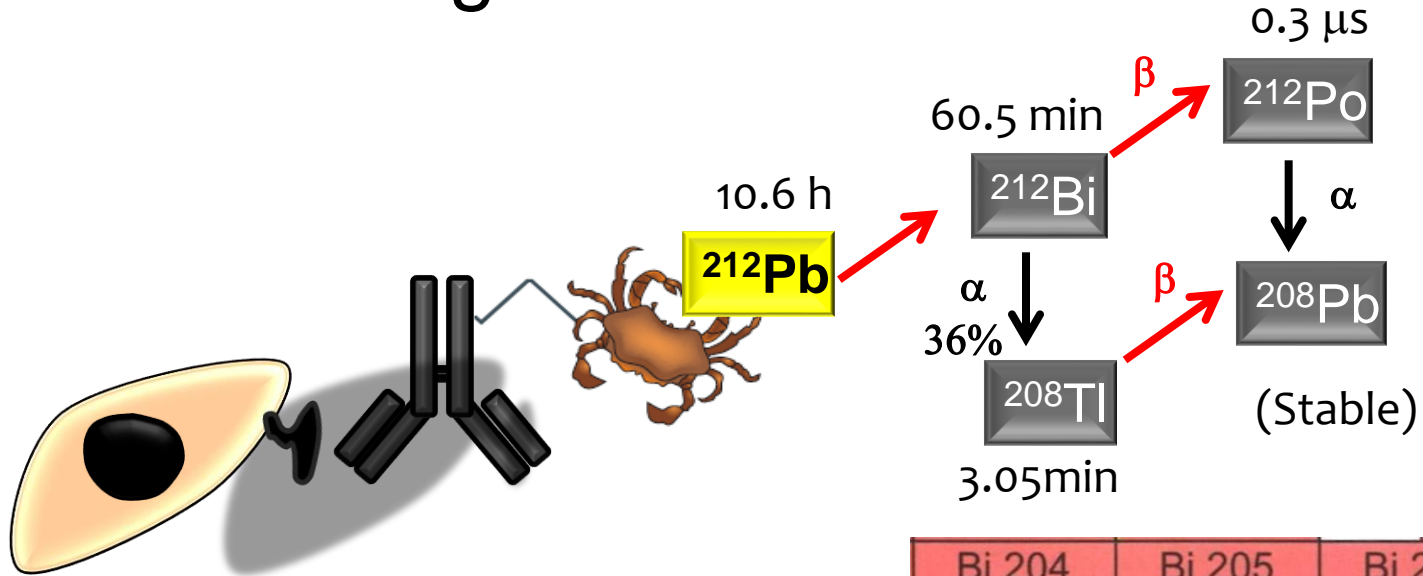


- $^{212}\text{Pb}$ -Trastuzumab (0.37MBq)
- $^{212}\text{Pb}$ -Trastuzumab (0.74MBq)
- $^{212}\text{Pb}$ -Trastuzumab (1.48MBq)





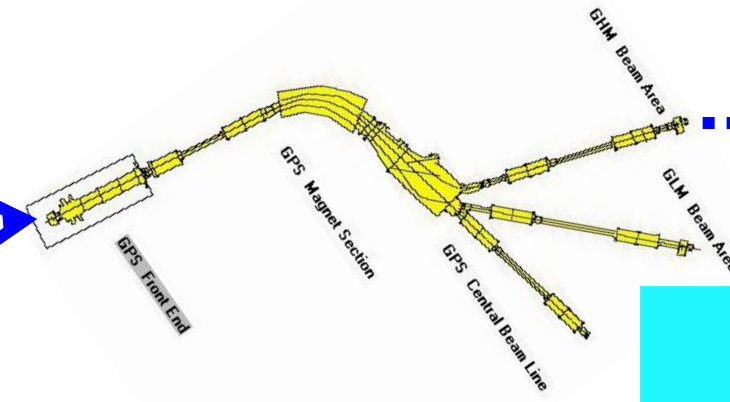
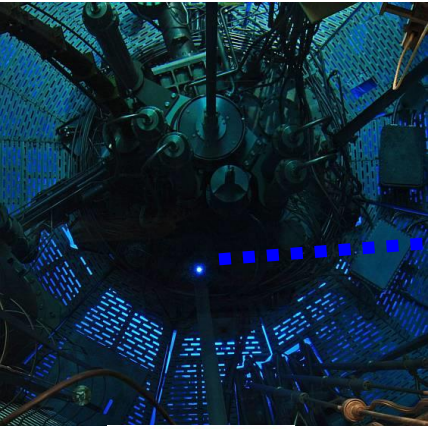
# Auger release of $^{212}\text{Bi}$ ?



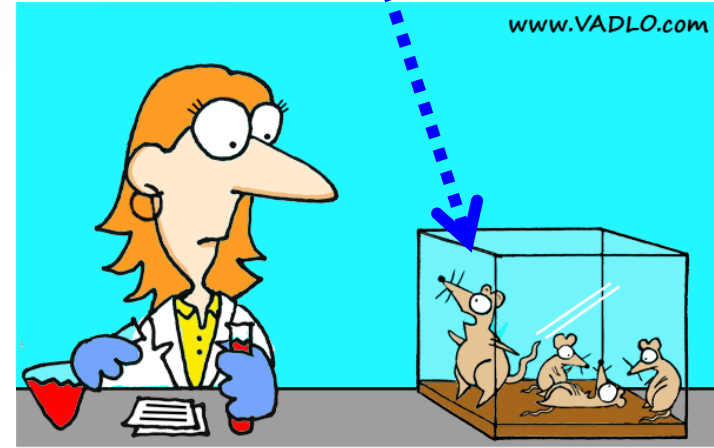
Bi 204 11.22 h ε γ 899, 375 984... g, m	Bi 205 14.91 d ε, β+... γ 1764, 703 988...	Bi 206 6.24 d ε, β+... γ 803, 881, 516 1719, 537...	Bi 207 31.55 a ε, β+... γ 570, 1064 1770...
Pb 203 6.2 s ly 825 820...	Pb 204 51.9 h 67.2 m 1.4 ly 899, 912 375... σ 0.68	Pb 205 1.5·10 <sup>7</sup> a ε no γ σ ~5	Pb 206 24.1 σ 0.027
Tl 202	Tl 203	Tl 204	Tl 205

45.1% conversion electrons  
 ⇒ Auger cascades  
 ⇒ partial delabeling?

# $^{169}\text{Er}$ (beta<sup>-</sup>) vs. $^{165}\text{Er}$ (Auger) radiobiology



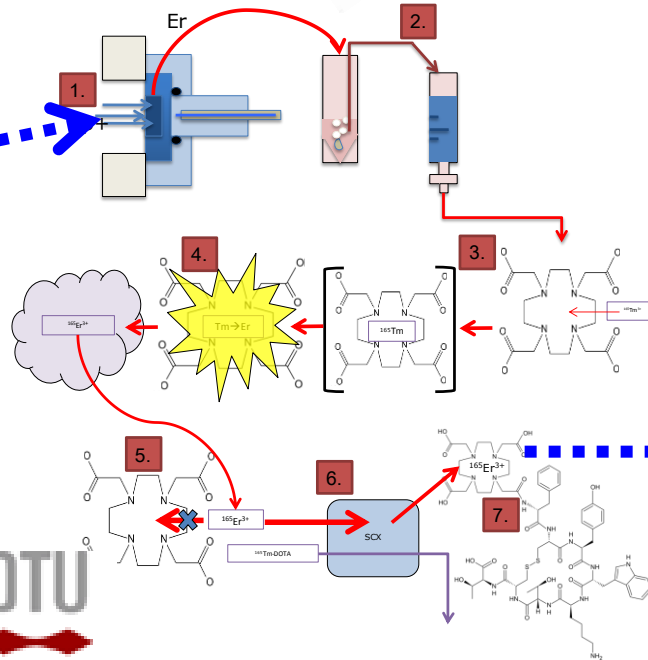
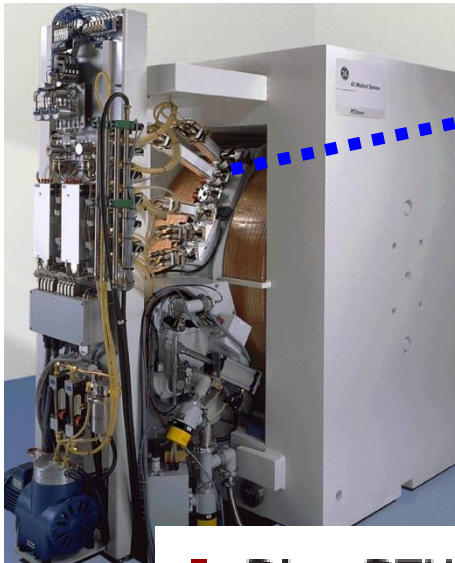
Er 169  
9.40 d  
β<sup>-</sup> 0.3...  
γ (110...)  
e<sup>-</sup>



"Hey, my pup is sick. Are you a real doctor or just PhD?"

**ILL**  
NEUTRONS  
FOR SCIENCE

**ISOLDE**



Er 165  
10.3 h  
ε  
no γ

**Risø DTU**

# Beam request

	Shifts
A) $^{149}\text{Tb}$ -cm09 dose escalation study	8
B) $^{149}\text{Tb}$ -PRRT pilot study	3
C) $^{152}\text{Tb}/^{155}\text{Tb}$ companion diagnostics	incl.
D) $^{140}\text{Nd}/^{134}\text{Ce}$ chelator optimization	6
$^{140}\text{Nd}/^{134}\text{Ce}$ immuno-PET	6
E) exploratory experiments (Pb, Bi,...)	3
F) mass separation of $^{169}\text{Er}/^{168}\text{Er}$	6 (offline)
Total	26 + 6
Available	-10
<b>New request</b>	<b>16 + 6 (offline)</b>





# Off-line separation of $^{169}\text{Er}$

- Therapy study with 6 mice, 70 MBq  $^{169}\text{Er}$ -DOTATOC per mouse
- factor 2 for decay losses and labeling yield
- 850 MBq needed (1E15 atoms collected)
- $\text{LA}[^{169}\text{Er}] = 5 \text{ MBq} \Rightarrow$  up to 500 MBq can be handled in “class C” bat. 170  
 $\Rightarrow$  collect and ship two separate samples of 425 MBq each  
 $\Rightarrow$  ship as UN2910 (“excepted package”)
- implantation current  $\sim 1 \text{ nA}$  of  $^{169}\text{Er}$  for 24 h (3 shifts per sample)
- total current  $\sim 1 \text{ }\mu\text{A}$  Er ( $^{168}\text{Er} + ^{169}\text{Er}$ ) [cf.  $^7\text{Be}$  collections]
- ionization potential 6.11 eV  $>$   $\sim 0.5\%$  thermal ionization efficiency
- RILIS efficiency  $> 5\%$ ? (to be tested!)
- ship  $\sim 20 \text{ GBq}$  from ILL (2% of A2 limit  $>$  “type A” transport)
- Note:  $^{169}\text{Er}$  is a low-energy beta emitter, with very low emission of  $\gamma$  rays:  
0.16% 8 keV, 0.01% 110 keV  
 $\Rightarrow$  very low dose rate:  $< 1 \text{ }\mu\text{Gy/h}$  at 1 m from unshielded 1 GBq sample.

# Indirect production of $^{203}\text{Pb}$ , $^{205}\text{Bi}$

<b>Fr 206</b> 0.7 s   15.9 s   15.9 s $\alpha$ 6.792   $\alpha$ 6.792 $\gamma$ 575   $\gamma$ 829... $\alpha$ 6.930   $\alpha \rightarrow m_2$ $\alpha \rightarrow m_2$	<b>Fr 207</b> 14.8 s $\alpha$ 6.767 $\epsilon$	<b>Fr 208</b> 58.6 s $\alpha$ 6.636 $\epsilon$ $\gamma$ 636, 779 325...	<b>Fr 209</b> 50.0 s $\alpha$ 6.648 $\epsilon$	<b>Fr 210</b> 3.18 m $\alpha$ 6.543 $\epsilon$ $\gamma$ 644, 817...	<b>Fr 211</b> 3.10 m $\alpha$ 6.535 $\epsilon$ $\gamma$ 540, 918 281...	<b>Fr 212</b> 20.0 m $\epsilon$ $\alpha$ 6.262, 6.384 6.408, 6.340... $\gamma$ 1274, 227, 1185...	<b>Fr 213</b> 34.6 s $\alpha$ 6.775 $\epsilon$
<b>Rn 205</b> $t_{1/2} > 10$ s   2.83 m $\epsilon$ $\alpha$ 6.263... $\gamma$ 265, 465 620... $\gamma$ 657	<b>Rn 206</b> 5.67 m $\alpha$ 6.260... $\epsilon$ $\gamma$ 498, 325 387...	<b>Rn 207</b> 9.3 m $\epsilon$ , $\alpha$ 6.133... $\beta^+$ $\gamma$ 345, 747... g	<b>Rn 208</b> 24.4 m $\alpha$ 6.138... $\epsilon$ $\gamma$ 427, 251, 350 287, 952...	<b>Rn 209</b> 28.5 m $\epsilon$ , $\alpha$ 6.039 $\beta^+$ 2.2, 2.6 $\gamma$ 408, 746, 338 689...	<b>Rn 210</b> 2.4 h $\alpha$ 6.040... $\epsilon$ $\gamma$ 458, (571, 649 73...)	<b>Rn 211</b> 14.6 h $\epsilon$ $\alpha$ 5.783, 5.851... $\gamma$ 674, 1363 678..., g	<b>Rn 212</b> 24 m $\alpha$ 6.264... $\gamma$
<b>At 204</b> 9.2 m $\epsilon$ , $\beta^+$ $\alpha$ 5.951 $\gamma$ 684, 516 426...	<b>At 205</b> 26.2 m $\epsilon$ , $\alpha$ 5.902 $\beta^+$ $\gamma$ 719, 669 629..., g	<b>At 206</b> 29.4 m $\epsilon$ , $\beta^+$ 3.1, 3.5... $\alpha$ 5.703 $\gamma$ 701, 477 396...	<b>At 207</b> 1.8 h $\epsilon$ , $\beta^+$ $\alpha$ 5.759 $\gamma$ 815, 588 301..., g	<b>At 208</b> 1.63 h $\epsilon$ $\alpha$ 5.640... $\gamma$ 686, 660 177...	<b>At 209</b> 5.4 h $\epsilon$ $\alpha$ 5.647 $\gamma$ 545, 782 790...	<b>At 210</b> 8.3 h $\epsilon$ , $\alpha$ 5.524 5.442, 5.361... $\gamma$ 1181, 245 1483...	<b>At 211</b> 7.22 h $\epsilon$ $\alpha$ 5.867... $\gamma$ (687...) g
<b>Po 203</b> 45 s   36 m $\epsilon$ , $\beta^+$ $\alpha$ 5.384 $\gamma$ 909 1091, 894 215... $\gamma$ 641...	<b>Po 204</b> 3.53 h $\epsilon$ $\alpha$ 5.377 $\gamma$ 884, 270 1016...	<b>Po 205</b> 1.66 h $\epsilon$ , $\beta^+$ ... $\alpha$ 5.22, $\alpha \rightarrow g$ $\gamma$ 872, 1001 850, 837...	<b>Po 206</b> 8.8 d $\epsilon$ , $\alpha$ 5.2233 $\gamma$ 1032, 511 286, 807... $e^-$ , g	<b>Po 207</b> 2.8 s   5.34 h $\epsilon$ , $\beta^+$ ... $\alpha$ 5.116 $\gamma$ 992, 743 $\gamma$ 815, 268 912... 301   g	<b>Po 208</b> 2.898 a $\alpha$ 5.1152... $\epsilon$ $\gamma$ (292, 571...) g	<b>Po 209</b> 102 a $\alpha$ 4.881... $\epsilon$ $\gamma$ (895, 261 263...)	<b>Po 210</b> 138.38 d $\alpha$ 5.30438... $\gamma$ (803) $\sigma < 0.0005 + < 0.030$ $\sigma_{n,\alpha} 0.002$ $\sigma_f < 0.1$
<b>Bi 202</b> 1.72 h $\epsilon$ , $\beta^+$ ... $\gamma$ 961, 422 657... g	<b>Bi 203</b> 11.76 h $\epsilon$ , $\beta^+$ 1.4... $\gamma$ 820, 825, 897 1848... g, m	<b>Bi 204</b> 11.22 h $\epsilon$ $\gamma$ 899, 375 984... g, m	<b>Bi 205</b> 14.91 d $\epsilon$ , $\beta^+$ ... $\gamma$ 1764, 703 988...	<b>Bi 206</b> 6.24 d $\epsilon$ , $\beta^+$ ... $\gamma$ 803, 881, 516 1719, 537...	<b>Bi 207</b> 31.55 a $\epsilon$ , $\beta^+$ ... $\gamma$ 570, 1064 1770...	<b>Bi 208</b> 3.68 $\cdot 10^5$ a $\epsilon$ $\gamma$ 2615	<b>Bi 209</b> 100 1.9 $\cdot 10^{19}$ a $\alpha$ 3.077... $\sigma 0.011 + 0.023$ $\sigma_{n,\alpha} < 3E-7$
<b>Pb 201</b> 61 s   9.4 h $\epsilon$ , $\beta^+$ $\gamma$ 331, 361 946... $\gamma$ 629	<b>Pb 202</b> 3.62 h   5.25 $\cdot 10^4$ a $\gamma$ 961, 422 787... $\epsilon$ $\gamma$ 490, 460 390... $\epsilon$ no $\gamma$	<b>Pb 203</b> 6.2 s   51.9 h $\gamma$ 825 820... $\epsilon$ $\gamma$ 279 401...	<b>Pb 204</b> 67.2 m   1.4 $\gamma$ 899, 912 375... $\sigma 0.68$	<b>Pb 205</b> 1.5 $\cdot 10^7$ a $\epsilon$ no $\gamma$ $\sigma \sim 5$	<b>Pb 206</b> 24.1 $\sigma 0.027$	<b>Pb 207</b> 22.1 $\sigma 0.61$	<b>Pb 208</b> 52.4 $\sigma 0.00023$ $\sigma_{n,\alpha} < 8E-6$
<b>Tl 200</b>	<b>Tl 201</b>	<b>Tl 202</b>	<b>Tl 203</b>	<b>Tl 204</b>	<b>Tl 205</b>	<b>Tl 206</b>	<b>Tl 207</b>

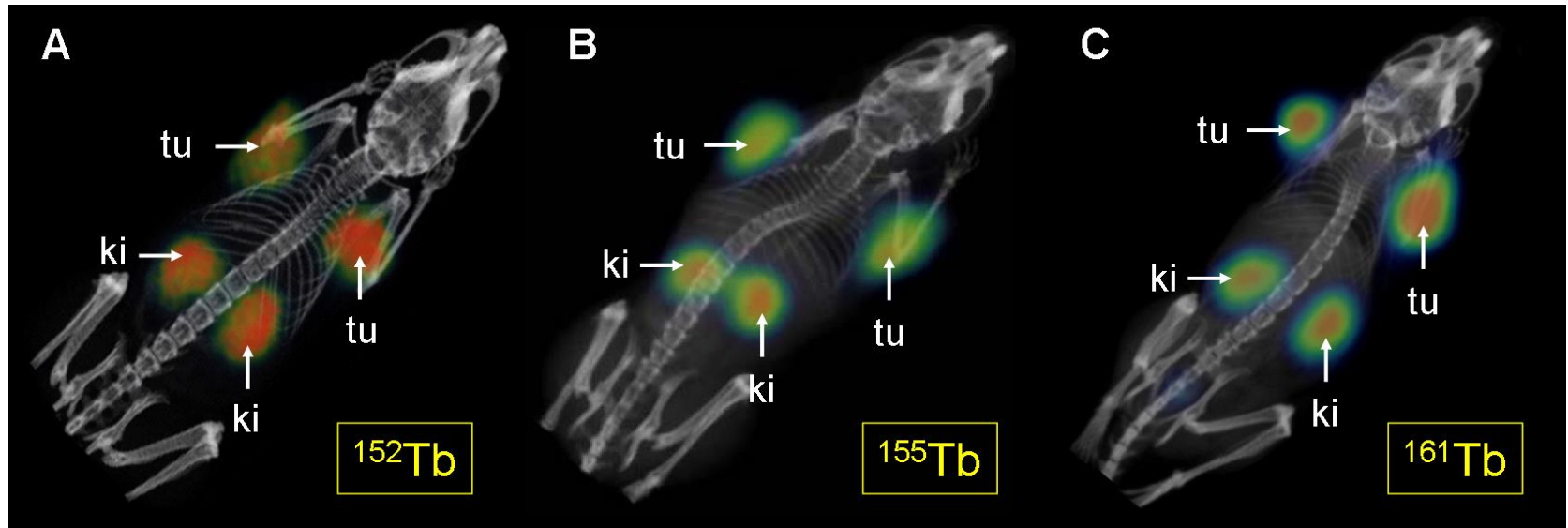
# Imaging Studies Using PET and SPECT

## KB Tumor-Bearing Nude Mice

PET

SPECT

SPECT



$^{152}\text{Tb}$ -folate: 9 MBq  
 Scan Start: 24 h p.i.  
 Scan Time: 4 h

$^{155}\text{Tb}$ -folate: 4 MBq  
 Scan Start: 24 h p.i.  
 Scan Time: 1 h

$^{161}\text{Tb}$ -folate: 30 MBq  
 Scan Start: 24 h p.i.  
 Scan Time: 20 min





# Arsenic: another theranostic multiplet

<b>Se 72</b> 8.5 d ε no β <sup>+</sup> γ 46	<b>Se 73</b> 39 m / 7.1 h I <sub>γ</sub> (25), e <sup>-</sup> β <sup>+</sup> 1.3 1.7... γ 67, 254 84, 393... 67...	<b>Se 74</b> 0.89 σ 50	<b>Se 75</b> 119.64 d ε γ 265, 136, 280 121, 401... σ 330	<b>Se 76</b> 9.37 σ 22 + 63	<b>Se 77</b> 17.5 s / 7.63 I <sub>γ</sub> 162 σ 41.5	<b>Se 78</b> 23.77 σ 0.38 + 0.05	<b>Se 79</b> 3.9 m / 3.27·10 <sup>5</sup> a I <sub>γ</sub> 96, e <sup>-</sup> β <sup>-</sup> 0.2... no γ g
<b>As 71</b> 65.28 h ε β <sup>+</sup> 0.8... γ 175, 1095...	<b>As 72</b> 26.0 h β <sup>+</sup> 2.5, 3.3... γ 834, 630...	<b>As 73</b> 80.3 d ε no β <sup>+</sup> γ 53... e <sup>-</sup>	<b>As 74</b> 17.77 d ε β <sup>+</sup> 0.9, 1.5... β <sup>-</sup> 1.4... γ 596, 635...	<b>As 75</b> 100 σ 4.0	<b>As 76</b> 26.4 h β <sup>-</sup> 3.0 γ 559, 657 1216...	<b>As 77</b> 38.8 h β <sup>-</sup> 0.7... γ 239, 521 250... g	<b>As 78</b> 1.5 h β <sup>-</sup> 4.4... γ 614, 695 1309...
<b>Ge 70</b> 20.57 σ 3.0	<b>Ge 71</b> 11.43 d ε no γ	<b>Ge 72</b> 27.45 σ 0.9	<b>Ge 73</b> 7.75 σ 15	<b>Ge 74</b> 36.50 σ 0.14 + 0.28	<b>Ge 75</b> 47 s / 83 m I <sub>γ</sub> 140... e <sup>-</sup> β <sup>-</sup> ... γ (280...)	<b>Ge 76</b> 7.73 1.5·10 <sup>21</sup> a 2β <sup>-</sup> σ 0.09 + 0.06	<b>Ge 77</b> 53 s / 11.3 h β <sup>-</sup> 2.9... γ 216... I <sub>γ</sub> 160 β <sup>-</sup> 2.2... γ 264, 211 216, 416...

**<sup>71</sup>As:**

low-energy β<sup>+</sup> emitter for  
high-resolution PET ?

**<sup>74</sup>As:**

long-lived β<sup>+</sup> emitter for  
longitudinal PET studies

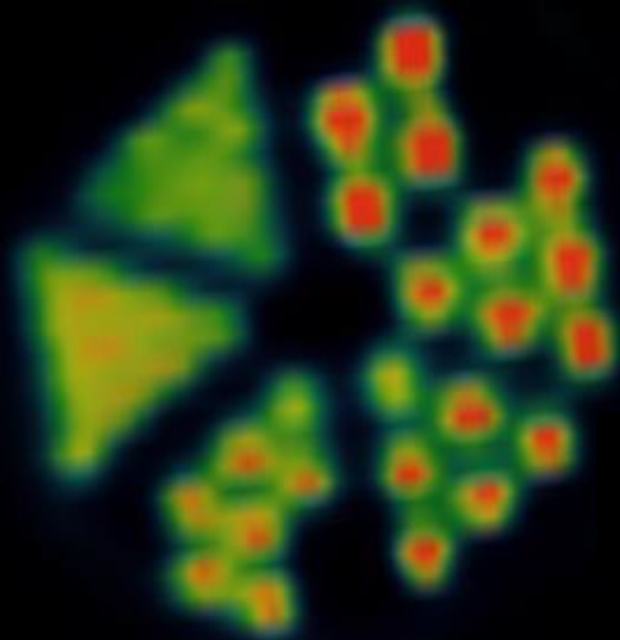
**<sup>77</sup>As:**

reactor-produced β<sup>-</sup>  
emitter for therapy

**<sup>72</sup>As:**

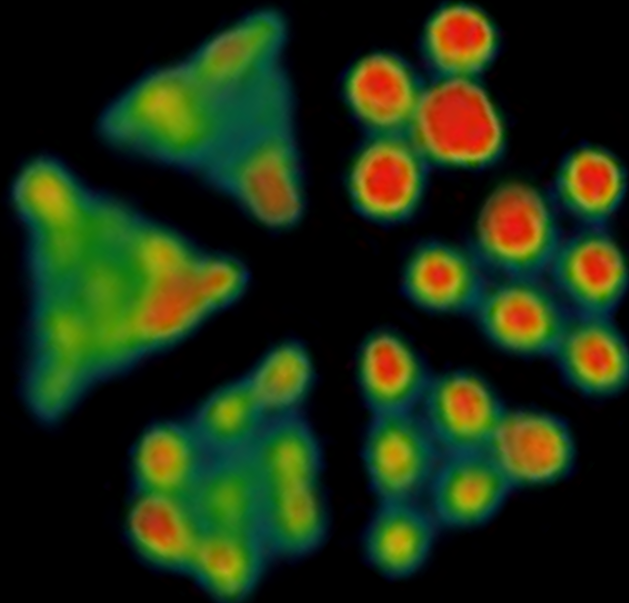
generator-produced  
β<sup>+</sup> emitter for PET

# Excellent resolution with Derenzo phantom



$^{18}\text{F}$

$E_{\beta^+} = 0.25 \text{ MeV}$



$^{71}\text{As}$

$E_{\beta^+} = 0.35 \text{ MeV}$