

# Nuclear-reaction theory as a research tool for innovative radioisotope production in nuclear medicine.

Canton L. INFN - Sezione di Padova, Italy

Projects: REMIX, METRICS CS5 (Interdisciplinary); NUCSYS CS4

Collaboration: LNL, PD, PV, MI, FE, Arronax (Nantes), Ospedale Sacro Cuore Don Calabria (Negrar, Verona), IOV



# Ricordo di Gianni Fiorentini

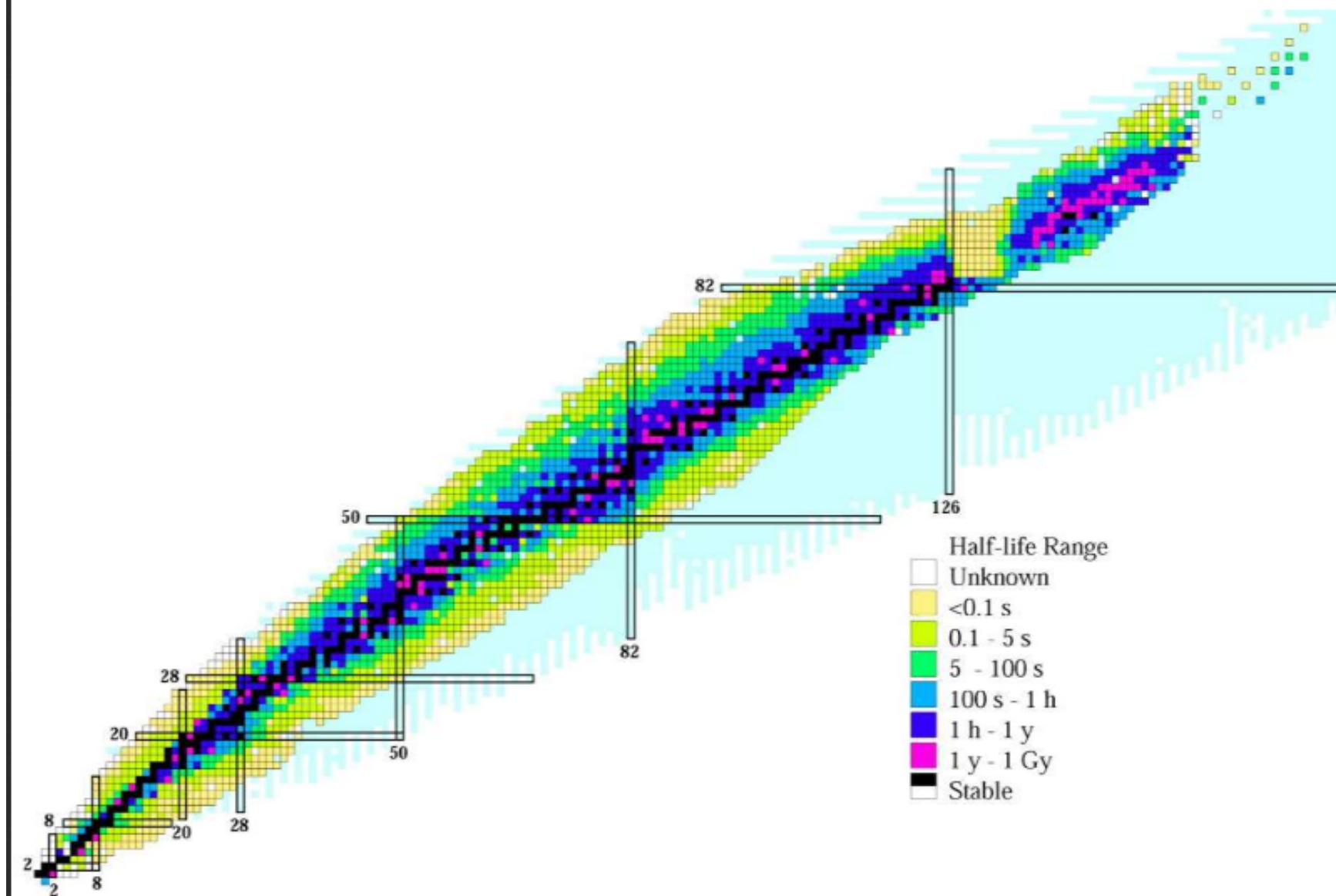
22 febbraio 1948 – 18 giugno 2022



**Come direttore di Laboratorio LNL,  
Gianni ha avuto un ruolo fondamentale e cruciale, fra le moltissime altre cose,  
nel portare la ricerca sui radiofarmaci nei laboratori LNL, e in particolare è la  
persona che mi ha incoraggiato ad impegnarmi in questa linea di ricerca.**

# Introduction to radionuclides for medicine

## Nuclear physicist perspective



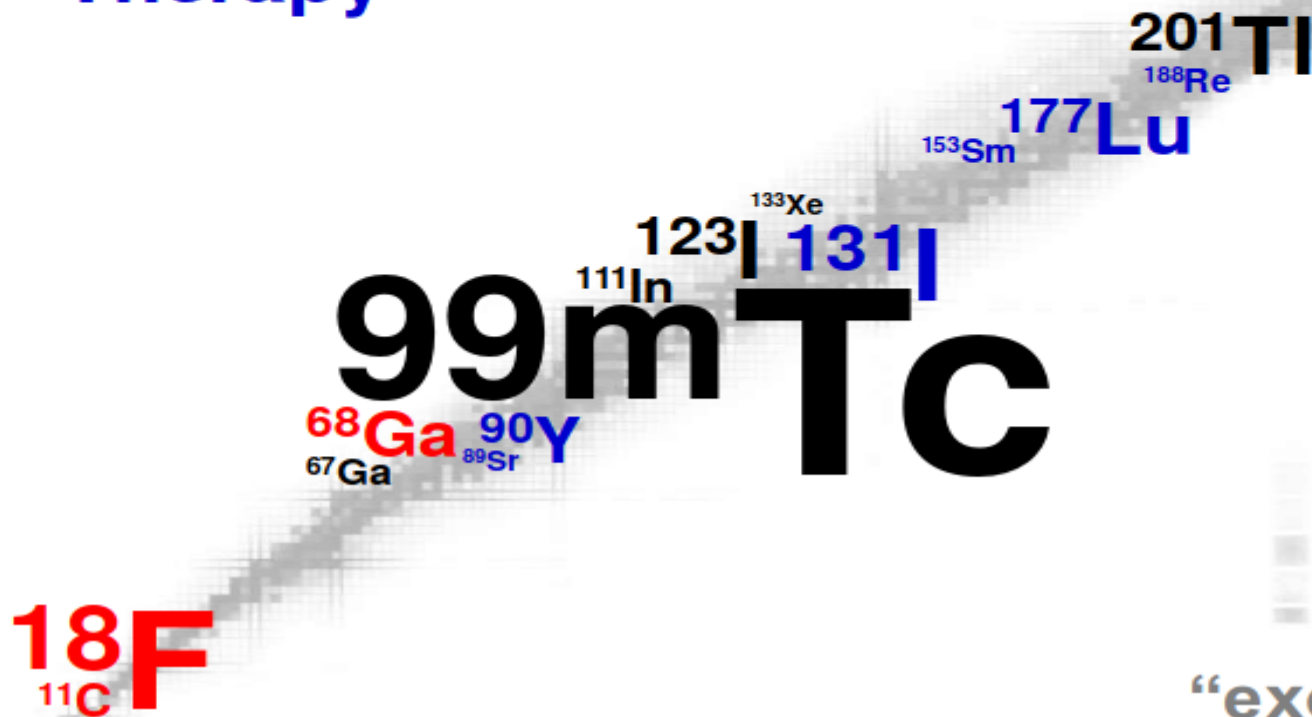
# Introduction to radiotargeted therapy

## Nuclear medicine perspective

**SPECT**

**PET**

**Therapy**

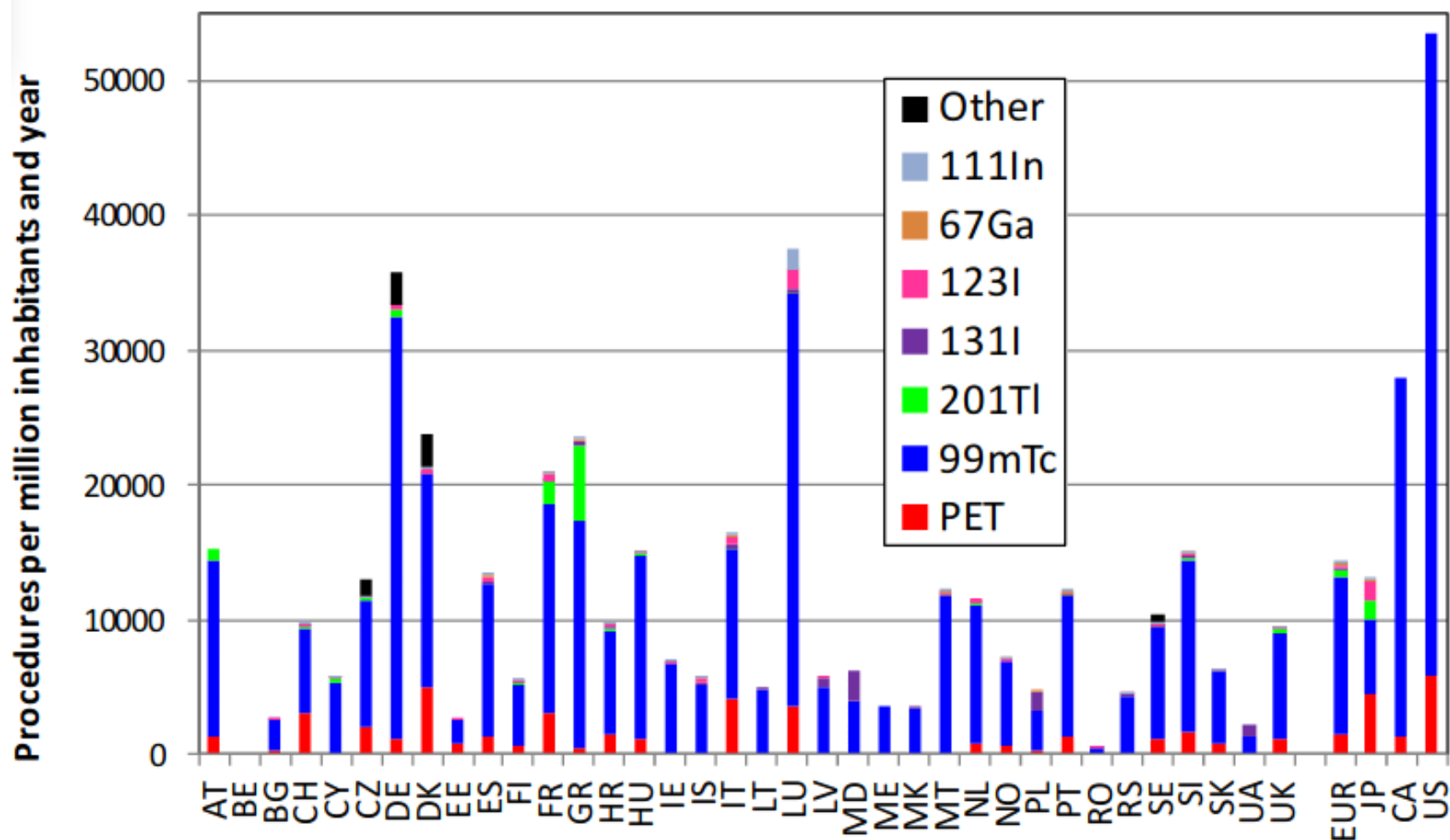


“exotic” isotopes



# Introduction to radionuclides for medicine

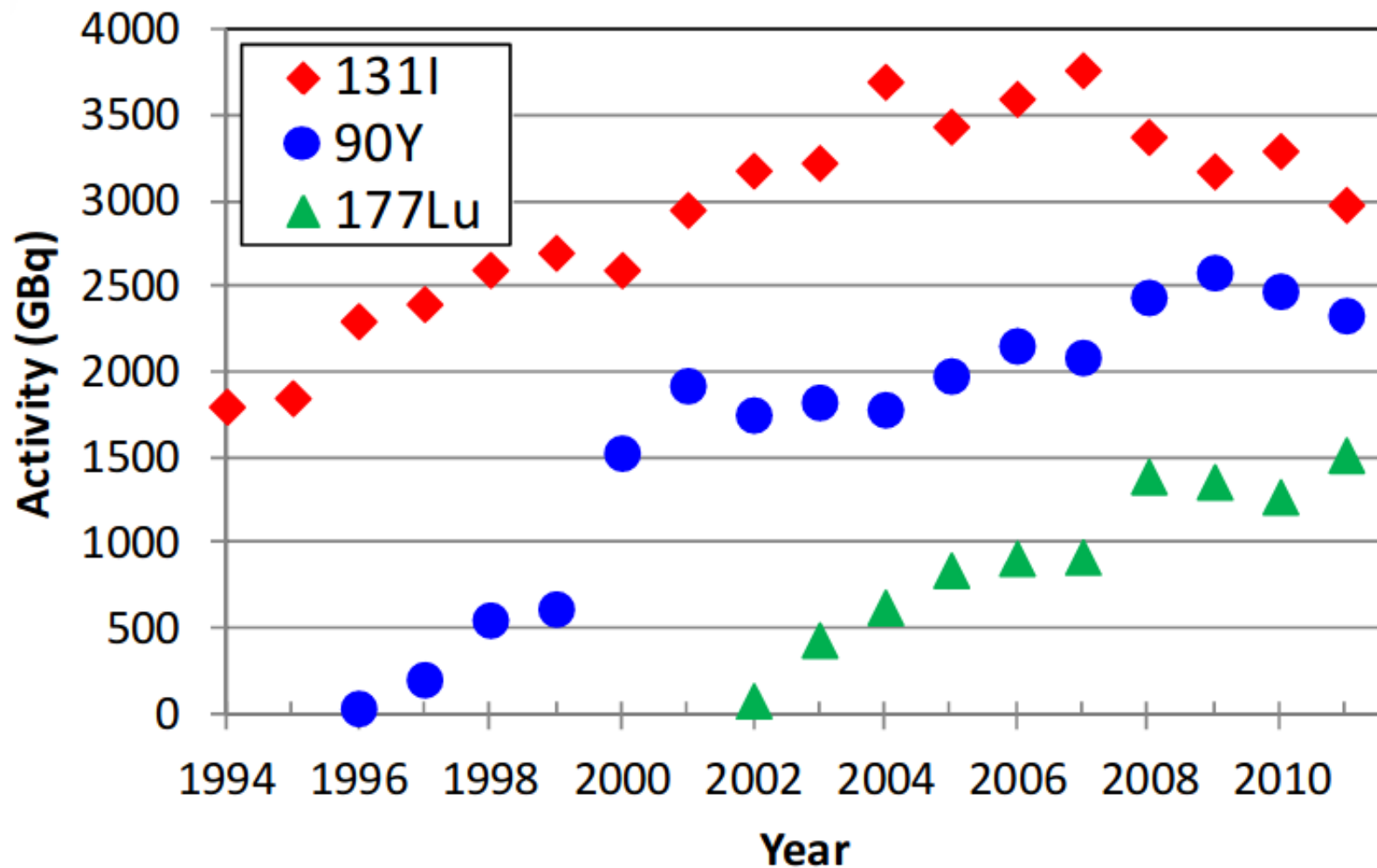
## Statistics of radionuclide use in Europe



Use of diagnostic isotopes in Europe, USA, Canada and Japan

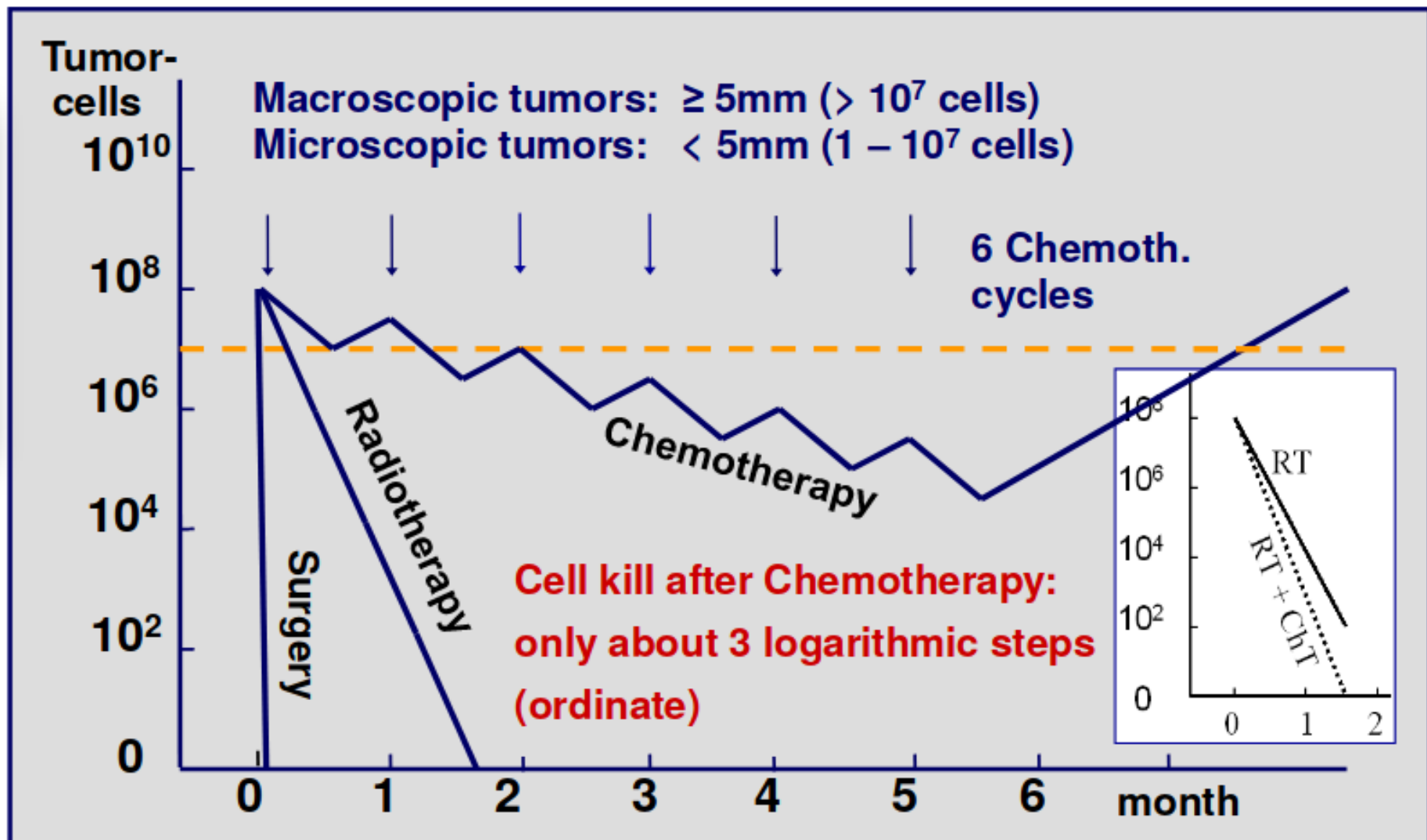
# Introduction to radiotargeted therapy

## Evolution of use of therapeutic isotopes in Switzerland



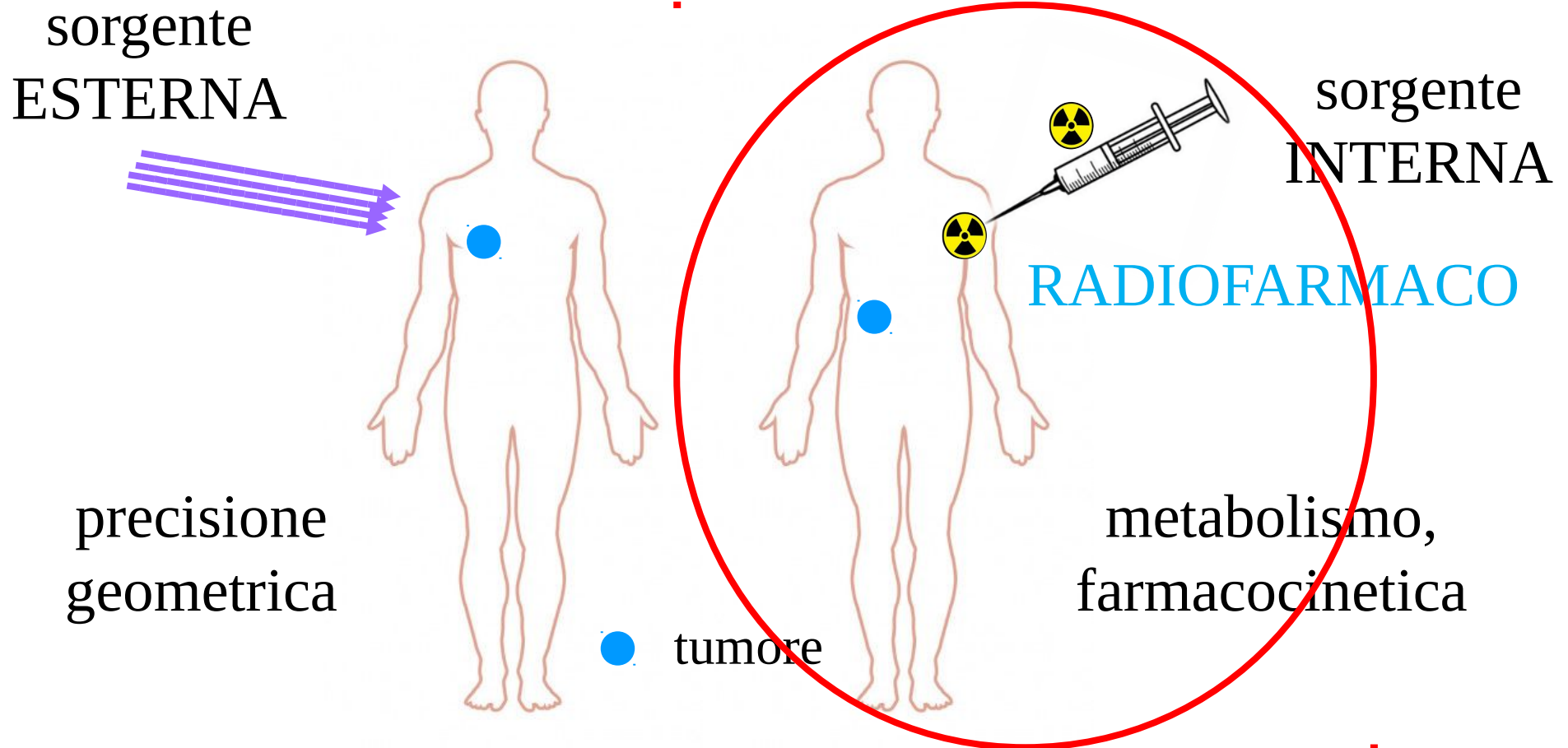
# Introduction to radiotargeted therapy

## Comparison of Cancer Therapies



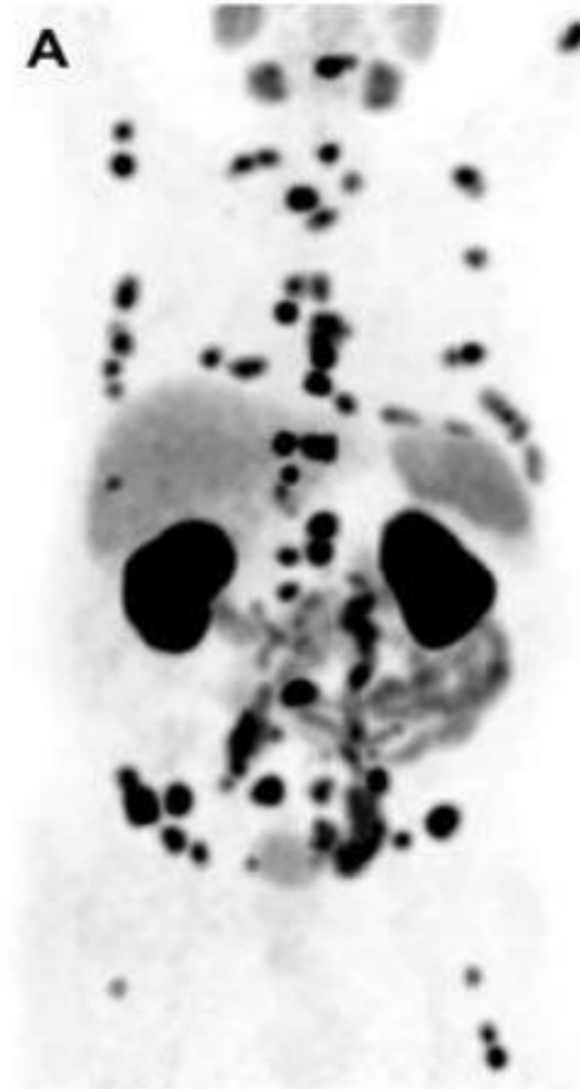
(Molls, TU München; according to Tannock: Lancet 1998, Nature 2006)

# Introduction to radiotargeted therapy



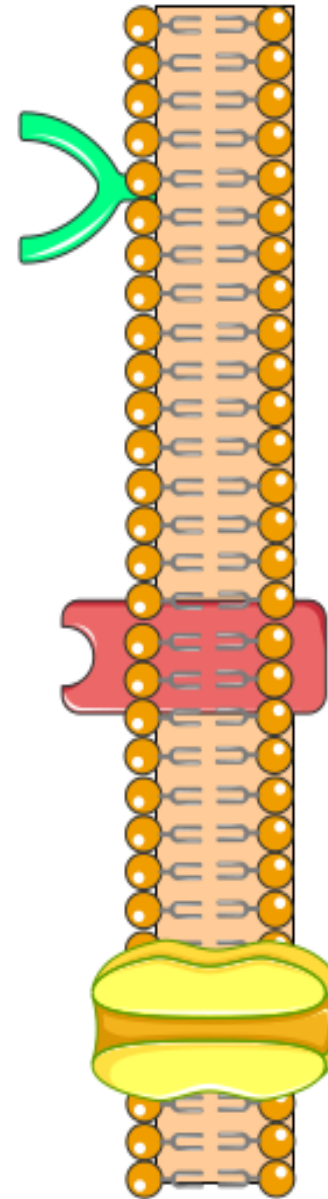
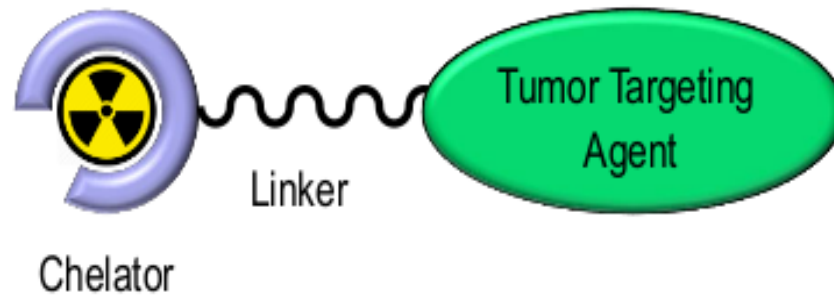
# Introduction to radiotargeted therapy

**Question:** How to treat such patients?





# Radiopharmaceuticals - The Concept Simplified



## Examples:

$^{68}\text{Ga}$ -DOTATATE

$^{111}\text{In}$ -Octreotide

$^{68}\text{Ga}$ -PSMA-11

$^{18}\text{F}$ -Fluorodeoxy-Glucose (FDG)

$^{18}\text{F}$ -Fluoro-ethyltyrosin (FLT)

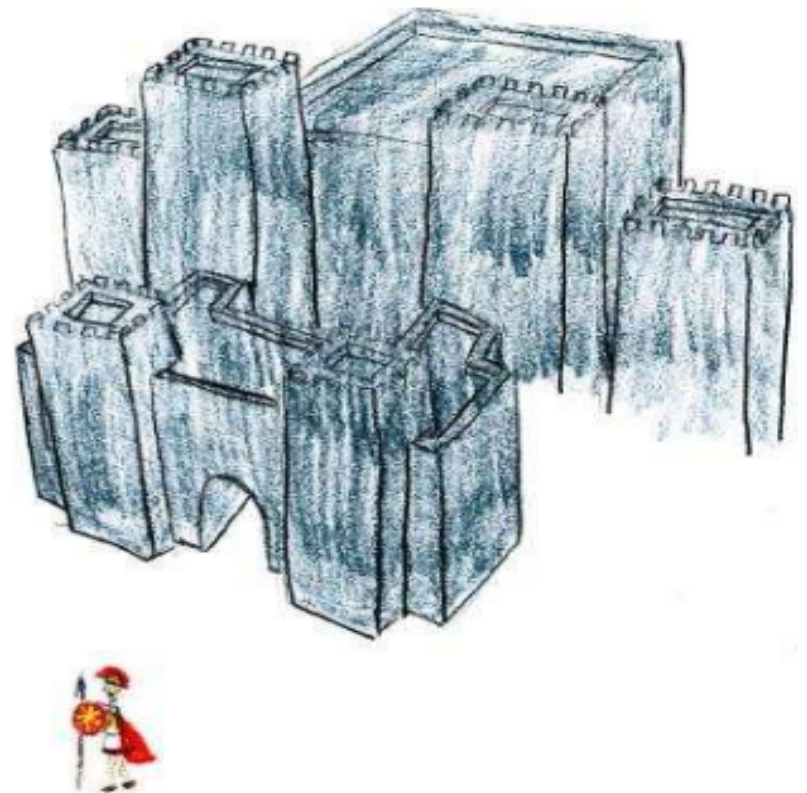
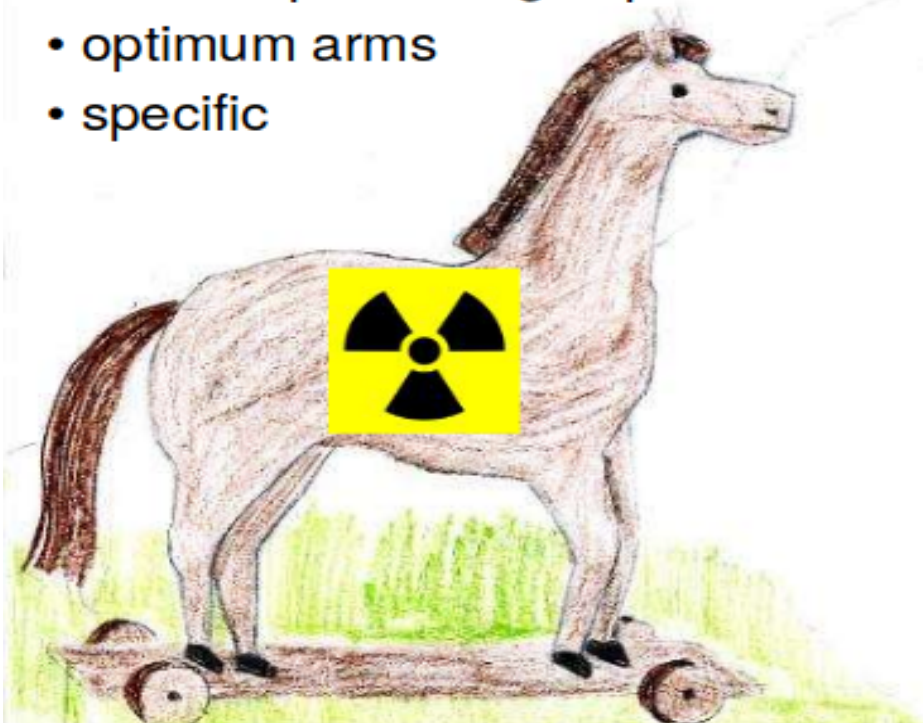
$^{123}\text{I}$ -Iodine

$^{223}\text{Ra}$ -Radium

# Introduction to radiotargeted therapy

## The principle of targeted therapies

- “attractive” vector > high uptake by the target
- transportable
- good in-vivo stability
- warriors “not visible”
- delayed uptake > suitable half-life
- limited space > high specific activity
- optimum arms
- specific



# Introduction to radiotargeted therapy

## Targeted radionuclide therapies in the clinic

**Thyroid:**  $^{131}\text{I}^-$

**Lymphoma:**

**Zevalin®** ( $^{90}\text{Y}$ -mab)

**Bexxar®** ( $^{131}\text{I}$ -mab)

$^{131}\text{I}/^{177}\text{Lu}$ -mabs (I/II)

**Bone metastases:**

**Metastron®** ( $^{90}\text{SrCl}_2$ )

**Quadramet®** ( $^{153}\text{Sm-EDTMP}$ )

**Xofigo®** ( $^{223}\text{RaCl}_2$ )

**Neuroblastoma:**

$^{131}\text{I}$ -MIBG

**Neuroendocrine (GEP-NET):**

**Lutathera®** ( $^{177}\text{Lu}$  pept.)

$^{177}\text{Lu}$ -peptides (III)

**Liver (HCC):**

**Theraspheres® & SIRspheres®** ( $^{90}\text{Y}$ )

$^{188}\text{Re}$ -Lipiodol (II)

$^{166}\text{Ho}$ -microspheres

$^{177}\text{Lu}$ -vitamin B7 (I)

**Brain:**  $^{90}\text{Y}$ -mab,  $^{131}\text{I}$ -mab (I/II),  $^{211}\text{At}$ -mab (I),  $^{213}\text{Bi}$ -pept. (I)

**Leukemia, myeloma:**

$^{131}\text{Y}$ -mab (III),

$^{213}\text{Bi}/^{225}\text{Ac}$ -mab (II)

**Medullary Thyroid:**

$^{131}\text{I}$ -mab (II)

$^{177}\text{Lu}$ -pept. (I)

**Breast:**

$^{90}\text{Y}$ -mab,  $^{131}\text{I}$ - (II),

$^{212}\text{Pb}$ -mab (I)

$^{177}\text{Lu}$ -mab (I)

**Lung (SCLC):**

$^{177}\text{Lu}$ -mab (II)

**Pancreas:**

$^{90}\text{Y}$ -mab (III)

**Ovary:**

$^{212}\text{Pb}$ -mab (I)

$^{90}\text{Y}/^{177}\text{Lu}$ -mab

**Prostate:**

$^{177}\text{Lu}$ -mab (II)

$^{177}\text{Lu}$ -PSMA (II)

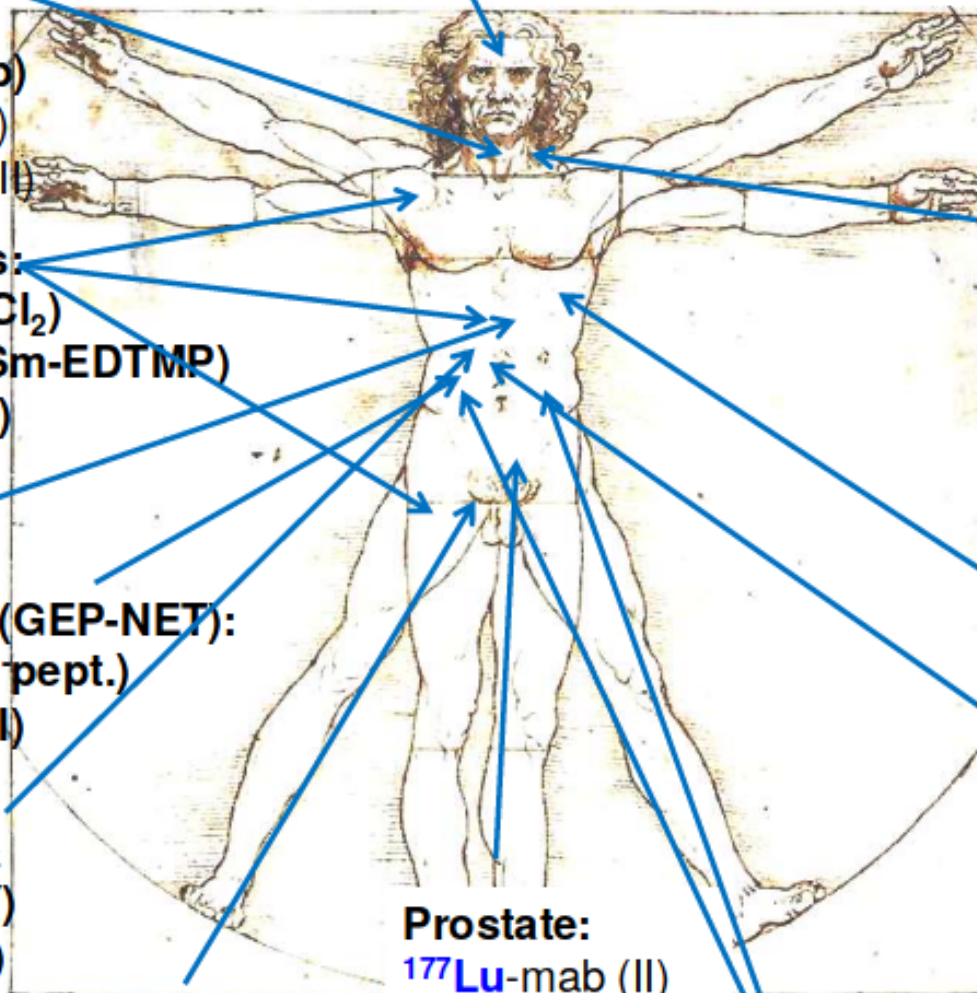
$^{225}\text{Ac}$ -PSMA (I)

**Kidneys (RCC):**

$^{90}\text{Y}/^{177}\text{Lu}$ -mab (II)

**Melanoma:**

$^{213}\text{Bi}$ -mab (I)



**Colon & rectum:**

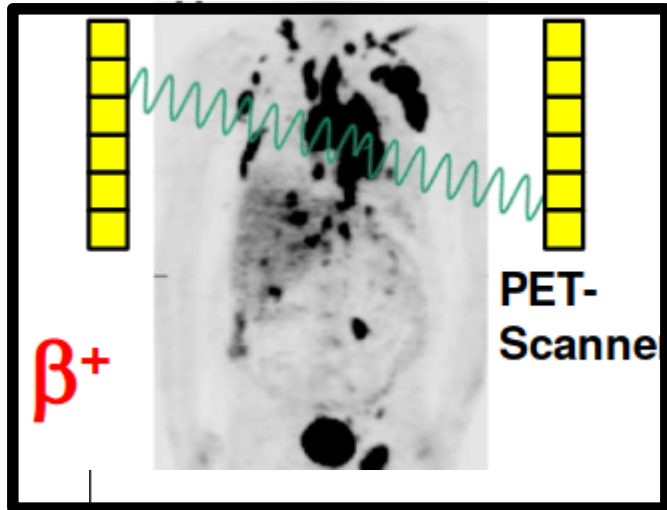
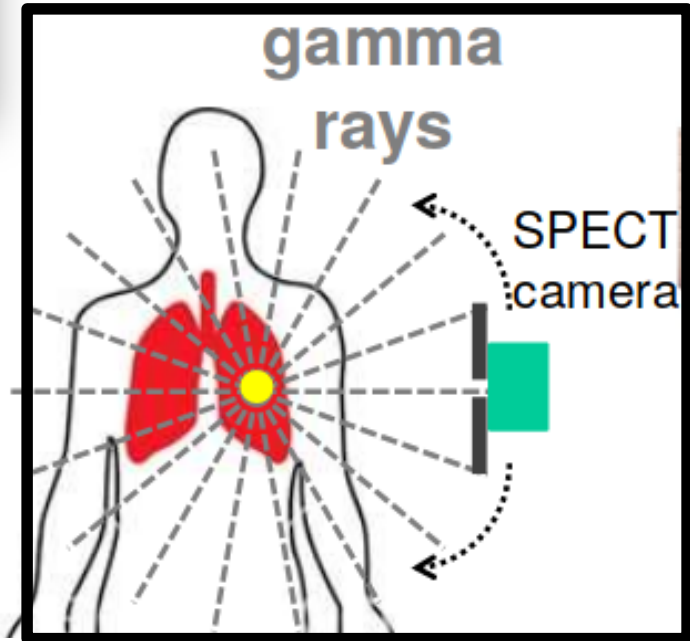
$^{131}\text{I}$ -mab (II)



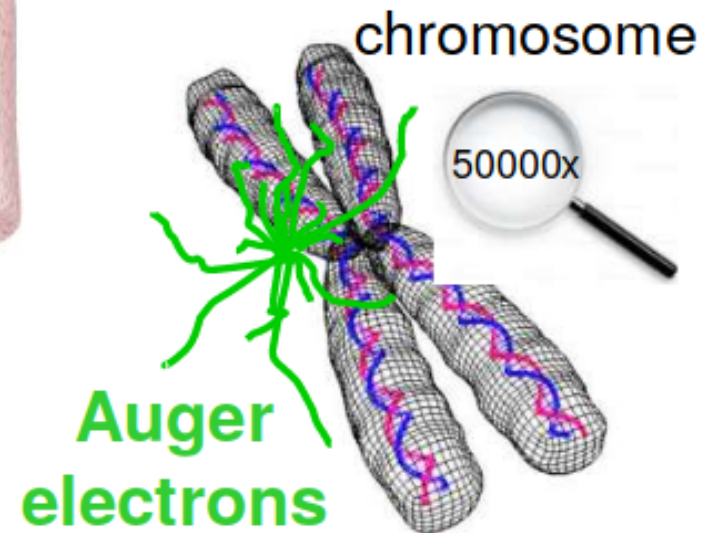
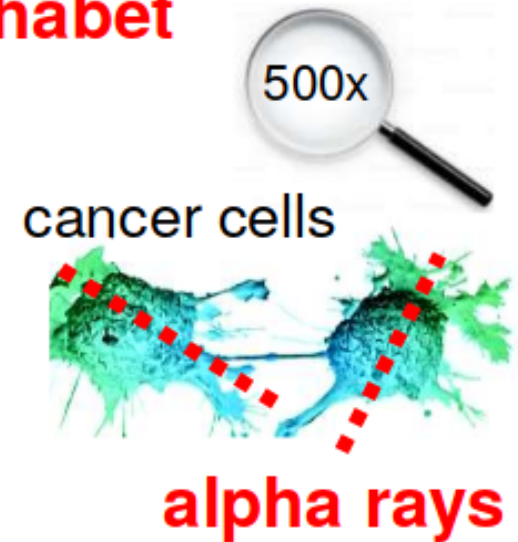
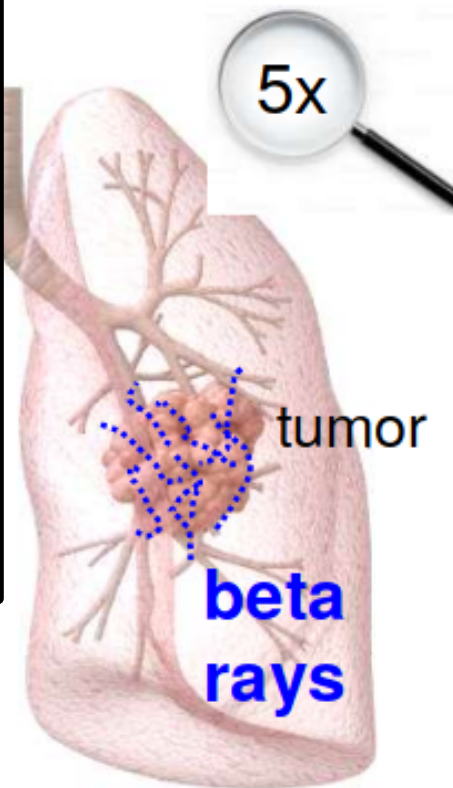
# Introduction to radiotargeted therapy

## The nuclear medicine alphabet

$^{99m}\text{Tc}$   
 $^{111}\text{In}$   
 $^{123}\text{I}$   
 $^{201}\text{Tl}$   
 $^{67}\text{Ga}$   
...



$^{18}\text{F}$   
 $^{11}\text{C}$   
 $^{73}\text{Se}$   
 $^{68}\text{Ga}$   
 $^{124}\text{I}$ , ...



# Range of therapeutic nuclides

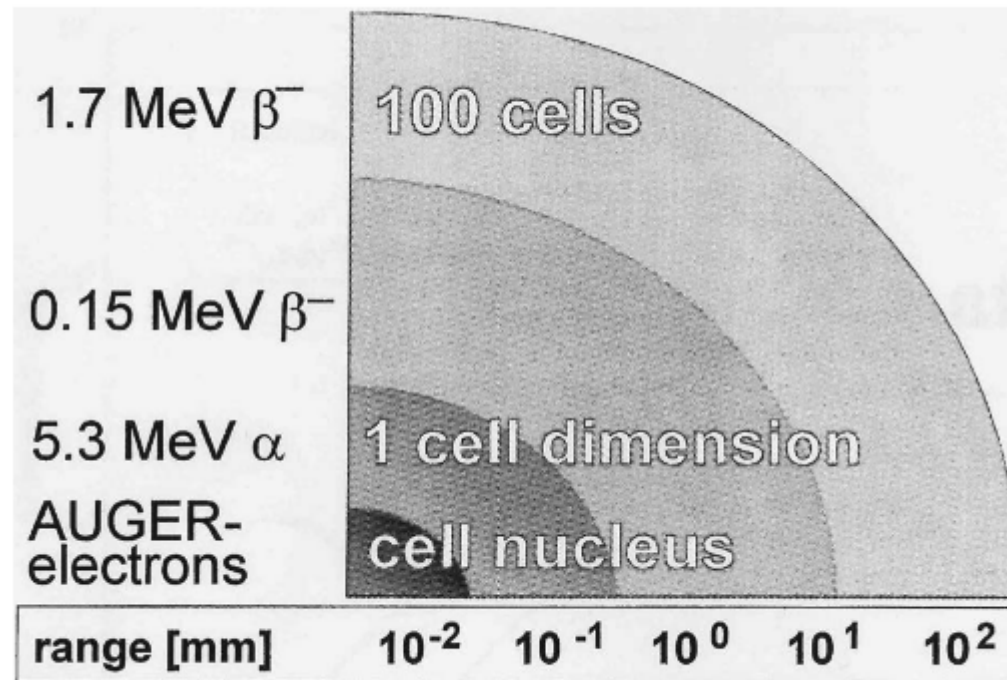


FIG. 1.1. Correlation between type and energy of corpuscular radiation, and the range in tissue

## Range

Beta-  
Fino a 10 mm  
(500 cellule)

Alpha  
Fino a 100  $\mu\text{m}$   
(10 cellule)

Auger  
 $\sim 10 \mu\text{m}$   
(meno di una cellula)



# Introduction to radiotargeted therapy

Lymphoma therapy: RITUXIMAB+ $^{177}\text{Lu}$

E.B., 1941 (m): UPN 6

$^{18}\text{F}$ FDG PET



1.9.2002

$^{177}\text{Lu}$ -Scan



13.9.2002

$^{18}\text{F}$ FDG PET



15.11.2002

**Still  
in  
CR**

15.9.2009

*F. Forrer et al., J Nucl Med 2013;54:1045.*

# Introduction to radiotargeted therapy



Syed M Qaim,  
Lecture IAEA, dec 2018

## New Directions in Radionuclide Applications

- **Theranostic approach**

(combination of PET / Targeted therapy)

$^{44}\text{Sc}/^{47}\text{Sc}$ ,  $^{64}\text{Cu}/^{67}\text{Cu}$ ,  $^{86}\text{Y}/^{90}\text{Y}$ , etc.

- **Multimode imaging**

(combination of PET/CT and PET/MRI)

- **Radioactive nanoparticles**

Possible improvement in delivery of radionuclide to tumour

CUPRUM ..? 2023  
COME INFN-LNL

PASTA, REMIX INFN-LNL

METRICS INFN-LNL

**Continuous radionuclide research is underway.**

# Another view at the chemical elements

<div><div><div><div></div><div>PET</div></div><div><div></div><div>SPECT</div></div></div><div><div><div></div><div>Beta Therapy</div></div><div><div></div><div>Alpha Therapy</div></div><div><div></div><div>Auger e<sup>-</sup> Therapy</div></div></div></div>																		<div>1 H Hydrogen 1.008</div>		<div>2 He Helium 4.0026</div>															
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<div>19 K Potassium 39.098</div>		<div>20 Ca Calcium 40.078(4)</div>		<div>21 Sc Scandium 44.956</div>		<div>22 Ti Titanium 47.887</div>		<div>23 V Vanadium 50.942</div>		<div>24 Cr Chromium 51.996</div>		<div>25 Mn Manganese 54.938</div>		<div>26 Fe Iron 55.845(2)</div>		<div>27 Co Cobalt 58.933</div>		<div>28 Ni Nickel 58.693</div>		<div>29 Cu Copper 63.546(3)</div>		<div>30 Zn Zinc 65.38(2)</div>		<div>31 Ga Gallium 69.723</div>		<div>32 Ge Germanium 72.630(8)</div>		<div>33 As Arsenic 74.922</div>		<div>34 Se Selenium 78.971(8)</div>		<div>35 Br Bromine 79.904</div>		<div>36 Kr Krypton 83.798(2)</div>	
<div>37 Rb Rubidium 85.468</div>		<div>38 Sr Strontium 87.62</div>		<div>39 Y Yttrium 88.906</div>		<div>40 Zr Zirconium 91.224(2)</div>		<div>41 Nb Niobium 92.906</div>		<div>42 Mo Molybdenum 95.95</div>		<div>43 Tc Technetium</div>		<div>44 Ru Ruthenium 101.07(2)</div>		<div>45 Rh Rhodium 102.91</div>		<div>46 Pd Palladium 106.42</div>		<div>47 Ag Silver 107.87</div>		<div>48 Cd Cadmium 112.41</div>		<div>49 In Indium 114.82</div>		<div>50 Sn Tin 118.71</div>		<div>51 Sb Antimony 121.76</div>		<div>52 Te Tellurium 127.60(3)</div>		<div>53 I Iodine 126.90</div>		<div>54 Xe Xenon 131.29</div>	
<div>55 Cs Caesium 132.91</div>		<div>56 Ba Barium 137.33</div>		<div>57-71 *</div>		<div>72 Hf Hafnium 178.49(2)</div>		<div>73 Ta Tantalum 180.95</div>		<div>74 W Tungsten 183.84</div>		<div>75 Re Rhenium 186.21</div>		<div>76 Os Osmium 190.23(3)</div>		<div>77 Ir Iridium 192.22</div>		<div>78 Pt Platinum 195.08</div>		<div>79 Au Gold 196.97</div>		<div>80 Hg Mercury 200.59</div>		<div>81 Tl Thallium 204.38</div>		<div>82 Pb Lead 207.2</div>		<div>83 Bi Bismuth 208.98</div>		<div>84 Po Polonium</div>		<div>85 At Astatine</div>		<div>86 Rn Radon</div>	
<div>87 Fr Francium</div>		<div>88 Ra Radium</div>		<div>89-103 **</div>		<div>104 Rf Rutherfordium</div>		<div>105 Db Dubnium</div>		<div>106 Sg Seaborgium</div>		<div>107 Bh Bohrium</div>		<div>108 Hs Hassium</div>		<div>109 Mt Meitnerium</div>		<div>110 Ds Darmstadtium</div>		<div>111 Rg Roentgenium</div>		<div>112 Cn Copernicium</div>		<div>113 Nh Nihonium</div>		<div>114 Fl Flerovium</div>		<div>115 Mc Moscovium</div>		<div>116 Lv Livermorium</div>		<div>117 Ts Tennessine</div>		<div>118 Og Oganesson</div>	

*Lanthanoids	57 La Lanthanum 138.91	58 Ce Cerium 140.12	59 Pr Praseodymium 140.91	60 Nd Neodymium 144.24	61 Pm Promethium 144.91	62 Sm Samarium 150.36(2)	63 Eu Europium 151.96	64 Gd Gadolinium 157.25(3)	65 Tb Terbium 158.93	66 Dy Dysprosium 162.50	67 Ho Holmium 164.93	68 Er Erbium 167.26	69 Tm Thulium 168.93	70 Yb Ytterbium 173.05	71 Lu Lutetium 174.97
**Actinoids	89 Ac Actinium	90 Th Thorium 232.04	91 Pa Protactinium 231.04	92 U Uranium 238.03	93 Np Neptunium	94 Pu Plutonium	95 Am Americium	96 Cm Curium	97 Bk Berkelium	98 Cf Californium	99 Es Einsteinium	100 Fm Fermium	101 Md Mendelevium	102 No Nobelium	103 Lr Lawrencium

# Another view at the chemical elements

<div><div><div><div></div><div>PET</div></div><div><div></div><div>SPECT</div></div></div><div><div><div></div><div>Beta Therapy</div></div><div><div></div><div>Alpha Therapy</div></div><div><div></div><div>Auger e<sup>-</sup> Therapy</div></div></div></div>																																			
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87 Fr Francium 223		88 Ra Radium 226		89-103 **		104 Rf Rutherfordium 261		105 Db Dubnium 262		106 Sg Seaborgium 266		107 Bh Bohrium 264		108 Hs Hassium 277		109 Mt Meitnerium 268		110 Ds Darmstadtium 271		111 Rg Roentgenium 272		112 Cn Copernicium 285		113 Nh Nihonium 284		114 Fl Flerovium 289		115 Mc Moscovium 288		116 Lv Livermorium 293		117 Ts Tennessine 294		118 Og Oganesson 294	

\*Lanthanoids

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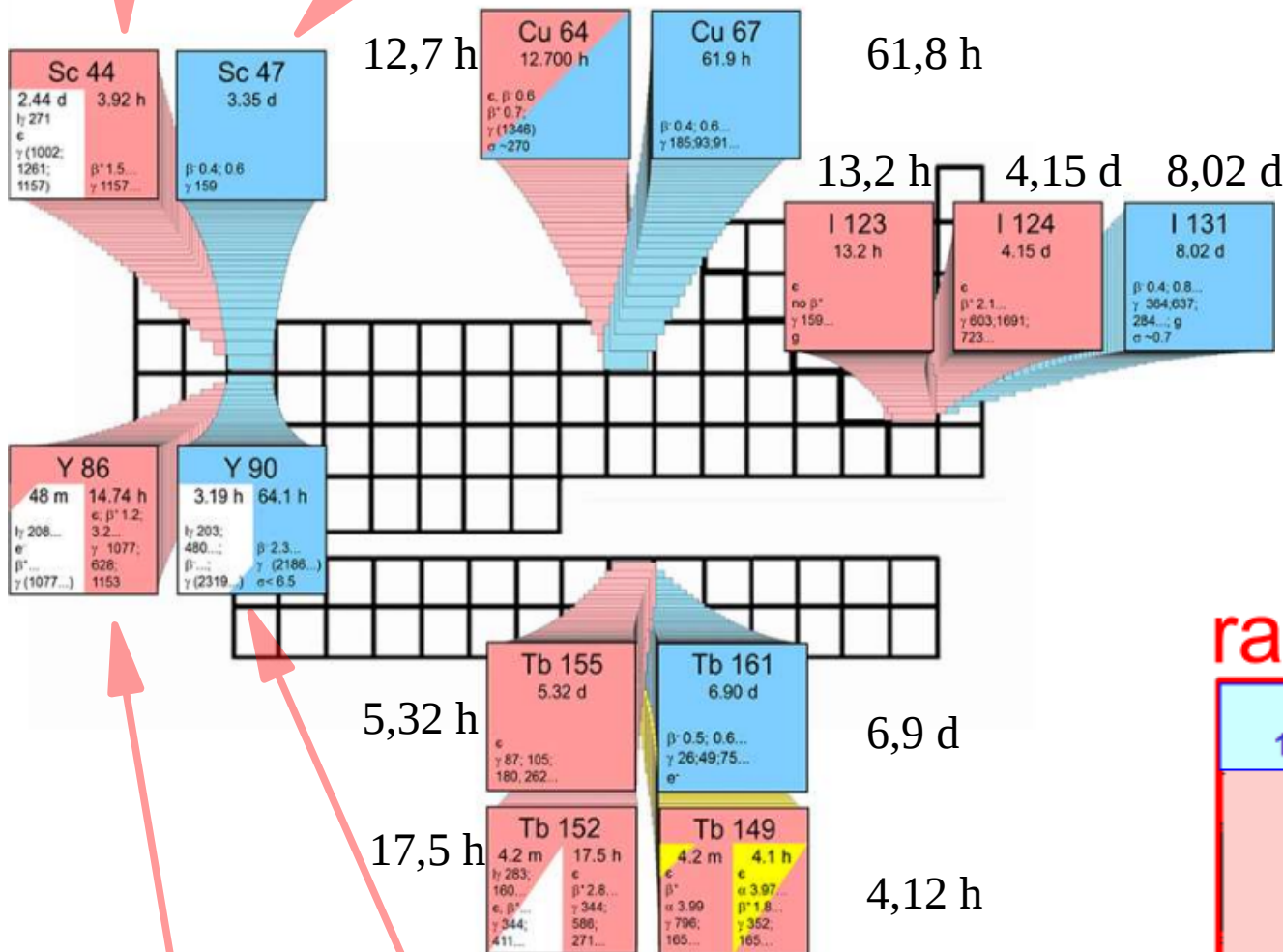
\*\*Actinoids



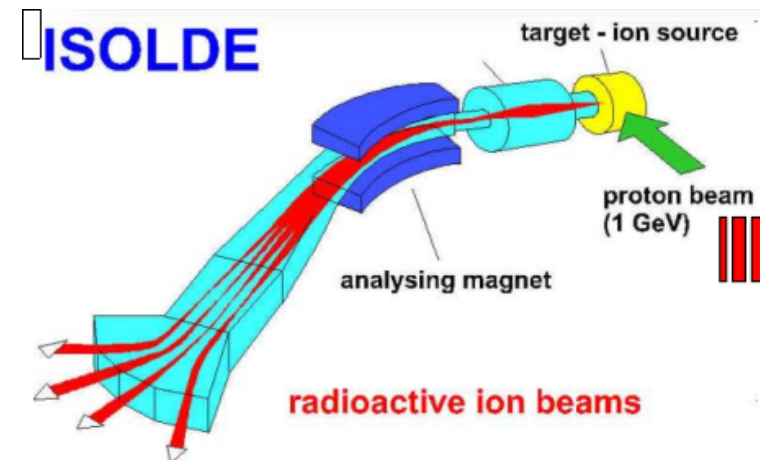
# Introduction to radiotargeted therapy

$t_{1/2} = 3,97 \text{ h}$ ;  $t_{1/2} = 3,35 \text{ d}$

Matched pairs for theranostics

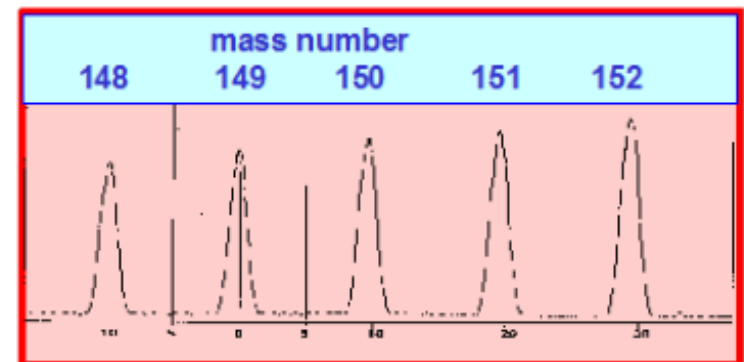


$T_{1/2} = 14,74 \text{ h}$ ;  $t_{1/2} = 64,05 \text{ d}$



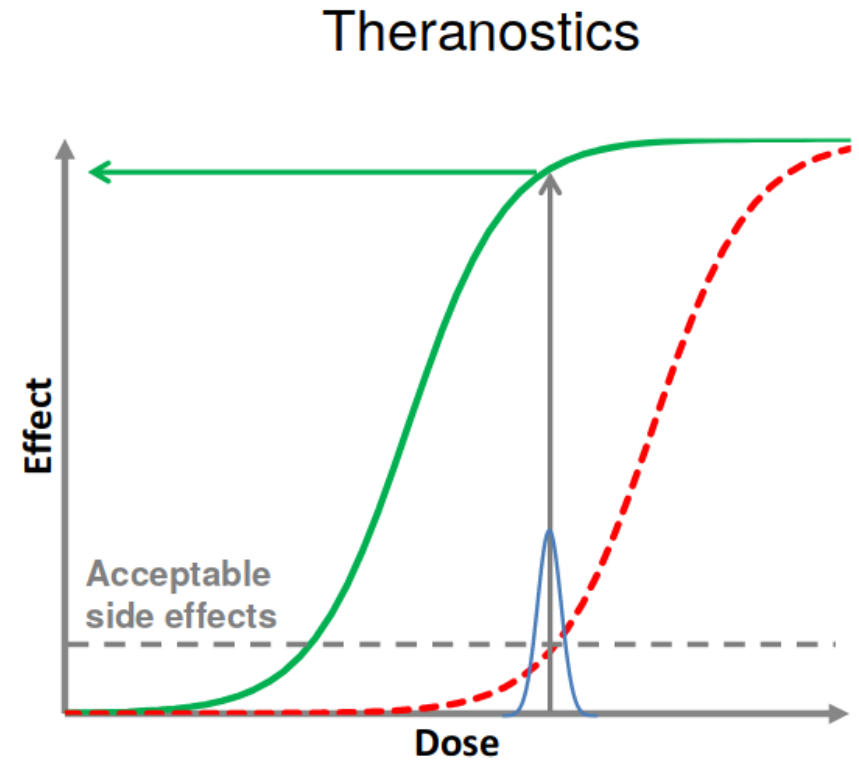
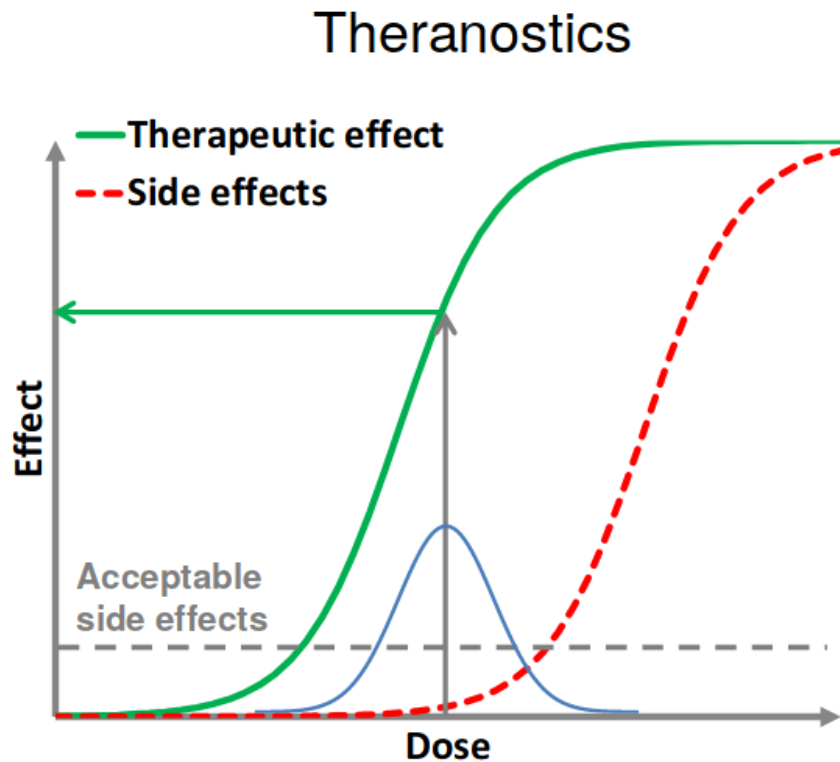
Spallation of Ta with high-energy protons following online mass separation

radioactive ion beams





# Therapeutic window



**Accurate dosimetry is essential for optimum use of the therapeutic window !!!**

# Introduction to radiotargeted therapy

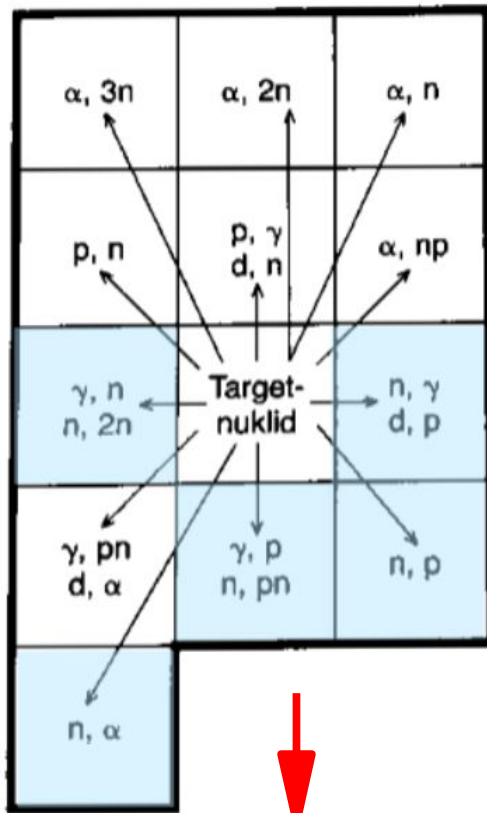
Which theranostic isotopes will we use in future ?

<b>Sc 47</b> 3.35 d $\beta^-$ 0.4; 0.6 $\gamma$ 159	<b>Cu 67</b> 2.6 d $\beta^-$ 0.4; 0.6 $\gamma$ 185; 93; 91...	<b>Tb 161</b> 6.9 d $\beta^-$ 0.5; 0.6 $\gamma$ 26; 49; 75... $e^-$	<b>Lu 177</b> 6.65 d $\beta^-$ 0.5 $\gamma$ 208; 113...	<b>At 211</b> 7.2 h $\epsilon$ $\alpha$ 5.867... $\gamma$ (687)	<b>Ac 225</b> 10.0 d $\alpha$ 5.830; 5.797... $\gamma$ 100; (150...) $e^-$
		<b>Tb 149</b> 4.1 h $\epsilon$ $\alpha$ 3.97 $\beta^+$ 1.4... $\gamma$ 352; 165...			
<b>Sc 43</b> 3.9 h $\beta^+$ 1.2... $\gamma$ 373...	<b>Cu 61</b> 3.4 h $\beta^+$ 1.2... $\gamma$ 283; 656; 67; 1186...	<b>Tb 152</b> 17.5 h $\epsilon$ $\beta^+$ 3.0; 2.6; 2.0... $\gamma$ 344; 271; 586...	<b>Ga 68</b> 1.1 h $\epsilon$ $\beta^+$ 1.9... $\gamma$ 1077; (1833)	<b>I 124</b> 4.15 d $\epsilon$ $\beta^+$ 2.1... $\gamma$ 603; 1691...	<b>Zr 89</b> 3.3 d $\epsilon$ $\beta^+$ 0.9 $\gamma$ (1713) m
<b>Sc 44</b> 4.0 h $\beta^+$ 1.5... $\gamma$ 1157...	<b>Cu 64</b> 12.7 h $\epsilon$ $\beta^-$ 0.6, $\beta^+$ 0.7 $\gamma$ (1346)	<b>Tb 155</b> 5.3 d $\epsilon$ $\gamma$ 87; 105; 180... $e^-$	<b>In 111</b> 2.8 d $\epsilon$ $\gamma$ 245; 171...	<b>I 123</b> 13.2 h $\epsilon$ $\gamma$ 159...	

IRST IRCCS  
Mendola, Italy,  
*Prof. Paganelli*

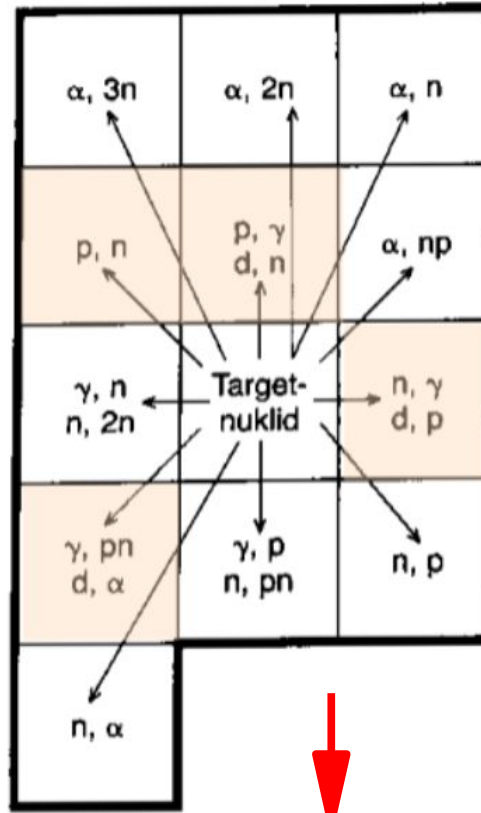
# Manufacturing radionuclides

Nuclear Reactor  
Neutron Source



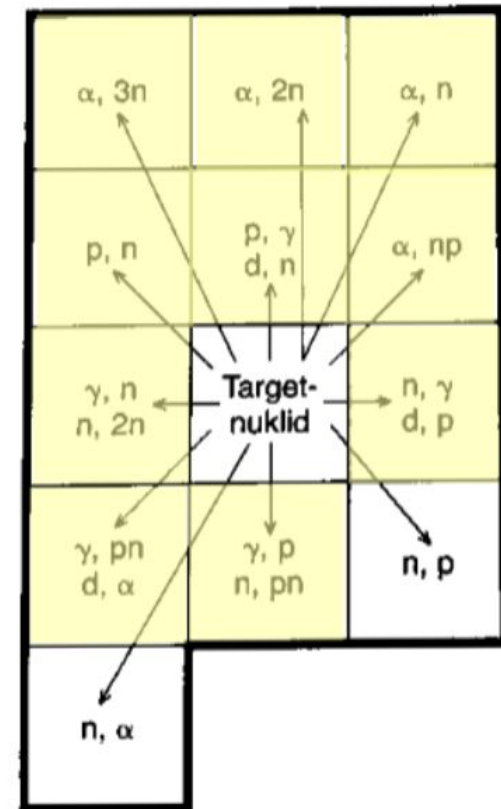
Often Beta- emitter  
Therapy nuclides

Medical  
Cyclotron



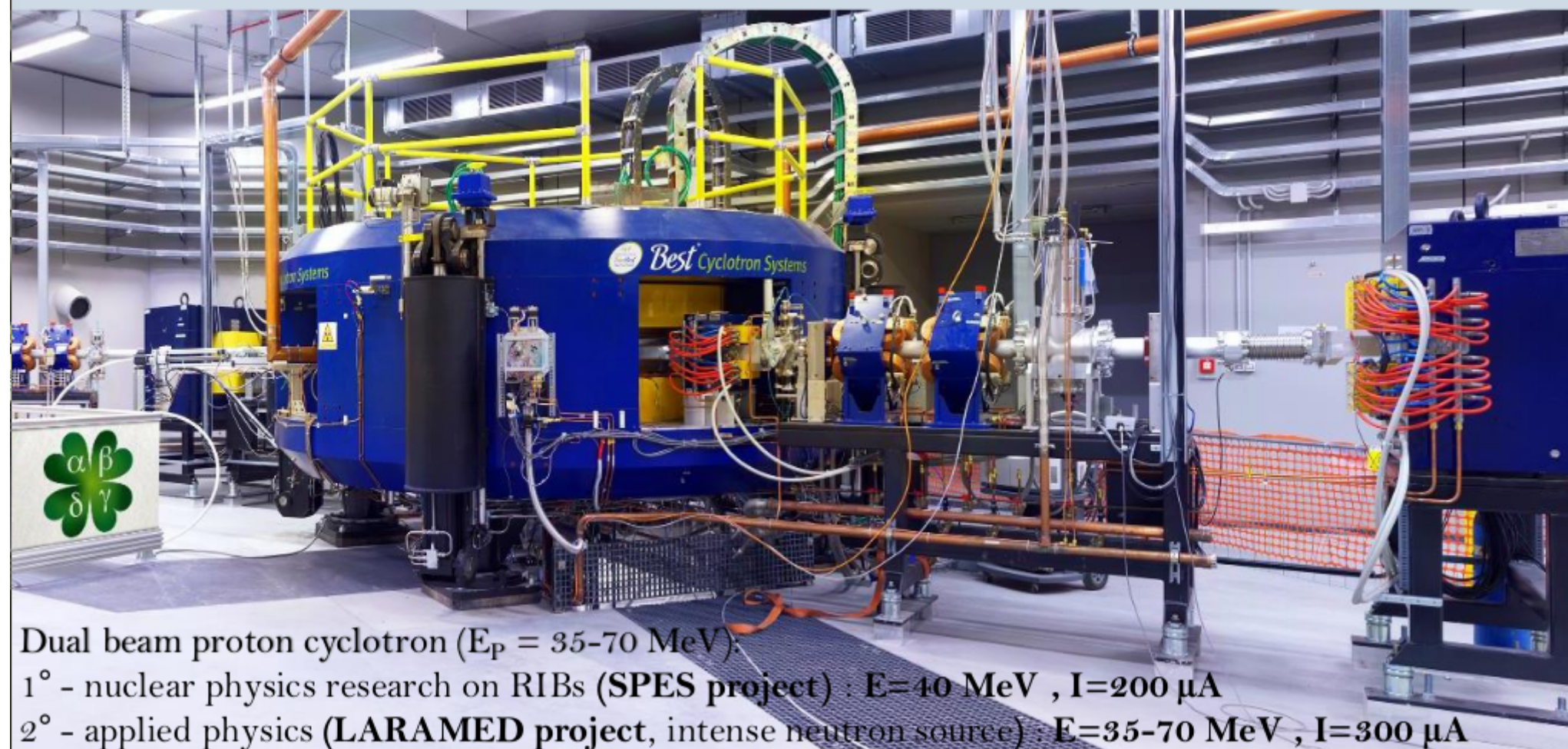
Often Beta+ emitter  
PET nuclides

Particle Accelerator  
(p, d, alpha)



# SPES INFN - Legnaro Padova

The new 70 MeV proton cyclotron @ INFN-LNL



Dual beam proton cyclotron ( $E_p = 35-70$  MeV):

1° - nuclear physics research on RIBs (SPES project) :  $E=40$  MeV ,  $I=200$   $\mu$ A

2° - applied physics (LARAMED project, intense neutron source) :  $E=35-70$  MeV ,  $I=300$   $\mu$ A

**DUAL RADIO PHARMACEUTICAL PRODUCTION:  
LARAMED - ISOLPHARM**



# Introduction to radiotargeted therapy

## Four Pillars of Radionuclide Development Work



Syed M Qaim,  
Lecture IAEA, dec 2018

**IAEA 473 technical report 2021**

- Nuclear data
  - decay properties
  - production cross sections
- High current targetry
- Chemical processing
  - isolation of radionuclide and recovery of enriched target material
- Quality control
  - radionuclidic, radiochemical, chemical, specific activity



# The case of $^{47}\text{Sc}$

Isotope	Half-life	$\beta^+$ $E_{\text{average}}$ [KeV](I)	X and $\gamma$ [KeV] (I)	$\beta^-$ $E_{\text{average}}$ [KeV](I)
$^{47}\text{Sc}$	3.35 d	-	159.38 (68.3%)	162 (100%)
$^{43}\text{Sc}$	3.9 h	476 (88.1%)	372 (23%)	-
$^{44}\text{Sc}$	4.0 h	632 (94.27 %)	1157 (100%)	-

PET      SPECT      Therapy

cf. Review  
Qaim, Scholten, Neumaler, JRNC **318**, 1493 (2018)

Production route	Irradiation	Batch yield	Laboratory
$^{47}\text{Tl}(n,p)^{47}\text{Sc}$	Fission spectrum	1.6 GBq	Brookhaven, 1998
$^{48}\text{Tl}(\gamma,p)^{47}\text{Sc}$	40 MeV	186 MBq (3 g $\text{TiO}_2$ target)	Argonne, 2018
$^{46}\text{Ca}(n,\gamma)^{47}\text{Ca} \xrightarrow{\beta^-} ^{47}\text{Sc}$	High thermal neutron flux	600 MBq 1 mg target, $^{46}\text{Ca}$ (31.7 % enriched)	Grenoble/PSI, 2014
$^{48}\text{Tl}(p,2p)^{47}\text{Sc}$	48 < 150 MeV	900 MBq Purity not acceptable	Brookhaven, 1998
$^{48}\text{Ca}(p,2n)^{47}\text{Sc}$	24 → 17 MeV	~ 10 MBq	Warsaw, 2017

All methods of  $^{47}\text{Sc}$  production need further development.

Isotope	half-life
$^{43}\text{Sc}$	3.89 h
$^{44g}\text{Sc}$	3.97 h
$^{44m}\text{Sc}$	58.6 h
$^{45}\text{Sc}$	stable
$^{46g}\text{Sc}$	83.79 d
$^{46m}\text{Sc}$	18.75 s
$^{47}\text{Sc}$	3.35 d
$^{48}\text{Sc}$	43.67 h
$^{49}\text{Sc}$	57.2 m

# The case of $^{47}\text{Sc}$

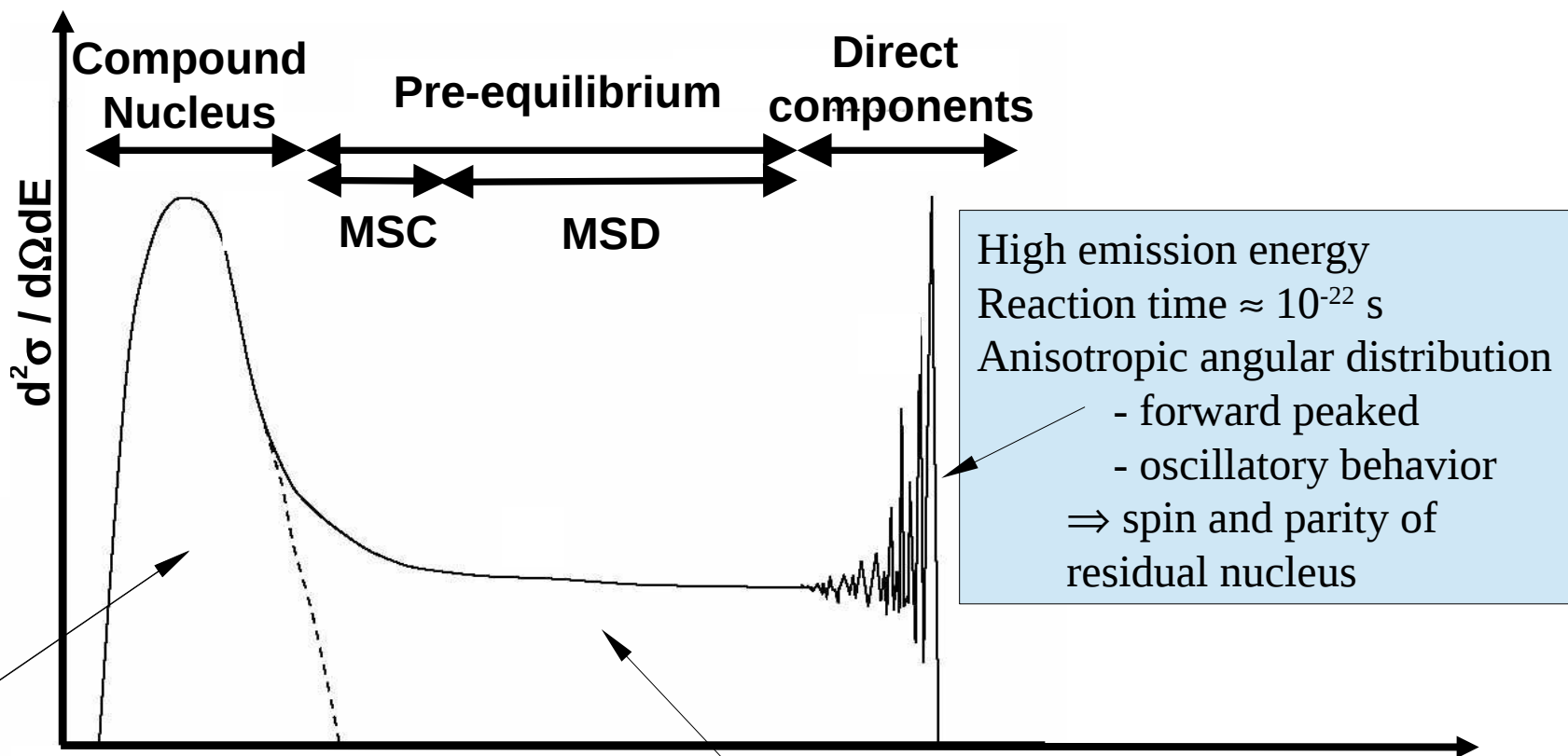
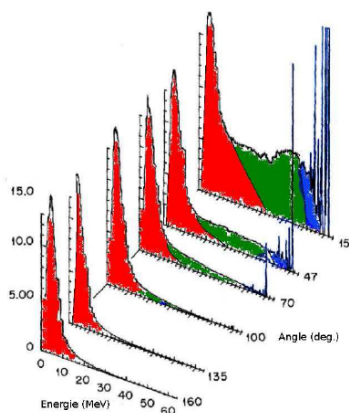
Enriched materials are **VERY** expensive!

Target (abundance)	Measured cross section	Comment
<b>Ti-48</b> (73.73%)	<ul style="list-style-type: none"> <li>• <i>Gadioli et al</i> (1981): Sc-47, Sc-46, Sc-44, Sc-43 (V-48, V-47, K-43, K-42, Cl-39, Cl-34m)</li> <li>▪ <i>Levkovskij</i> (1991): Sc-47, Sc-44m, Sc-44 (V-48, V-47)</li> </ul>	<p>Experiments done with oxide Ti-48 (99.1%) Not all the contaminant radionuclides were measured</p> <p>→ It is important to verify the cross sections by using updated nuclear data and metal targets (highest available enrichment)</p>
<b>Ti-49</b> (5.41%)	<ul style="list-style-type: none"> <li>▪ <i>Levkovskij</i> (1991): Sc-48, Sc-46 (V-48)</li> </ul>	No experimental data available for Sc-47
<b>Ti-50</b> (5.18%)	<ul style="list-style-type: none"> <li>• <i>Gadioli et al</i> (1981): Sc-48, Sc-47, Sc-46, Sc-44, Sc-43 (K-43, K-42, Cl-39, Cl-38)</li> </ul>	Experiments done with oxide Ti-50 enriched 69.7% and corrected with exp data for contamination of Ti-48 (23%) and theoretical data for Ti-49 (2.0%), Ti-47 (2.4%) and Ti-46 (3.1%)
<b>V-nat</b> (V-51: 99.750%)	<p>➤ Many authors:</p> <p>Sc-48, Sc-47, Sc-46, Sc-44m, Sc-44, Sc-43 (V-48, Cr-48, Cr-49, Cr-51, K-43, K-42)</p>	Very interesting due to the <b>low cost</b> and <b>highly available material</b> ; it is important to <b>verify quantity and quality of produced Sc-47</b>

# Nuclear reaction calculations ...

## TIME SCALES AND ASSOCIATED MODELS

62 MeV  $^{56}\text{Fe}$  (p,xp)  
Double differential cross sections



High emission energy  
Reaction time  $\approx 10^{-22}$  s  
Anisotropic angular distribution

- forward peaked
- oscillatory behavior

$\Rightarrow$  spin and parity of residual nucleus

Low emission energy  
Reaction time  $\approx 10^{-18}$  s  
Isotropic angular distribution

Intermediate emission energy  
Intermediate reaction time  
Anisotropic angular distribution smoothly increasing to forward peaked shape with outgoing energy

Emission energy

Reaction time

# Nuclear reaction theory: general

## S-matrix: the response of the target

The S-matrix measures the response of the target: a real potential cannot create or destroy particles, it can change only the phase of the outgoing wave, not the modulus

$$S_\ell = e^{2i\delta_\ell}$$

The total elastic cross section becomes:

$$\sigma_{el} = \frac{\pi}{k^2} \sum_0^\infty (2\ell + 1) |S_\ell - 1|^2$$

No nuclear reactions here!



# Nuclear reaction theory: general

■ loss of elastic flux:  $|S_\ell| < 1$

$$\sigma_{el} = \frac{\pi}{k^2} \sum_0^\infty (2\ell + 1) |S_\ell - 1|^2$$

$$\sigma_r = \frac{\pi}{k^2} \sum_0^\infty (2\ell + 1) (1 - |S_\ell|^2)$$

$$\sigma_{tot} = \sigma_{el} + \sigma_r = \frac{\pi}{k^2} \sum_0^\infty (2\ell + 1) (1 - \mathcal{R}e S_\ell)$$

The transmission coefficient  $T_\ell$  is

$$T_\ell = 1 - |S_\ell|^2 \quad (5)$$

# Nuclear reaction theory: general

## Optical Potential $U(r)$

Coulomb part:  $V_C(r) = Z_1 Z_2 e^2 / r$

Real Nuclear part:  $V(r)$  for nuclear attraction

Imaginary Part  $W(r)$ : for reaction to occur

Spin-Orbit part:  $V_{SO}(r)$  Important ingredient of nuclear force and for polarization data

$$U(r) = V_C(r) + V(r) + iW(r) + V_{SO}(r)$$

# Nuclear reaction theory: compound

## CN basics

1. Continuum overlapping levels
2. Independence **initial**/exit channel

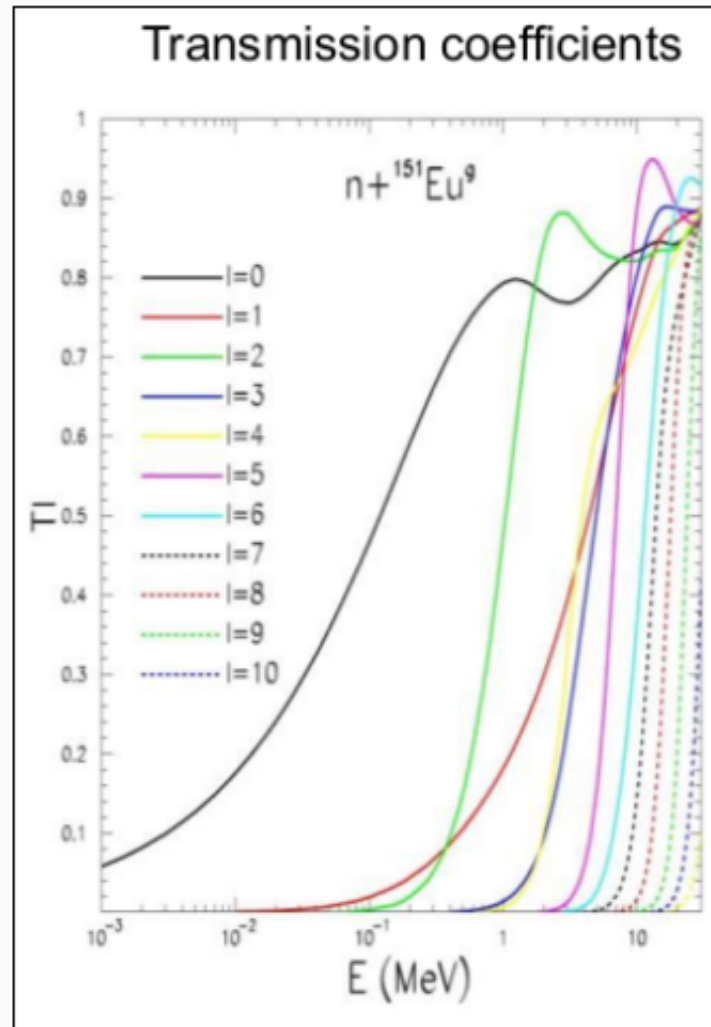
$$\sigma_{ab} = \sigma_a^{CN} P_b$$

Hauser-Feshbach formula:

$$\sigma_{ab} = \frac{\pi T_a}{k_a^2} \frac{T_b}{\sum_c T_c}$$

Need transmission coefficients (from optical potentials)

# Nuclear reaction theory: Compound





# Nuclear reaction theory: Compound

## CN Basic 2, complexities

**Loop over angular momentum and parity**

$$\sigma_{ab} = \frac{\pi}{k_a^2} \sum_{J,\pi} \sum_{\alpha,\beta} \frac{2J+1}{(2s+1)(2I+1)} \frac{\mathcal{P}_a^{J,\pi}(\alpha) \mathcal{P}_b^{J,\pi}(\beta)}{\sum_{\delta} \mathcal{P}_d^{J,\pi}(\delta)}$$

Adding the WIDTH-FLUCTUATION CORRECTION

$$\sigma_{ab} = \frac{\pi}{k_a^2} \sum_{J,\pi} \sum_{\alpha,\beta} \frac{2J+1}{(2s+1)(2I+1)} \frac{\mathcal{P}_a^{J,\pi}(\alpha) \mathcal{P}_b^{J,\pi}(\beta)}{\sum_{\delta} \mathcal{P}_d^{J,\pi}(\delta)} \mathbf{W}_{\alpha,\beta}$$

Adding the DENSITY OF RESIDUAL NUCLEUS LEVELS

$$\sigma_{ab} = \frac{\pi}{k_a^2} \sum_{J,\pi} \sum_{\alpha,\beta} \frac{2J+1}{(2s+1)(2I+1)} \frac{\mathcal{P}_a^{J,\pi}(\alpha) \langle \mathbf{T}_b^{J,\pi}(\beta) \rangle}{\sum_{\delta} \langle \mathbf{T}_d^{J,\pi}(\delta) \rangle} W_{\alpha,\beta}$$

# Nuclear reaction theory: compound

## Averaging over Residual Nucleus Density Levels

Emission  $\rightarrow$  discrete level with energy  $E_b$

$$\langle T_b(\beta) \rangle = T_b^{J\pi}(\beta) \text{ (from O.M.Potential)}$$

Emission in the continuum level

$$\langle T_b(\beta) \rangle = \int_E^{E+\Delta E} T_b^{J\pi}(\beta) \rho(E, J, \pi) dE$$

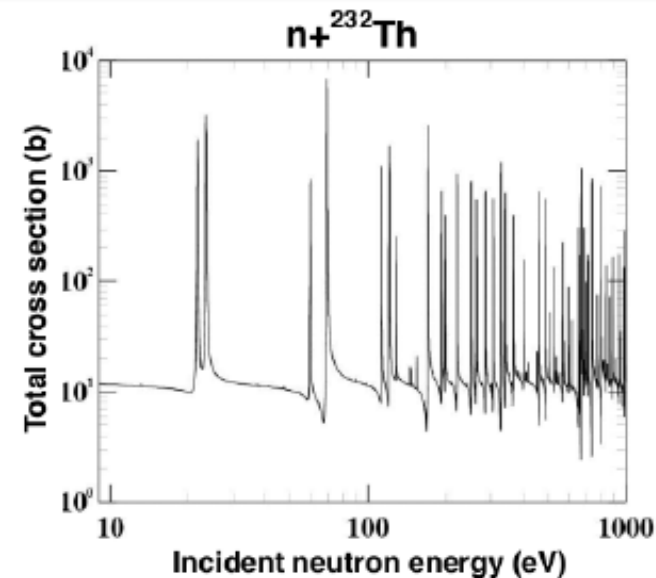
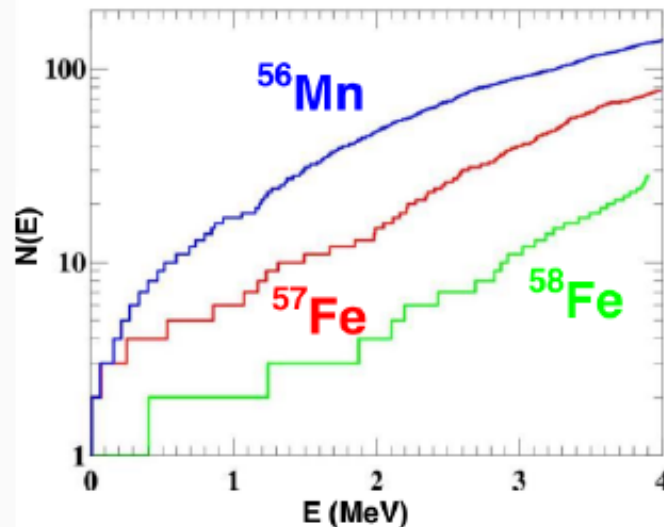
$\rho(E, J, \pi)$  DENSITY of residual nuclear levels  $(J, \pi)$  with excitation energy  $E$

## CN multiple emissions



# Nuclear reaction theory: compound

## Level Density : overview



- Exponential increase of the cumulated number of discrete levels  $N(E)$  with energy

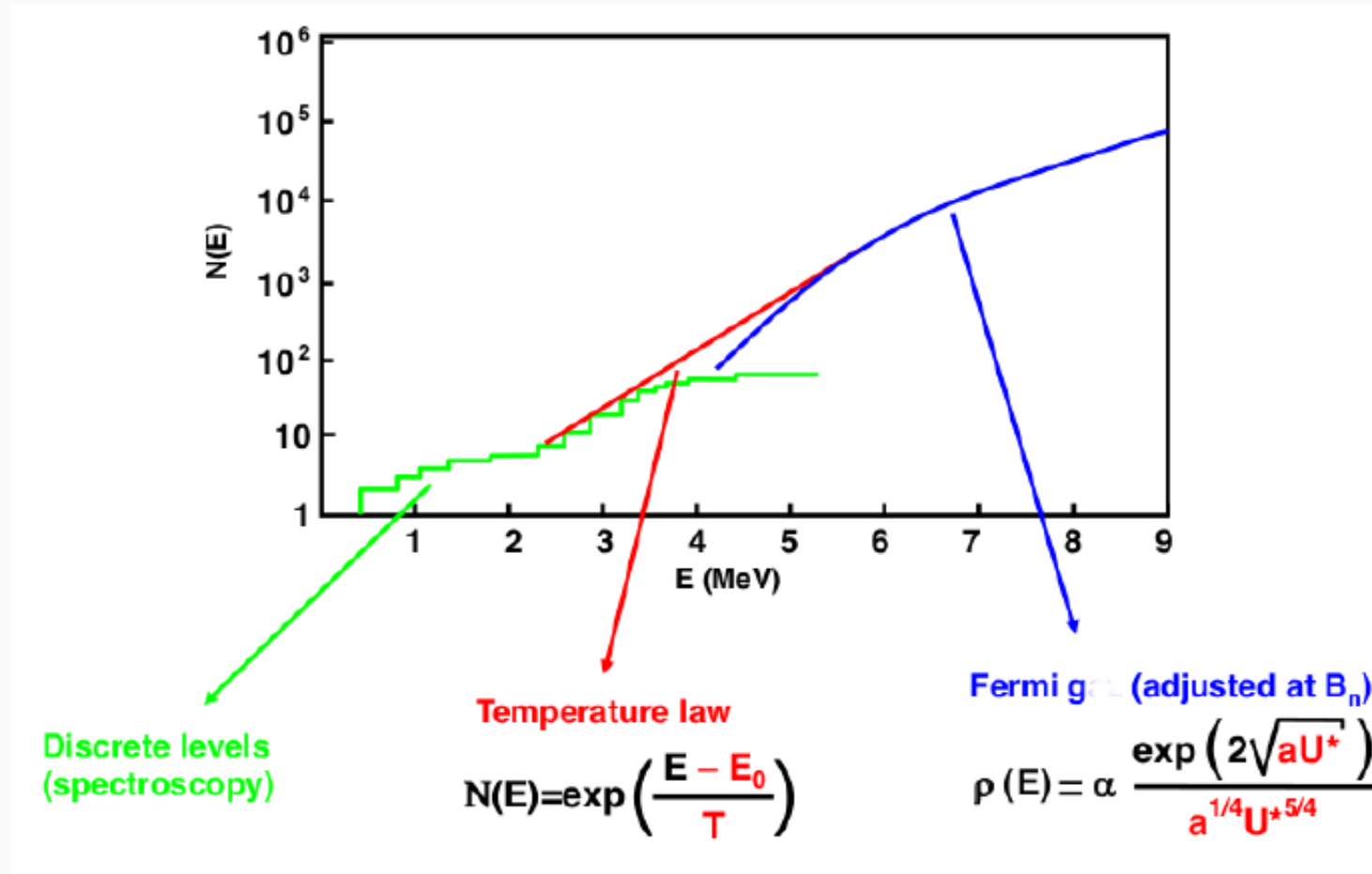
- $\Rightarrow \rho(E) = \frac{dN(E)}{dE}$  increases exponentially

$\Rightarrow$  odd-even effects



# Nuclear reaction theory: compound

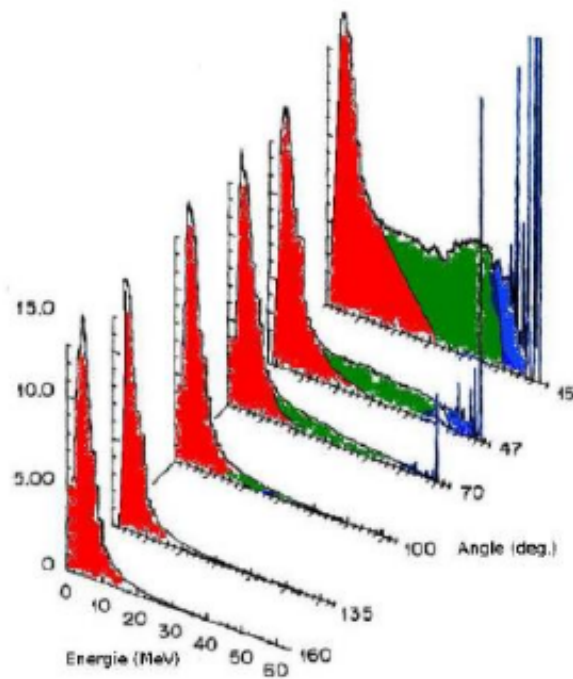
## Level Density : general description



# Nuclear reaction theory: pre-equilibrium

## Angular/energy distributions

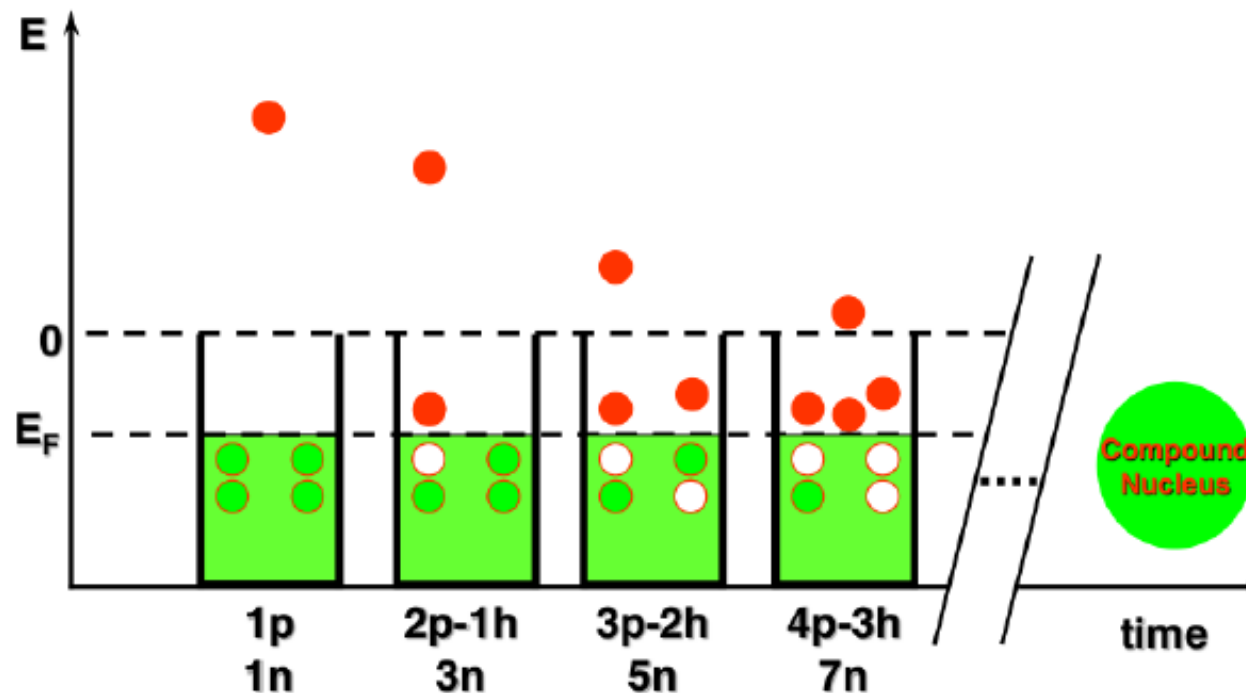
62 MeV  $^{56}\text{Fe}$  (p,xp)  
Double differential cross sections



- Always evaporation peak
- Discrete peaks at forward angles
- **Flat intermediate region**

# Nuclear reaction theory: pre-equilibrium

## Sketch of the excitation model



# Nuclear reaction theory: pre-equilibrium

## Sketch of the master equation

- $q(n, E, t)$  Probability of finding the composite system in exciton  $n$  and energy  $E$
- $\lambda^\pm(n, E)$  Transition rate  $n \rightarrow n \pm 2$
- $w(n, E)$  Total emission rate from  $n$  excitons

$$\dot{q}(n, t) = \lambda^+(n-2)q(n-2, t) + \lambda^-(n+2)q(n+2, t) - (\lambda^+(n) + \lambda^-(n) + w(n))q(n, t)$$

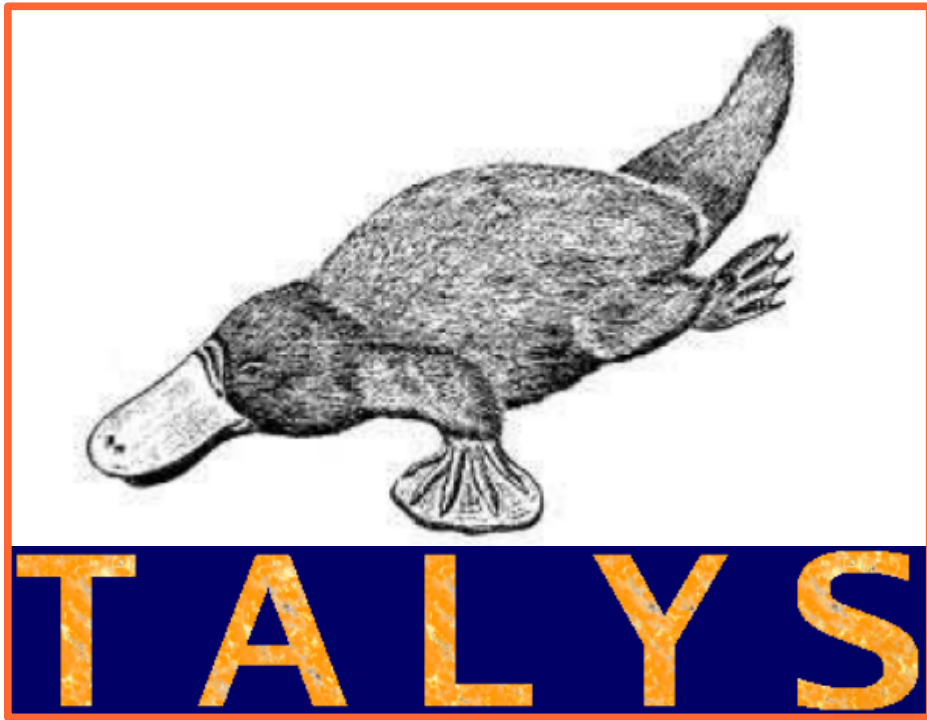
$$\frac{d\sigma^{P.E.}}{dE}(a, b) = \sigma_a \sum_{n, \Delta n=2} w_b(n, E) \int_0^\infty q(n, E, t) dt$$



# Nuclear reaction calculations ... codes

Talys 1.9, Fluka dev 2018.1, Empire 3.2

A. Koning, et al. "TALYS: A nuclear reaction program",  
User Manual (2015)



(developed by NRG-CEA)



M. Herman, et al, "EMPIRE: Nuclear Reaction Model  
Code System for Data Evaluation", Nucl. Data Sheets,  
108 (2007) 2655-2715.

(maintained by IAEA)

T.T. Böhlen, et al. "The FLUKA Code: Developments and  
Challenges for High Energy and Medical Applications",  
Nuclear Data Sheets 120, 211-214 (2014)

(developed by INFN-CERN)



# Nuclear Reaction Calculations

Table 1: Pre-equilibrium (PE) and level density (LD) Models used by the referenced codes. <sup>1</sup>

Code	Pre-equilibrium		Level density	
	Model		Model	
Talys	1	Exciton (analytical)	1	CT+FG
	2	Exciton (numerical)	2	BSFG
	3	Exciton + Optical	3	GSFM
	4	MSD/MSD	4	Microscopic (Goriely)
	(5)	New Exciton	5	Microscopic (Hilaire)
		Geometry dependent	6	T-dep HFB
Empire	HMS		EGSM	
Fluka	PEANUT		Modified FG	

<sup>1</sup>MSD: Multi-Step Direct, MSC: Multi-Step Compound, CT: Constant temperature, FG: Fermi Gas, BSFG: Back Shifted Fermi Gas, GSFM: Generalized SuperFluid Model, HFB: Hartree-Fock-Bogoliubov. PEANUT: Pre-equilibrium Approach to Nuclear Thermalization, HMS: Hybrid Montecarlo Simulation, EGSM: Enhanced Generalized Superfluid Model.

# The importance of RIPL


## Nuclear Data Services

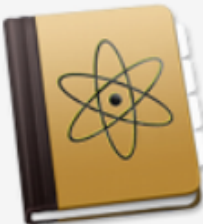
Provided by the Nuclear Data Section

Search..

EXFOR | ENDF | CINDA | IBANDL | Medical | PGAA | NGAtlas | RIPL | FENDL | IRDFF

Links  
Services  
Distribution  
(Nucl. Data)





### Reference Input Parameter Library (RIPL-3)

R. Capote, M. Herman, P. Oblozinsky, P.G. Young, S. Goriely, T. Belgia, A.V. Ignatyuk, A.J. Koning, S. Hilaire, V.A. Plujko, M. Avrigeanu, O. Bersillon, M.B. Chadwick, T. Fukahori, Zhigang Ge, Yinlu Han, S. Kailas, J. Kopecky, V.M. Maslov, G. Reffo, M. Sin, E.Sh. Soukhovitskii and P. Talou

*Nuclear Data Sheets - Volume 110, Issue 12, December 2009, Pages 3107-3214*

RIPL dis

[Introduction](#) | [MASSES](#) | [LEVELS](#) | [RESONANCES](#) | [OPTICAL](#) | [DENSITIES](#) | [GAMMA](#) | [FISSION](#) | [CODES](#) | [Contacts](#)

### Introduction

We describe the physics and data included in the Reference Input Parameter Library, which is devoted to input parameters needed in calculations of nuclear reactions and nuclear data evaluations. Advanced modelling codes require substantial numerical input, therefore the International Atomic Energy Agency (IAEA) has worked extensively since 1993 on a library of validated nuclear-model input parameters, referred to as the Reference Input Parameter Library (RIPL). A final RIPL coordinated research project (RIPL-3) was brought to a successful conclusion in December 2008, after 15 years of challenging work carried out through three consecutive IAEA projects. The RIPL-3 library was released in January 2009, and is available on the Web through <http://www-nds.iaea.org/RIPL-3/>. This work and the resulting database are extremely

# Modeling of the relevant **cross sections** with nuclear reaction code

**TALYS**

1 – 4 **pre-equilibrium** models  
1 – 6 **level density** models

24 combinations of models  
(or 30 with pre-equilibrium 5)

Talys default  
& adjusted

Statistical band & **BTE**

$$BTE = \frac{Q_1 + Q_3}{2}$$

**Talys modified**

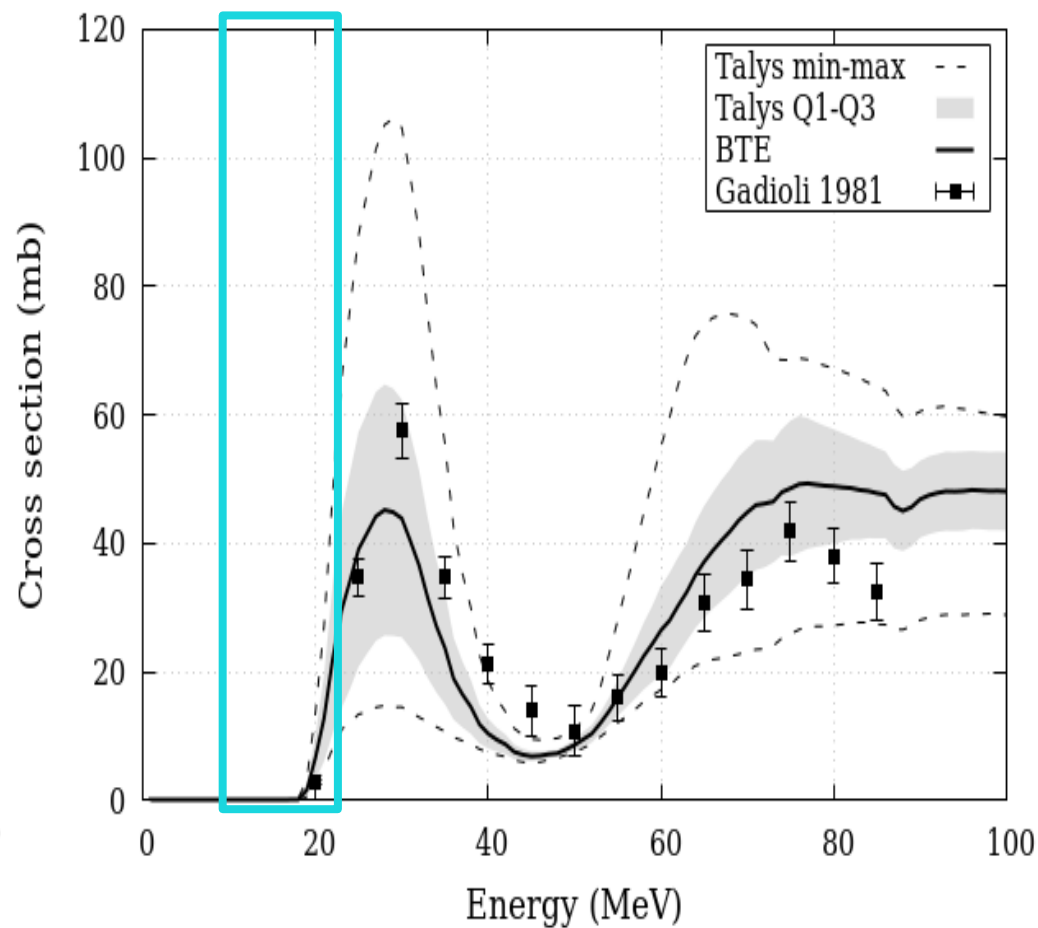
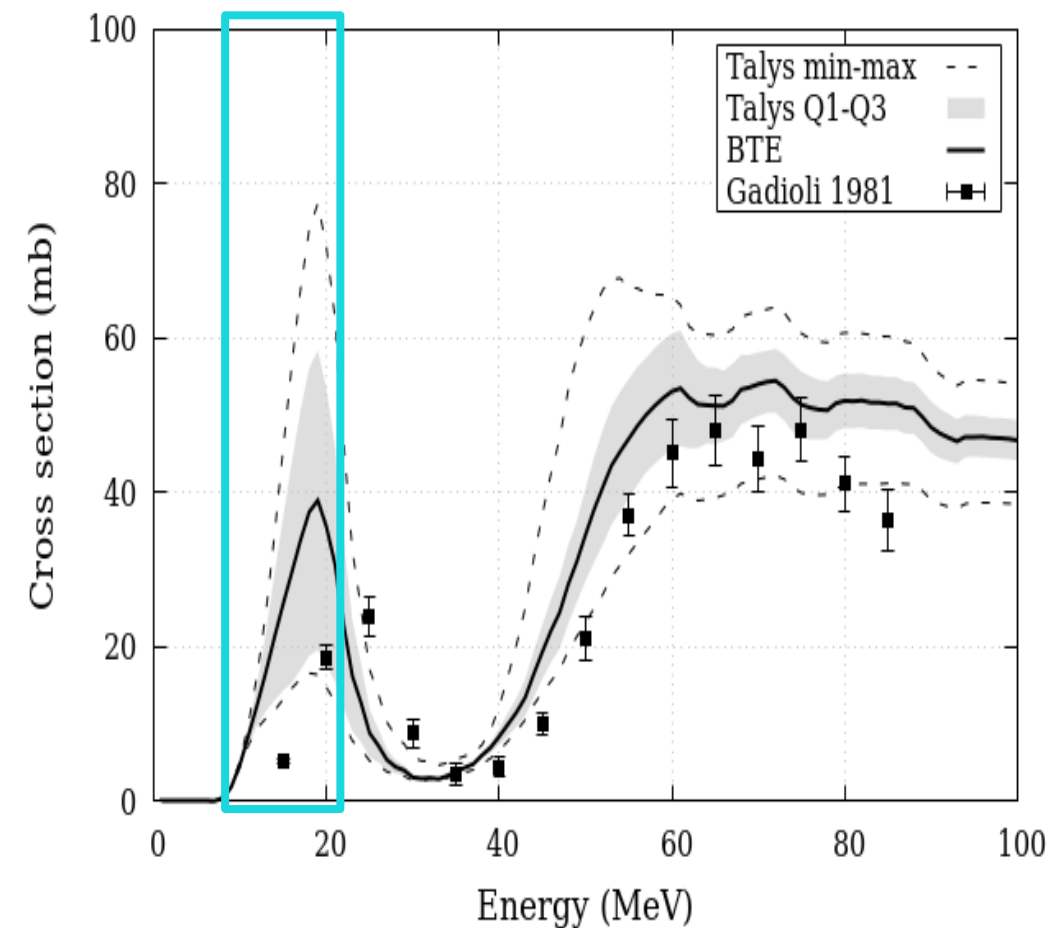
**c** normalization  
**p** energy shift

$$\rho(E) = \exp(c \sqrt{E - p}) \rho(E - p)$$

# $^{50}\text{Ti}$ – statistical band & BTE

$^{50}\text{Ti}(p,x)^{47}\text{Sc}$

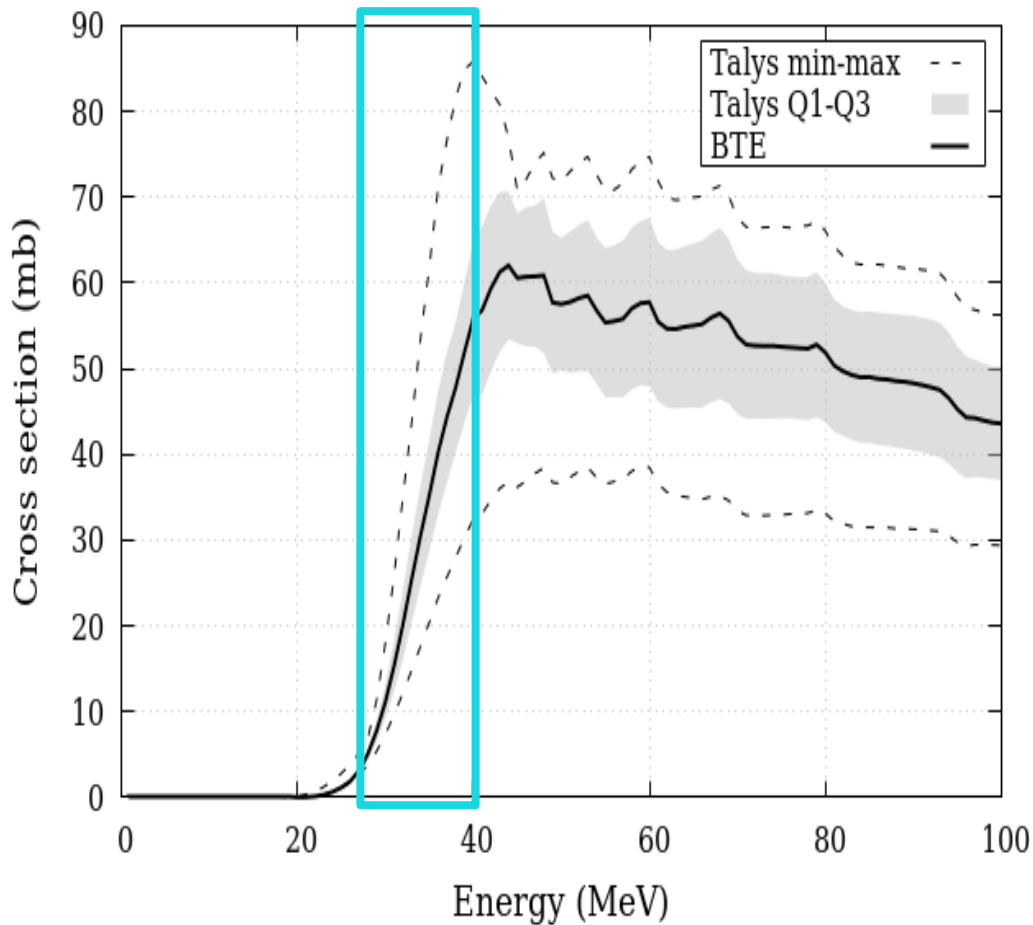
$^{50}\text{Ti}(p,x)^{46}\text{Sc}$



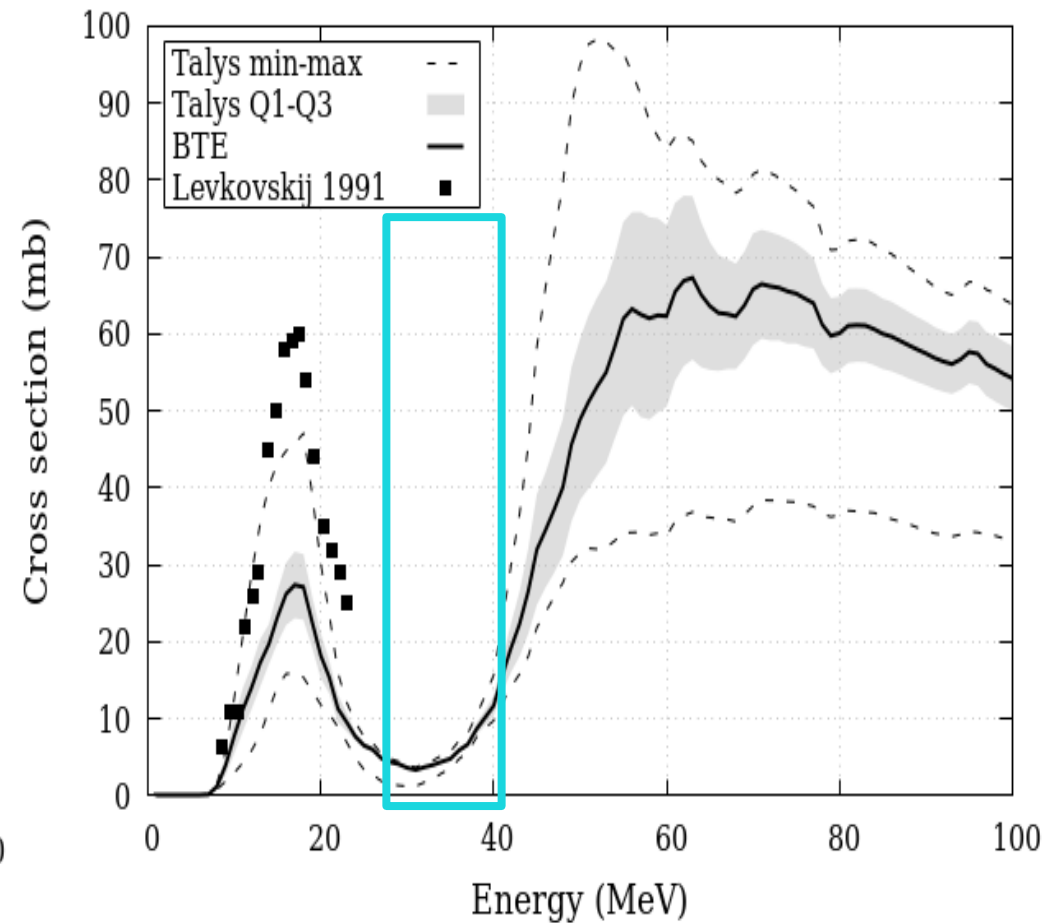


# $^{49}\text{Ti}$ – statistical band & BTE

$^{49}\text{Ti}(p,x)^{47}\text{Sc}$



$^{49}\text{Ti}(p,x)^{46}\text{Sc}$



# Microscopic NLD parameter optimization

**NEW DATA FROM REMIX! WORLD FIRST MEASUREMENT OF SC47 PRODUCTION FROM ENRICHED TI47 TARGETS.....**

PE 5 → Geometry Dependent Hybrid (GDH) model

LD 4 → Microscopic Hartree-Fock Nuclear Level Densities

(Skyrme Force, Goriely's tables)

$$\rho(E) = \exp\left(\frac{c}{\sqrt{E - p}}\right) \rho(E - p)$$

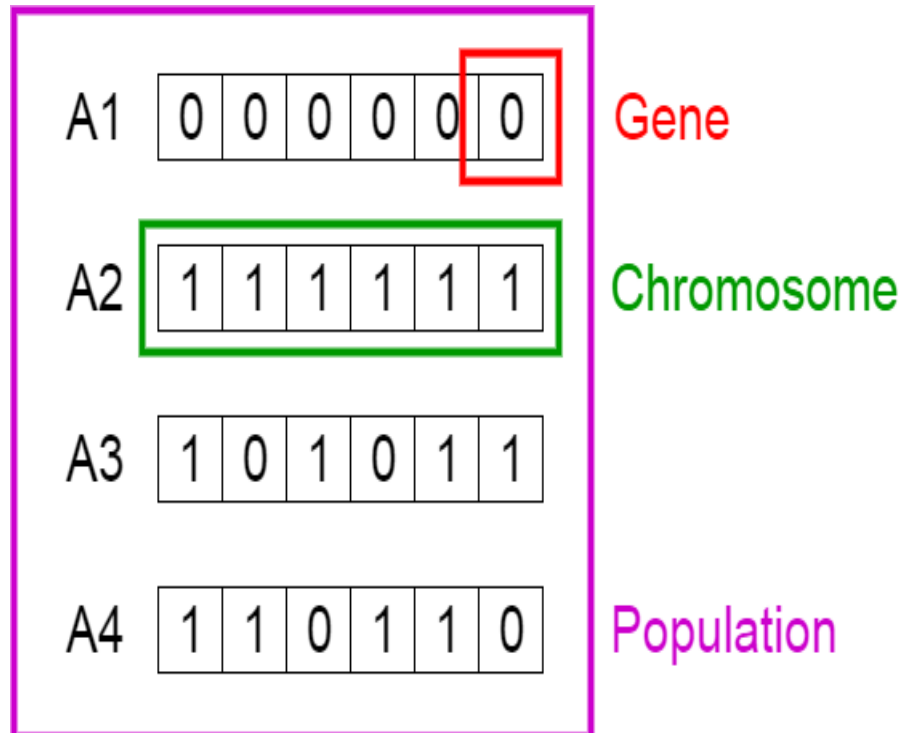
**OPTIMIZATION**

Based on **Genetic Algorithms**  
Multiparameter optimization for  
all related measured cross sections  
Sc(43,44g,44m,46,47,48); K(42,43);  
V(48)

# Genetic Algorithms

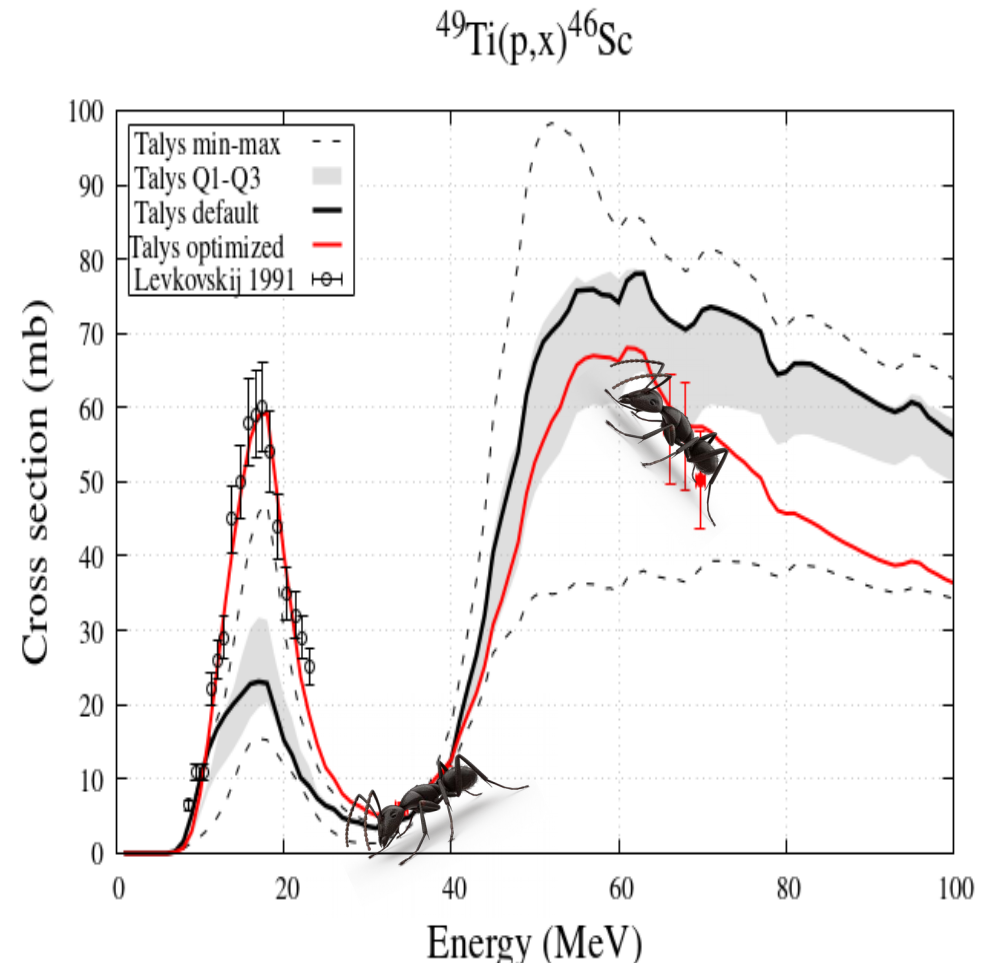
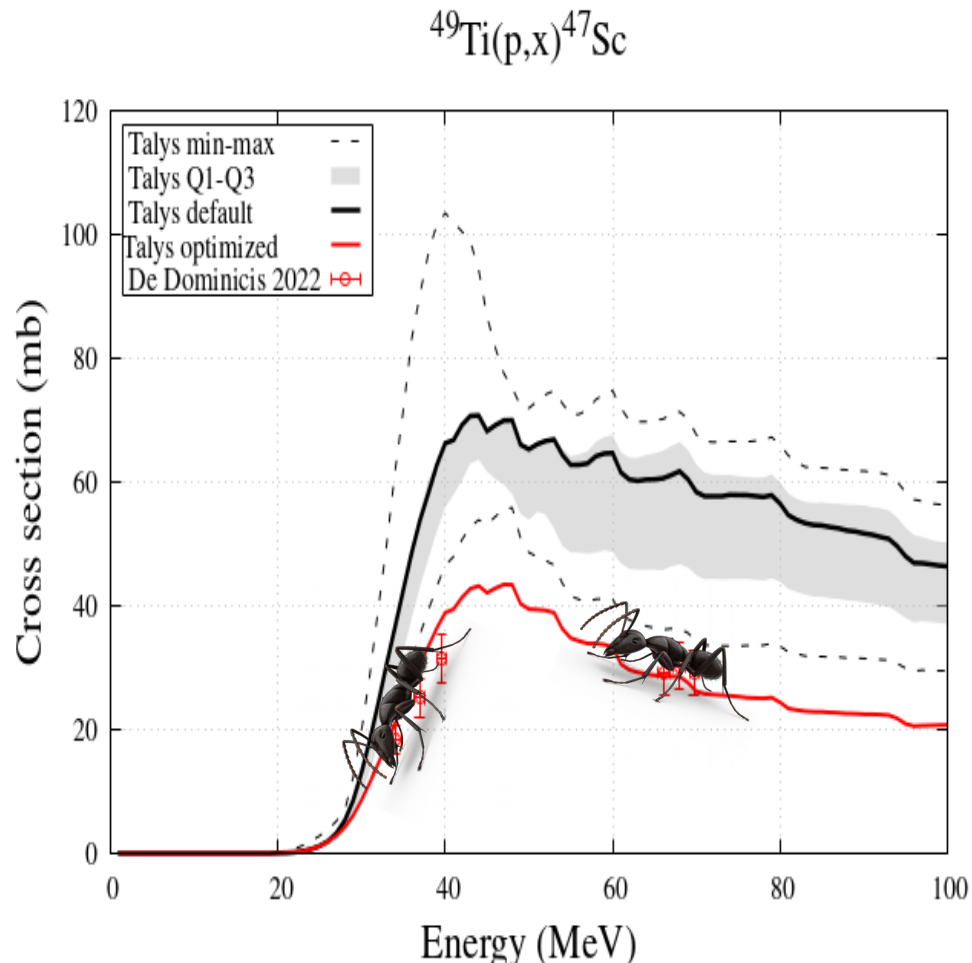
**Genetic Algorithm:** optimization inspired by Darwin's theory of natural evolution.

**Codifica del problema in "cromosomi"**



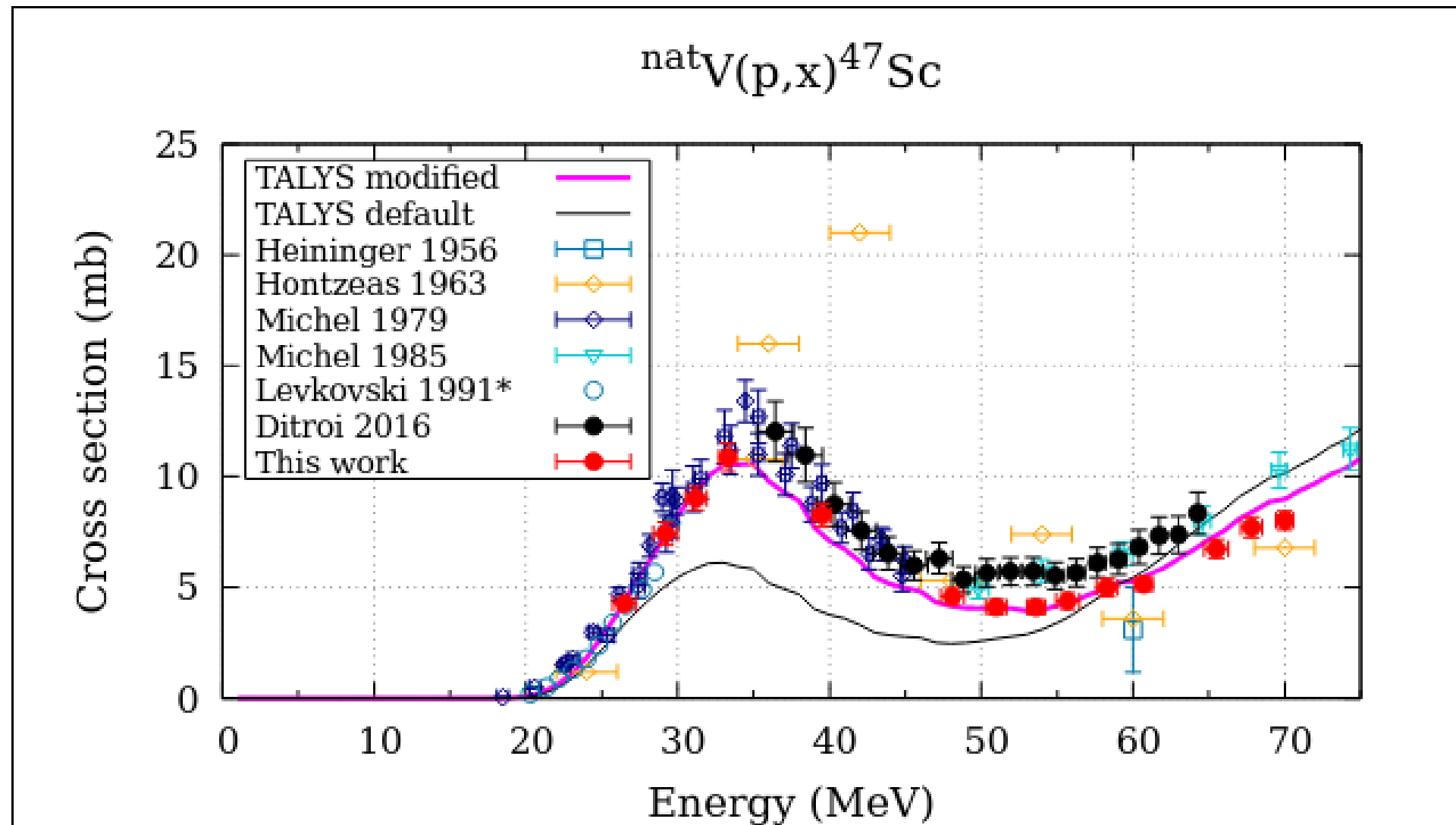
```
START
Generate the initial population
Compute fitness
REPEAT
    Selection
    Crossover
    Mutation
    Compute fitness
UNTIL population has converged
STOP
```

# $^{49}\text{Ti}$ – Genetic Algorithm for NLD



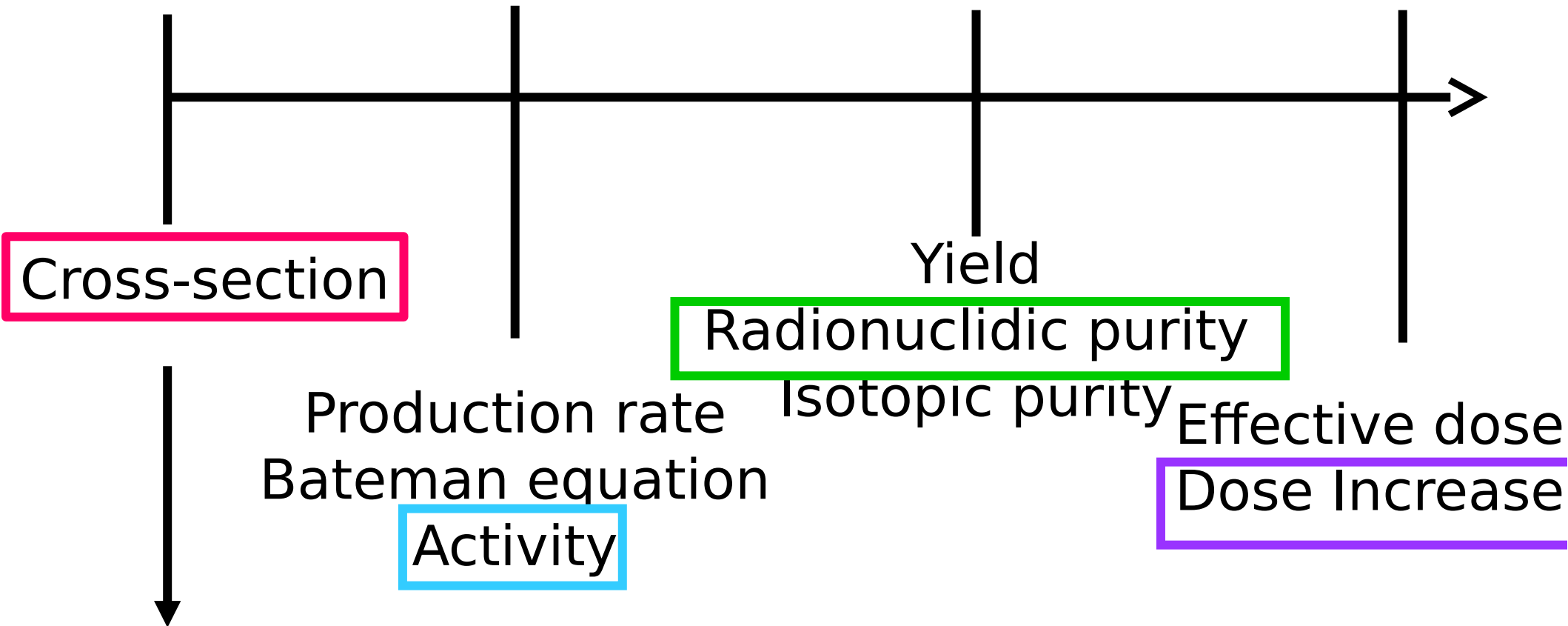
Preliminary REMIX data not yet validated and not public.

# Previous experience with Vnat targets Phys Rev C 2021





# Path to assess the production route



**nuclear reaction  
codes supported by nuclear data**

# Path to assess the production route (depends on irradiation conditions)

European Pharmacopoeia requires a  
**radionuclidic purity (RNP)** greater than **99%**

$$RNP = \frac{A_{^{52g}Mn}}{\sum_i A_i}$$

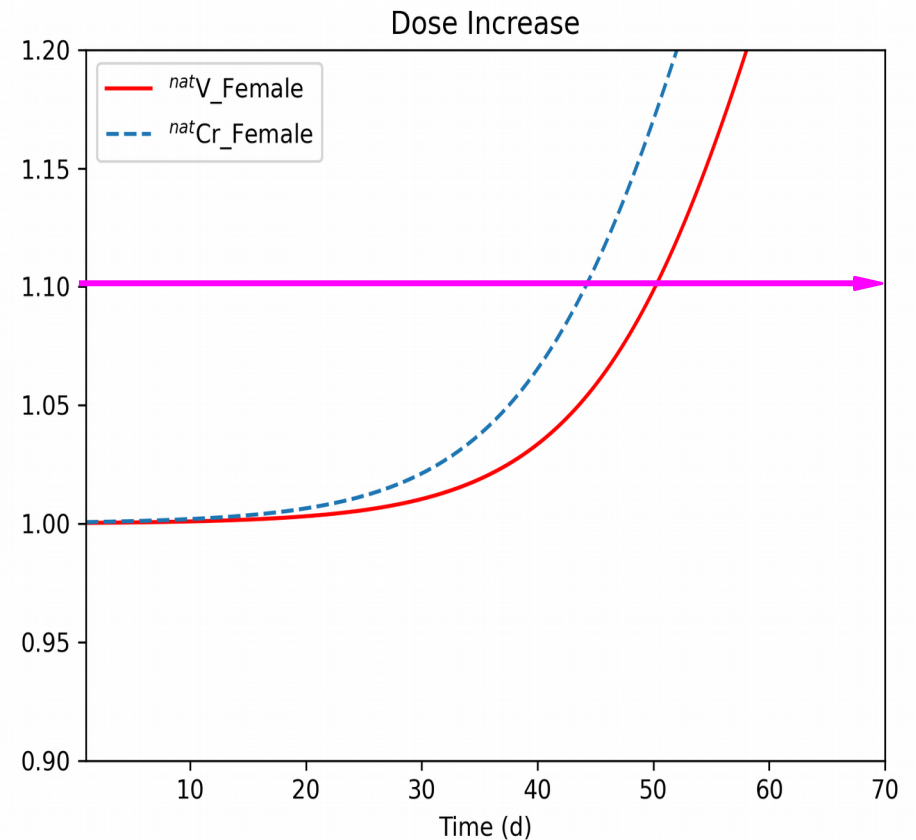
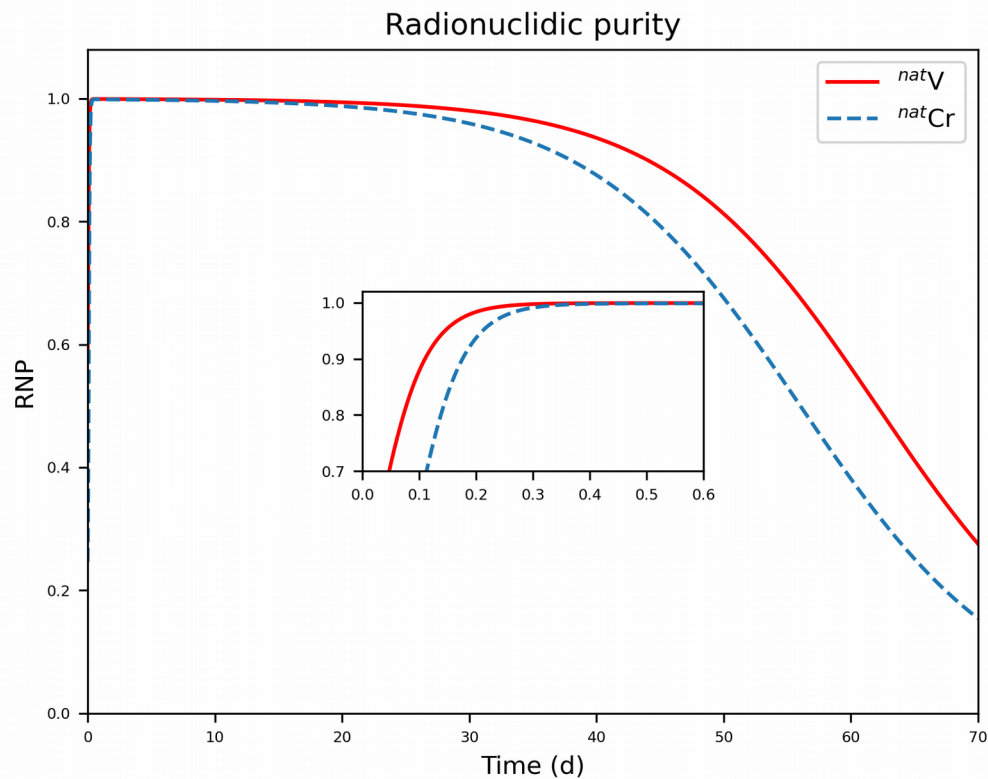
**<sup>52g</sup>Mn case**

**Dose Increase (DI)** caused by the impurities  
should be maintained within the **10% limit**

$$DI = \frac{ED_t(t)}{ED_{^{52g}Mn}}$$

**<sup>52g</sup>Mn case**

# Path to assess the 2 production routes ( $^{52}\text{gMn}$ case)



Conclusion: Nucl Tecn (2022) and arXiv:2204.00402  
 $\text{natV}(\alpha, x)^{52}\text{gMn}$  is more efficient than  $\text{natCr}(p, x)^{52}\text{gMn}$

# Conclusions

- Radiopharmaceutical production is a very interdisciplinary project involving Nuclear Science and Nuclear Data for medical applications.
- Nuclear modeling (cross sections, rates, activities, purities, etc) is an important aspect together with nuclear experiments and technology.
- So far, we have assessed and compared production routes including analysis of co-produced contaminants.
- $^{47}\text{Sc}$ :  $^{\text{nat}}\text{V}(\text{p},\text{x})$ ,  $^{50}\text{Ti}(\text{p},\text{x})$ ,  $^{49}\text{Ti}(\text{p},\text{x})$  [?]. Moderate production feasible.
- $^{52\text{g}}\text{Mn}$ :  $^{\text{nat}}\text{Cr}(\text{p},\text{x})$ ,  $^{\text{nat}}\text{V}(\alpha,\text{x})$ : better V targets than Cr.
- $^{117\text{m}}\text{Sn}$ :  $^{\text{nat}}\text{Cd}(\alpha,\text{x})$ ,  $^{\text{nat}}\text{In}(\alpha,\text{x})$ : better In than Cd.
- Next  $^{155}\text{Tb}$  : potentially producible with hospital cyclotrons  $^{155}\text{Gd}(\text{p},\text{n})$
- Societal impact:  
this type of research could lead to new lifesaving methods in the future.

# For 1h irradiation

Target	Energy Range	$^{47}\text{Sc}$ (MBq/ $\mu\text{A}$ )	$^{46}\text{Sc}$ (MBq/ $\mu\text{A}$ )
$^{50}\text{Ti}$	$\sim 10\text{-}20$	$\sim 5$	$1.1\text{E-}4$
natV	$\sim 20\text{-}30$	$\sim 1.0 - 1.5$	$6.0\text{E-}4$
$^{49}\text{Ti}$	$\sim 30\text{-}40$	$\sim 20$	0.13



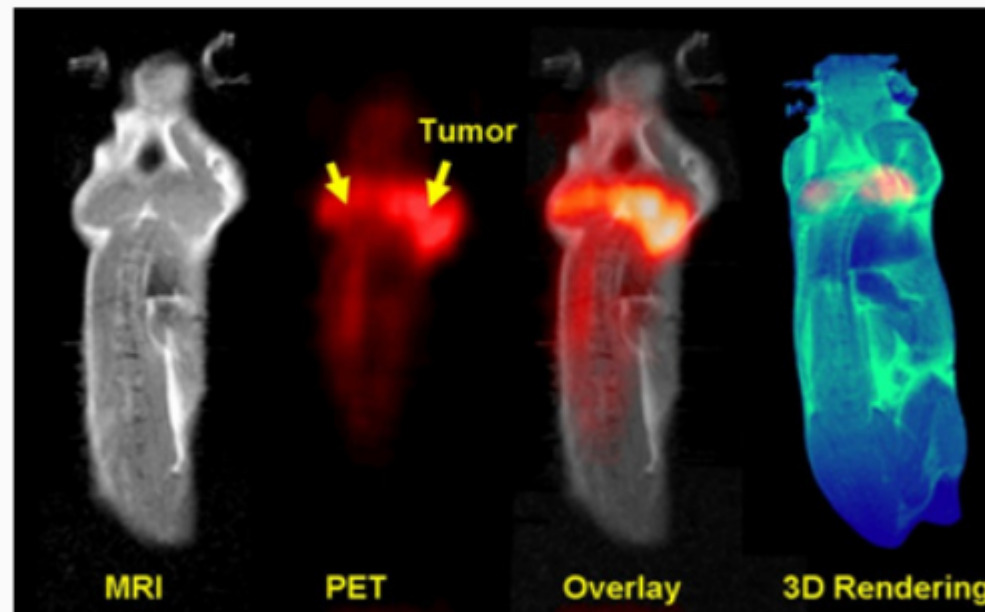
**NO**

Per il momento escluso, a causa della produzione del contaminante secondario  $^{48}\text{Sc}$ , e non solo...

# Multimodal pET/mRi Imaging with Cyclotron-produced $^{52/51}\text{Mn}$ and stable paramagnetic Mn iSotopes

## PET and MRI fusion

A breakthrough in **Multi-Modal Imaging** (MMI) diagnostic procedures may be achieved with a genuine fusion between PET/SPECT and MRI analyses. However that could be obtained only by using both a radioactive and contrast agent based upon the same chemical compound.



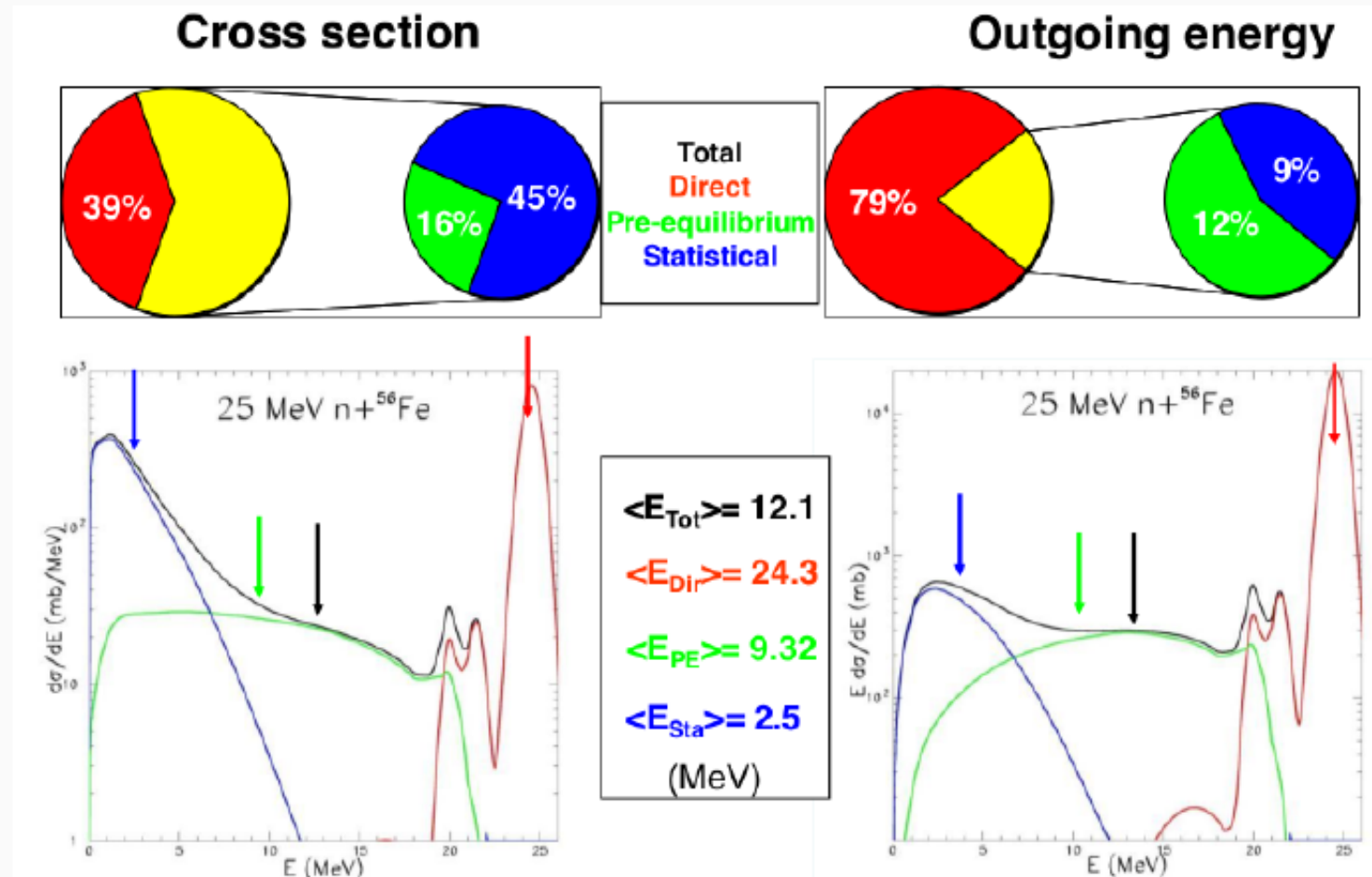
With the recent achievements in PET/MRI scanner technology, the use of radio-manganese, a manganese compound (i.e. a mixture of  $^{52g}\text{Mn}$  and  $^{51}\text{Mn}$ ), may enable future dual modal imaging techniques, having both properties for MRI and PET.

Feasibility study: INFN project **METRICS** (CSN5).



# Nuclear reaction theory: phenomenology

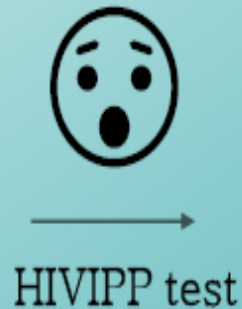
## Overview of reaction components



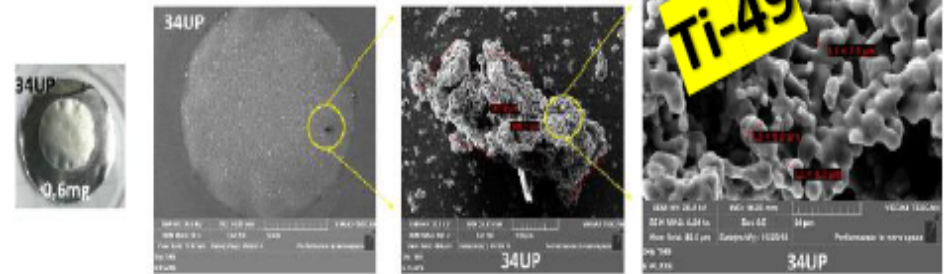
# The problem to work with enriched targets!

Less than 0.5 gram ( $^{49}\text{Ti}$  &  $^{50}\text{Ti}$ ) 27,3 Keuro

- HIVIPP method works with metal powders.. but we received metal sponges of  $^{49}\text{Ti}$  and  $^{50}\text{Ti}$  !



SEM analysis of  $^{49}\text{Ti}$  test target



A. Skliarova, LNL

- Manual test with liquid  $\text{N}_2$  to reduce the grains of  $^{49}\text{Ti}$  into metal powder; HIVIPP deposition and analysis:



$^{49}\text{Ti}$  after deposition No. 34



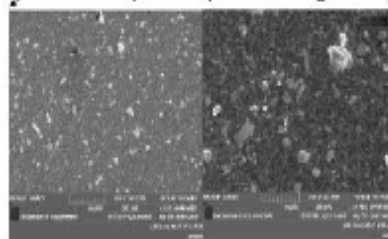
HIVIPP deposition test



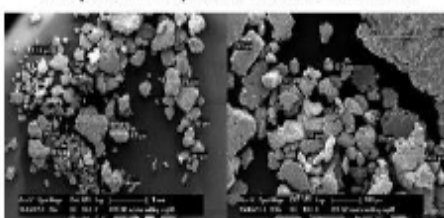
0.2 mg 0 mg



SEM analysis on deposit: "inset" grains



SEM powder analysis after the test: "flat" flakes



The positive outcomes encouraged the use of a **cryomill**, that is able to apply a multidirectional effect on the powder, thanks to a mechanical and vibrational movement.

