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ICTP-IAEA Joint Workshop on Nuclear Data for Science and Technology: Medical Applications

30 September - 4 October, 2013

Internal radionuclide therapy: Part I

F. Roesch

Institute of Nuclear Chemistry
University of Mainz
Germany

Strada Costiera, 11 - 34151 - Trieste - Italy • Tel. +39 0402240111 • Fax. +39 040224163 • sci_info@ictp.it • www.ictp.it
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Internal radionuclide therapy: Part I
(Radionuclides, chemical processing, quality control)

Frank Roesch
Institute of Nuclear Chemistry, University of Mainz, D-55128 Mainz, Germany

Workshop on Nuclear Data for Science and Technology: Medical Applications
30 September to 04 October 2013
Miramare – Trieste, Italy

Internal radionuclide therapy: Part I

(Radionuclides, chemical processing, quality control)

CANCER

and other diseases*

The wapons:

1. THE radionuclide
2. + a carrier,

   which delivers it selectively to the biological target

*Infection:
Within the 1.5 hour lecture 1.500 peoble will die from an infectious disease; Malaria kills every 30 seconds

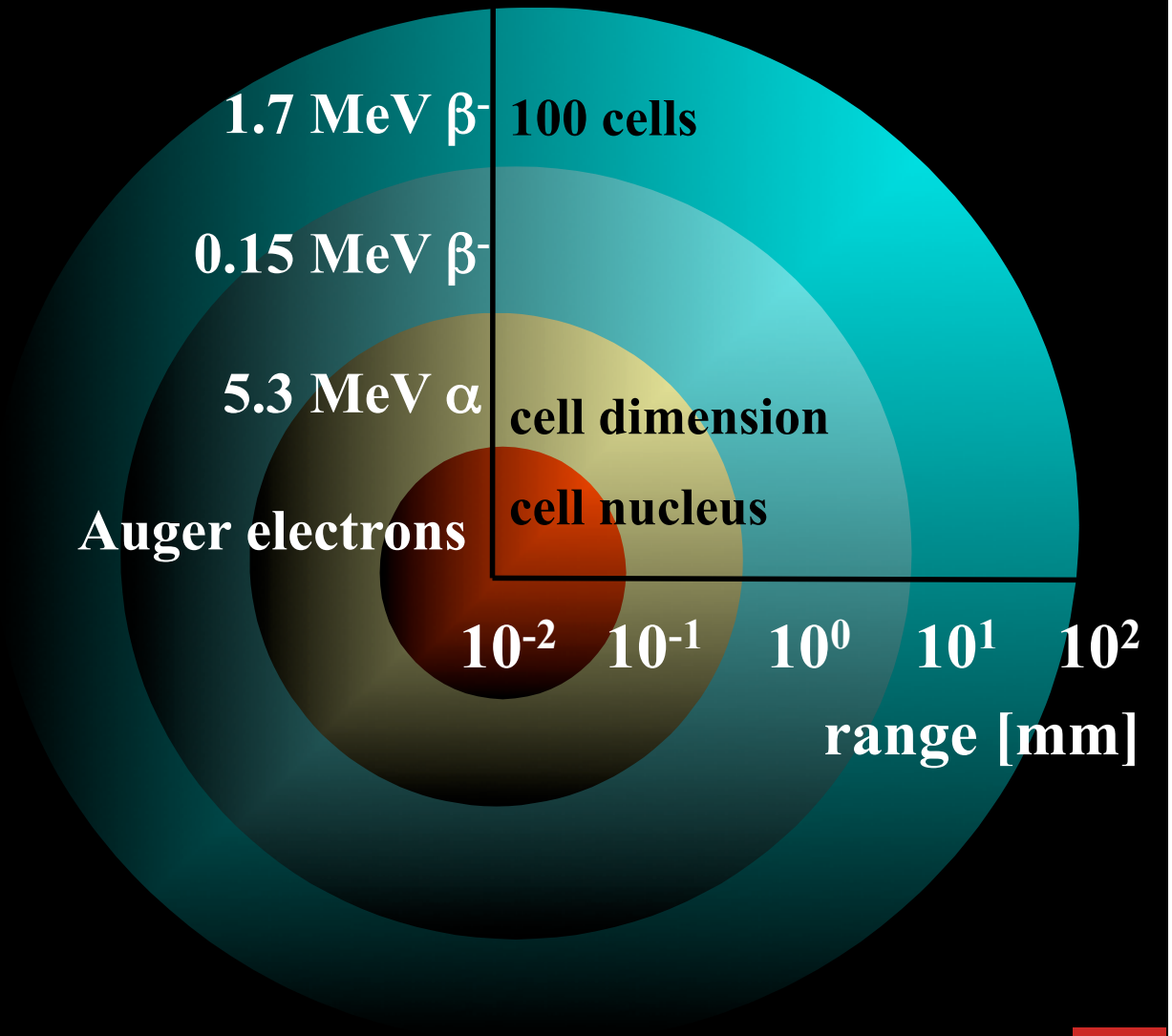
Radionuclides of different kinds of particle emission and varying particle energies / ranges

Selection criteria
(among many others):

Non-penetrating radiation

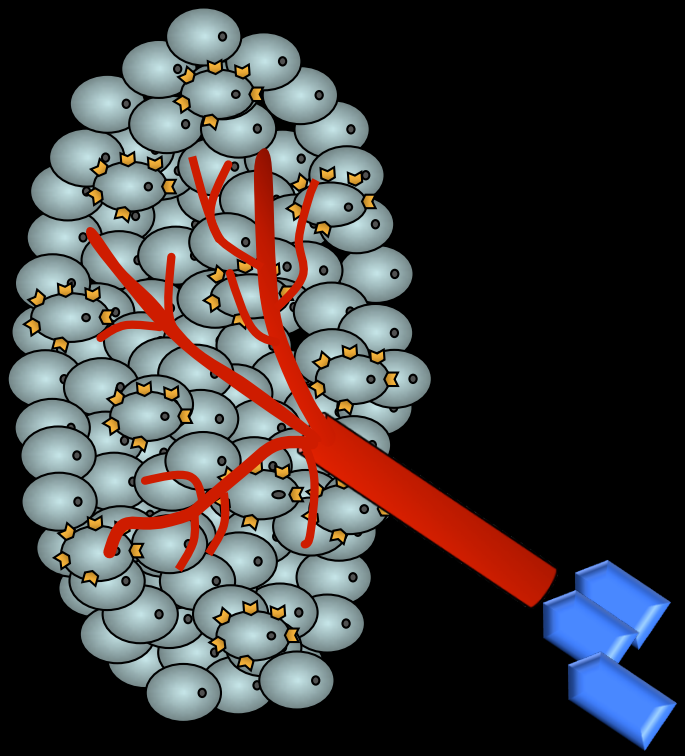
High LET

Focus
all(most) all
radiative emissions
to the target (tumour) cell
(or tissue)

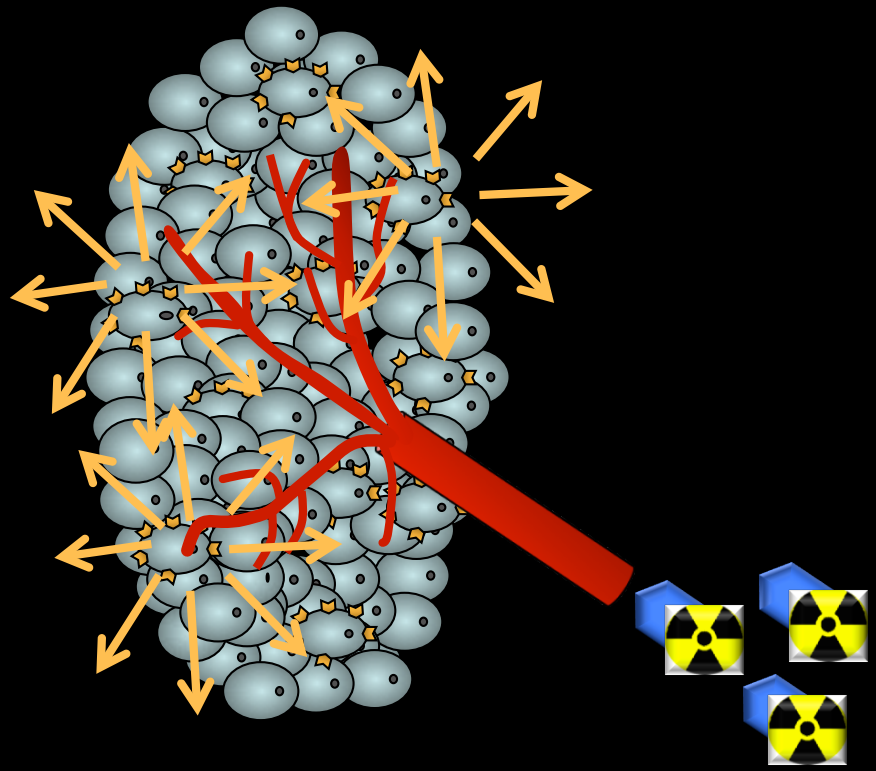


Radionuclides of different kinds of particle emission and varying particle energies / ranges

Targeted therapy



Targeted radionuclide therapy

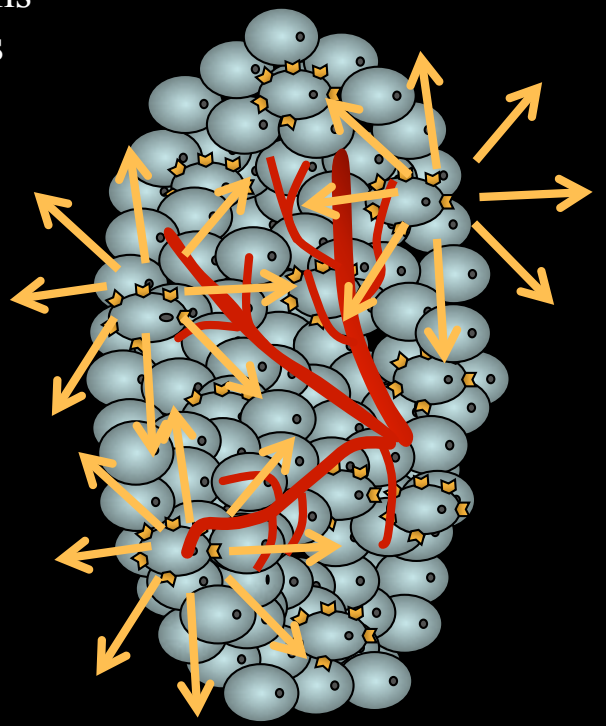


Courtesy Prof. Roger Schibli ETH Zürich

Radionuclides of different kinds of particle emission and varying particle energies / ranges

1.
Must be delivered by means of adequate carrier systems
by tumour-selective and specific radiopharmaceuticals
(“drug development”)

2.
once accumulated at the target,
the radionuclides should act selectively
through its characteristic decay / radiation



3.
… delivery of therapeutic doses
of ionizing radiation
to the malignant cells

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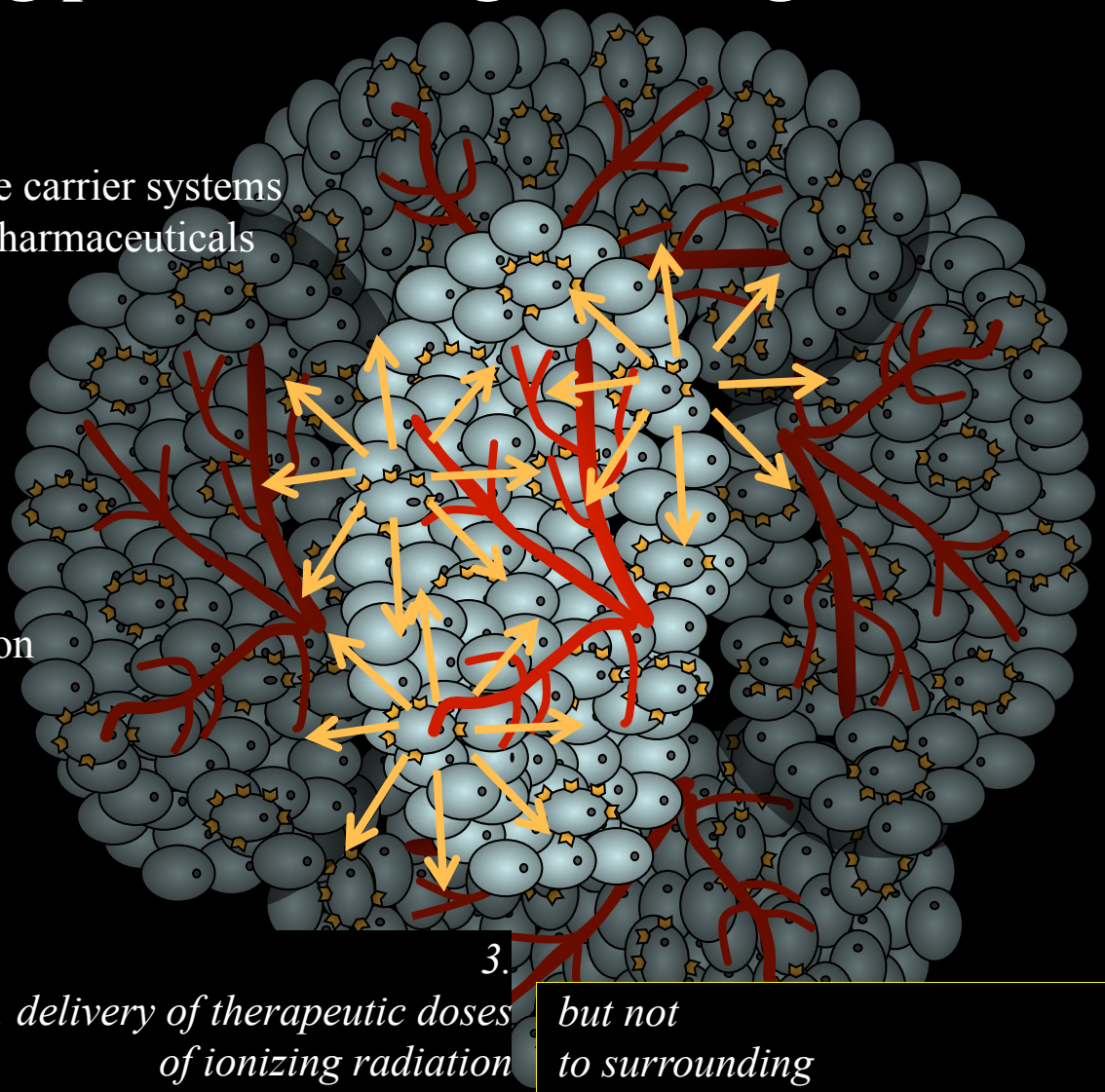


3.
... delivery of therapeutic doses
of ionizing radiation
to the malignant cells

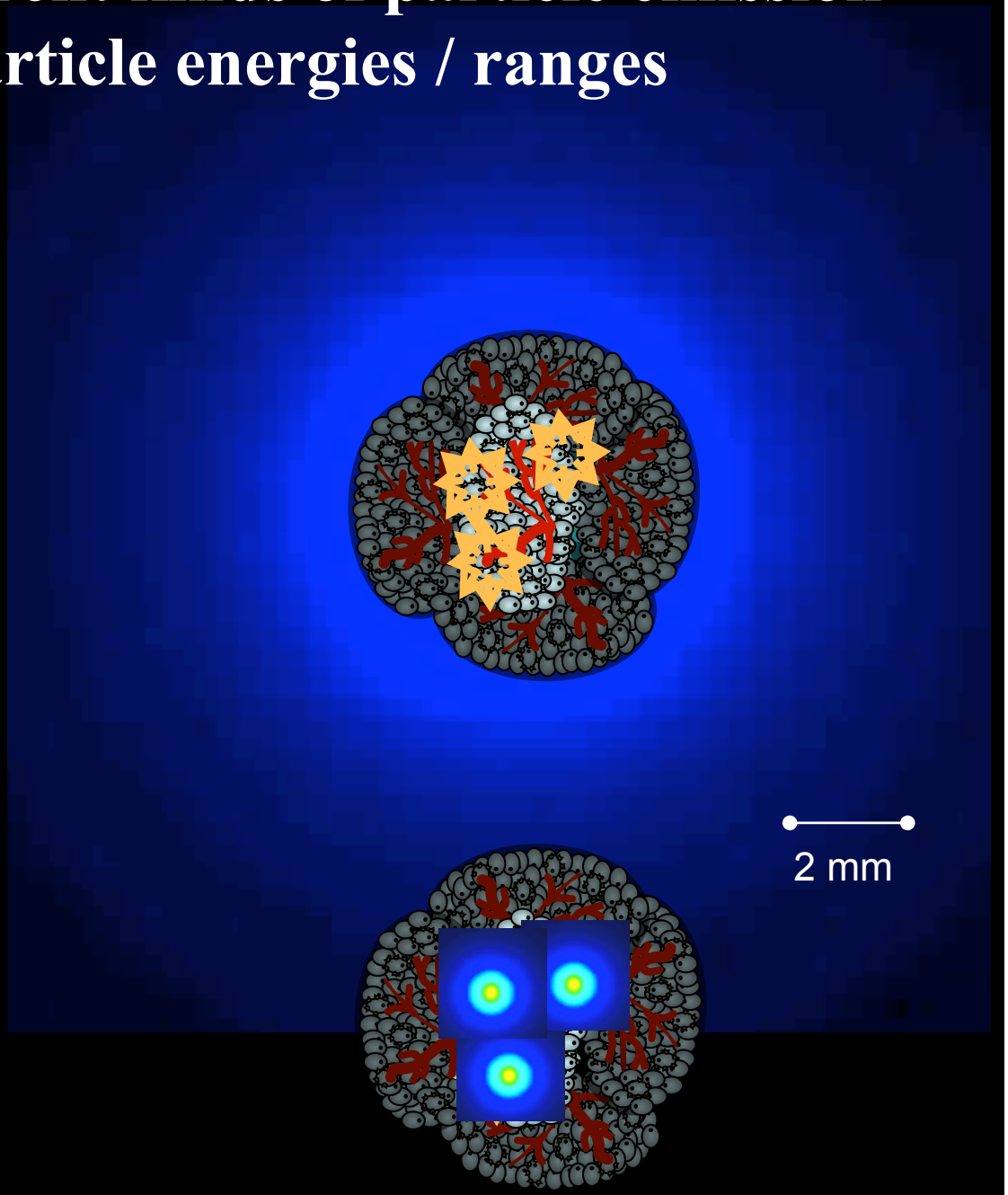
but not
to surrounding
healthy cells

Radionuclides of different kinds of particle emission and varying particle energies / ranges

Energy deposition in tissue

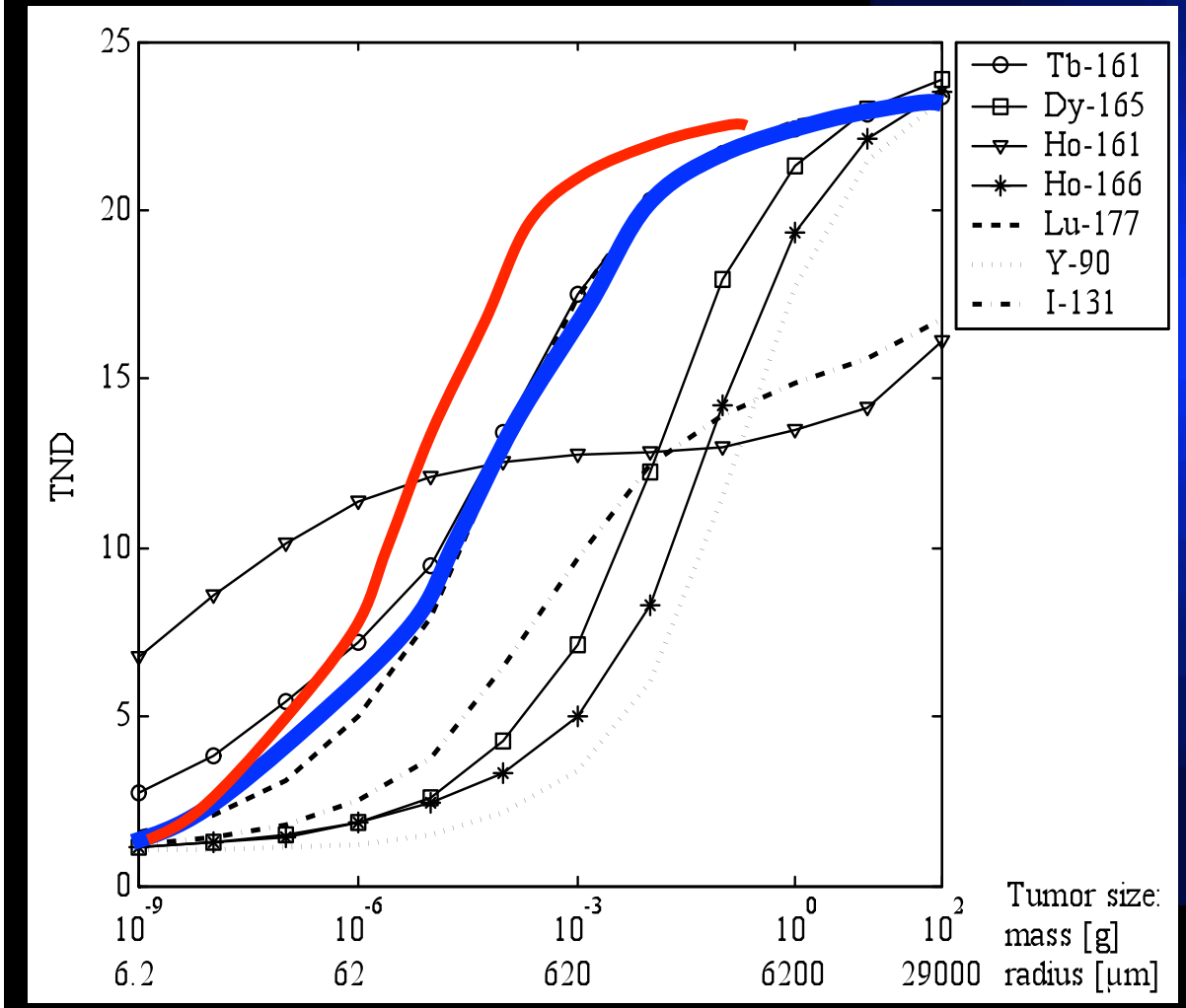
High-energy beta emitter ^{90}Y
mean particle energy 0.933 MeV
max. range 12 mm

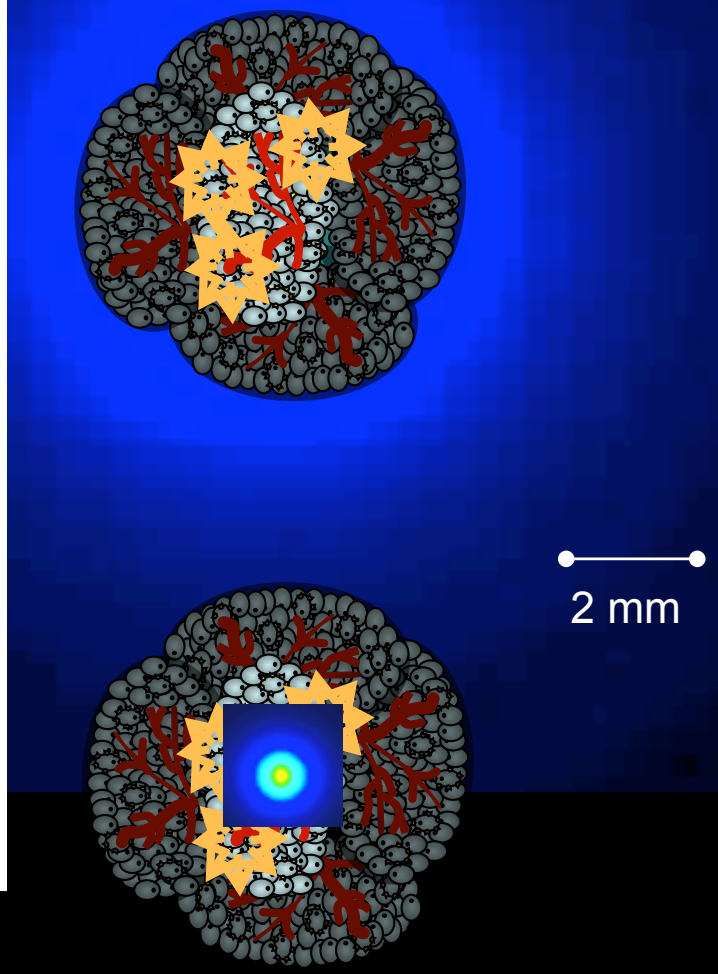
Low-energy beta emitter ^{177}Lu
mean particle energy 0.134 MeV
max. range 2 mm



Radionuclides of different kinds of particle emission and varying pa

TND: tumour-to-normal-tissue mean absorbed dose ratio





H Uusijarvi1, P Bernhardt, F Rosch, HR Maecke, E Forssell-Aronsson
Electron- and Positron-Emitting Radiolanthanides for Therapy: Aspects of Dosimetry and Production
J Nucl Med 2006; 47:807–814

Internal radionuclide therapy: Part I
(Radionuclides, chemical processing, quality control)

1	**Individual Radionuclides:**	**Selection Criteria**
2	**Individual Radionuclides: Production Routes**	**Reactors: Neutron Capture** **Cyclotrons: Charged projectiles** **Radionuclide Generators**
3	**Production Batch Activities vs.**	**Specific Radioactivity**
4	**(Radio)chemical Separation**	**Target / Product nuclide**
5	**Radionuclides**	**Chemistry general**
6	**(Radio)chemical Labelling**	

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Individual Radionuclides for Endoradiotherapy (ERT)
Selection Criteria

Emission profile	**Non-penetrating radiation vs. penetrating (γ-photons)**
	High LET
Purity	**Radionuclidic, specific activity**
Yield	**Adequate (also for commercial purposes)**
Production	**Nuclear reaction**
	Targetry
	Radochemical separation
	Target recovery
	Costs
Access	**high**
Half-life	**adequate**
Chemistry	**Adequate to radiopharmaceuticals ?**

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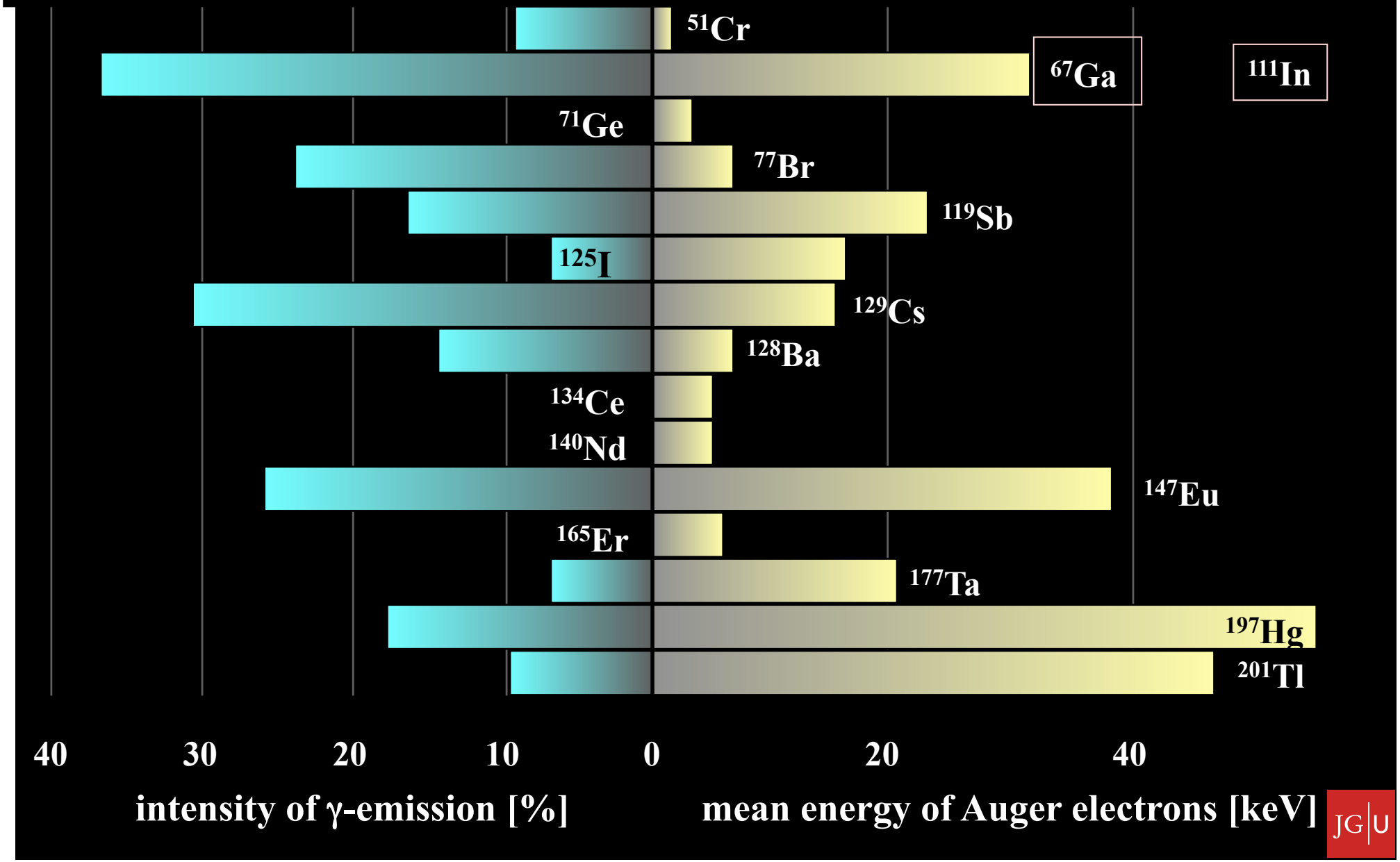
potential Auger / conversion electron emitters



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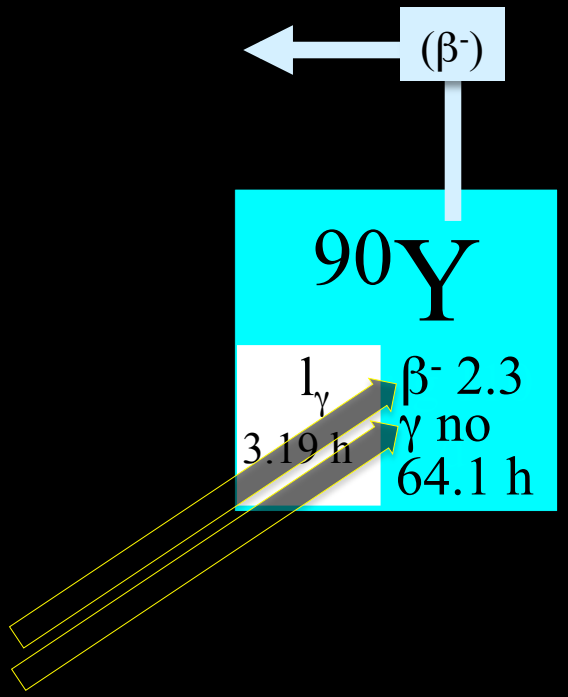

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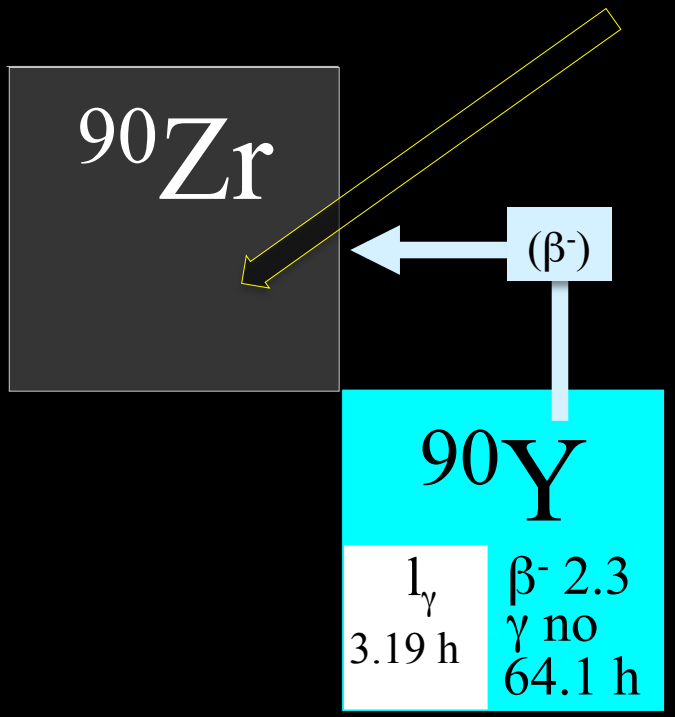

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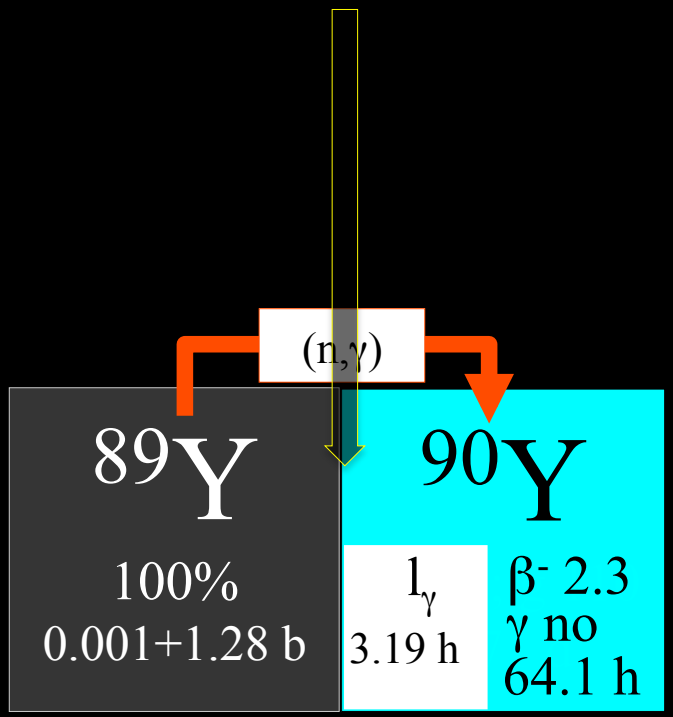

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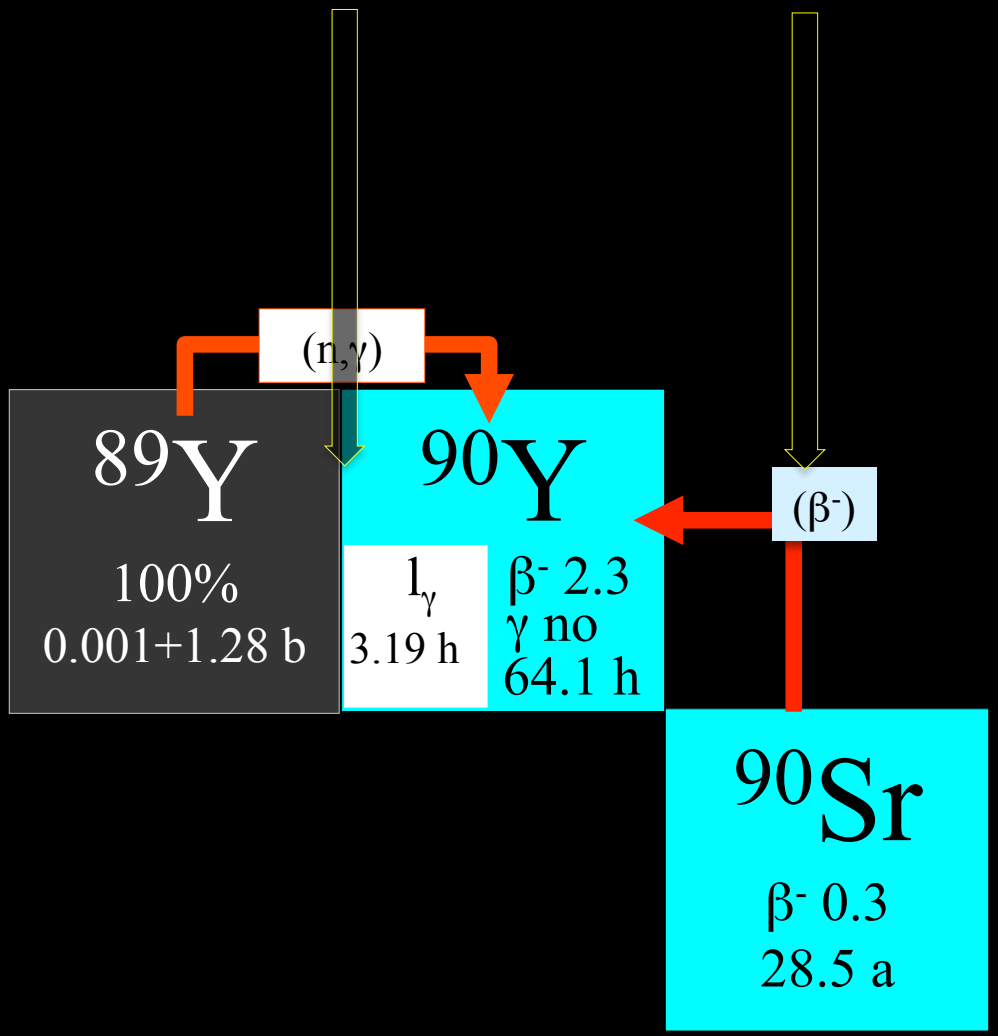

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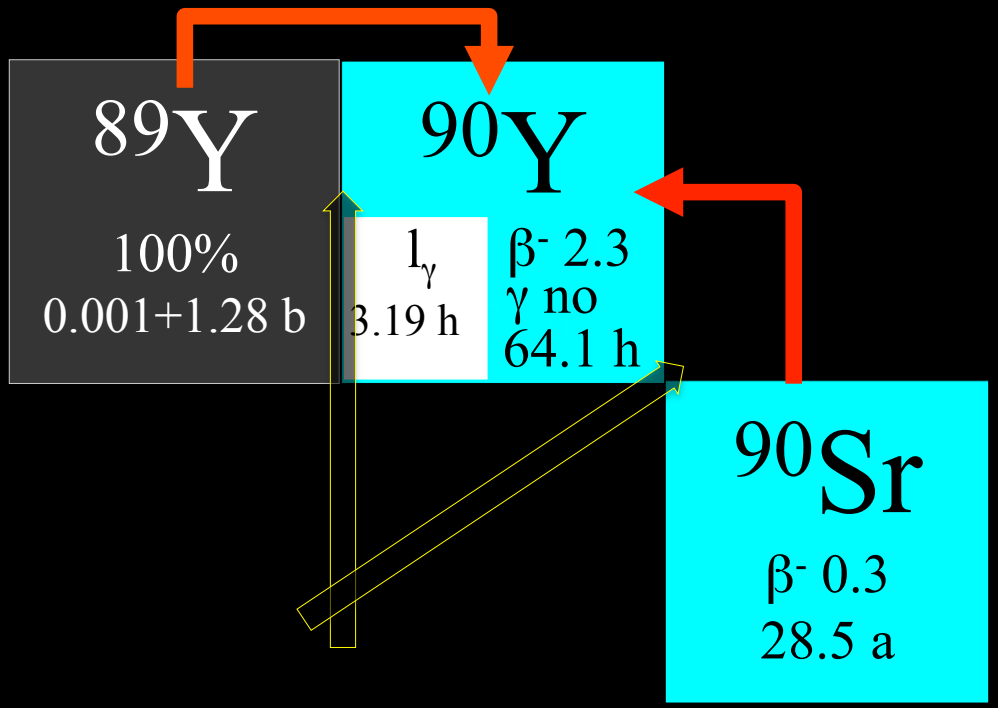

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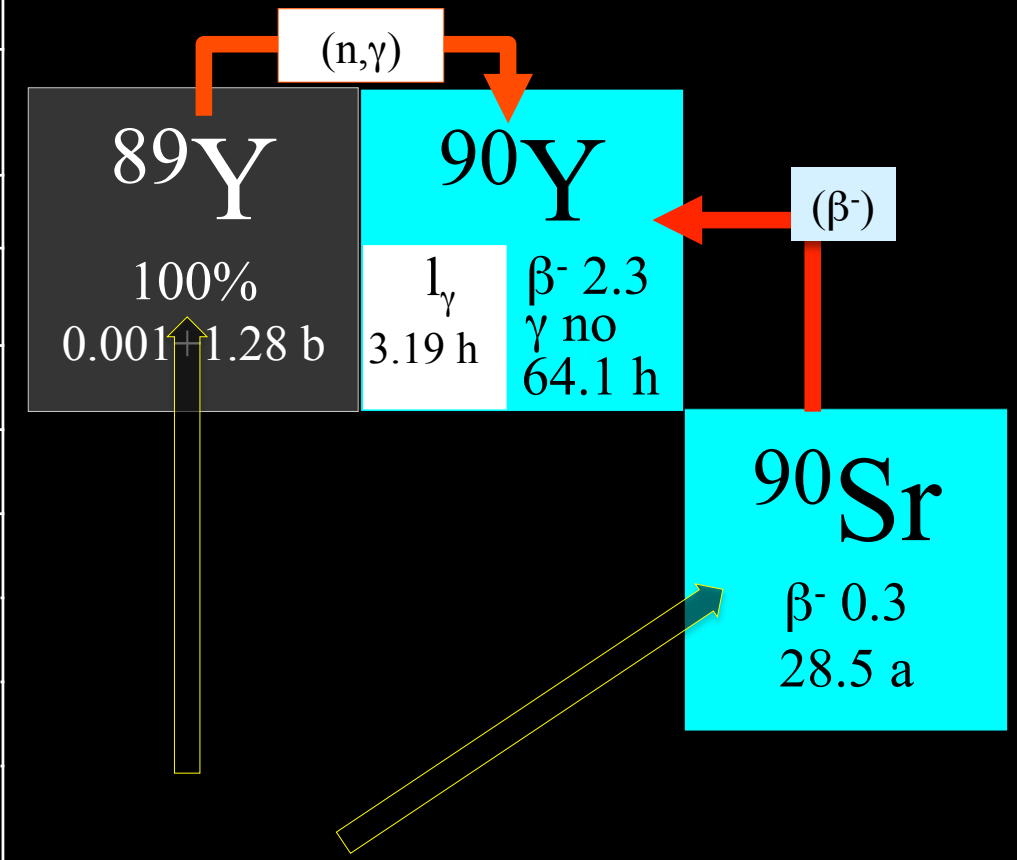

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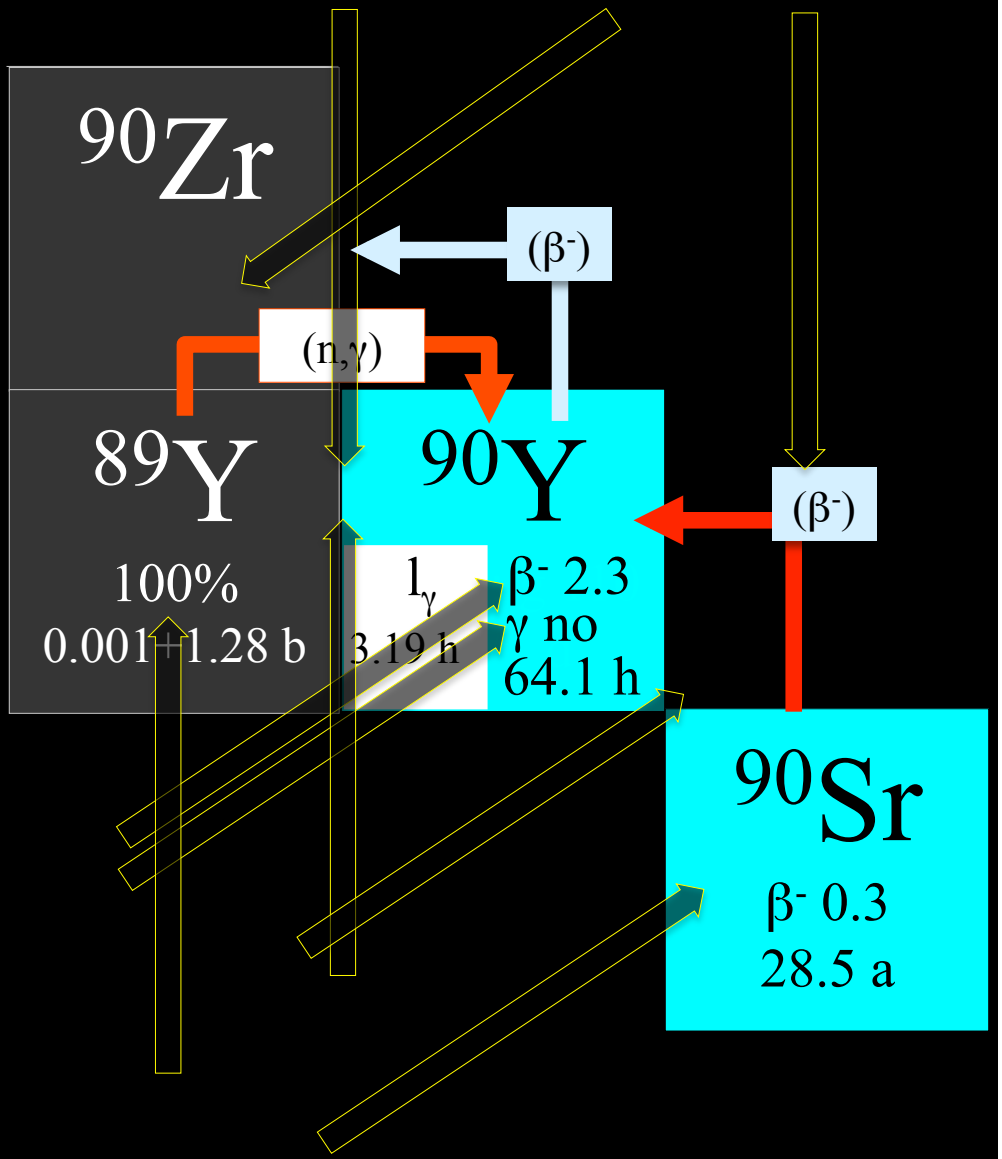

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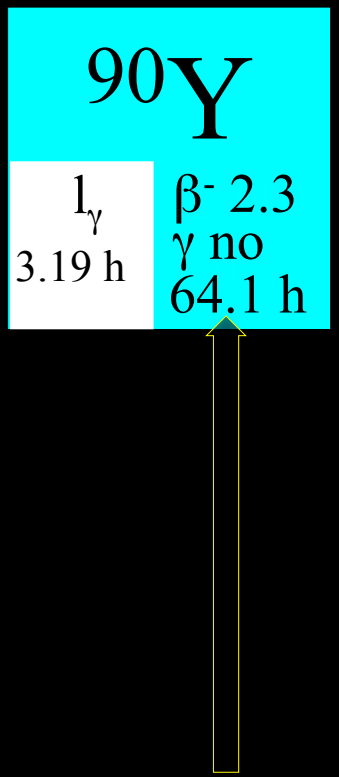

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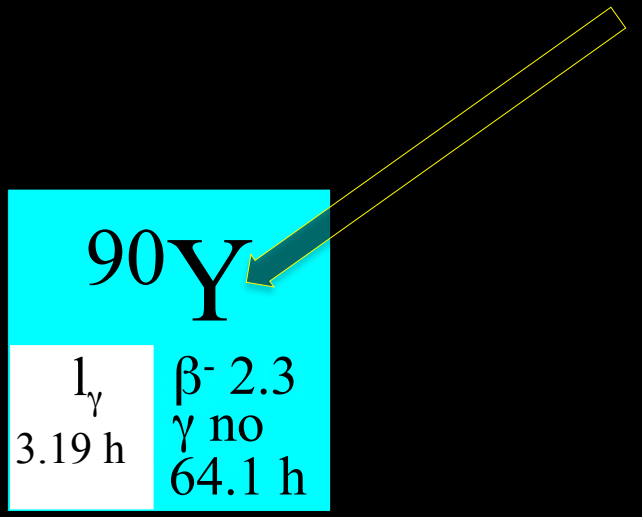

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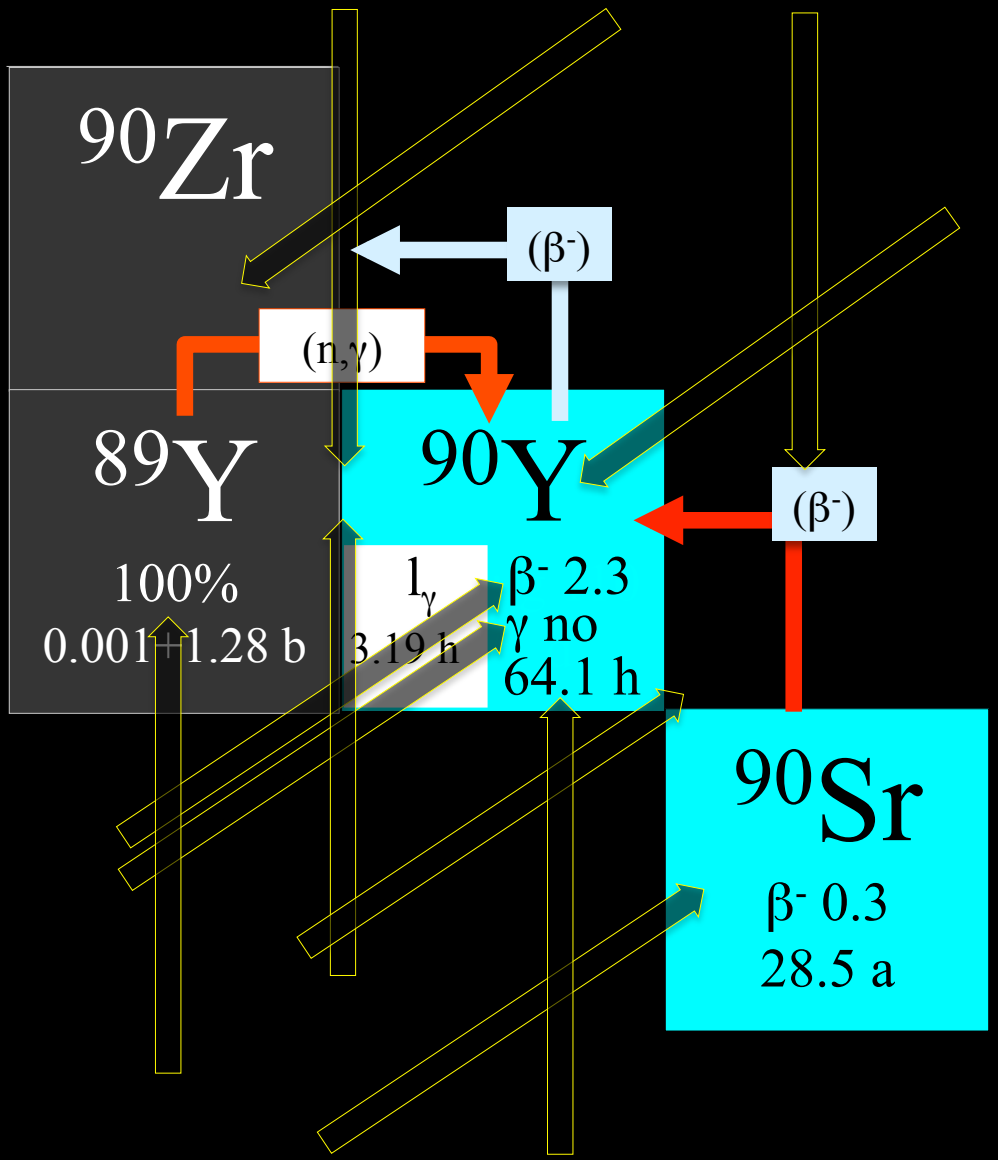


Individual Radionuclides: Production Routes

Reactors: Neutron Capture
Cyclotrons: Charged projectiles
Radionuclide Generators

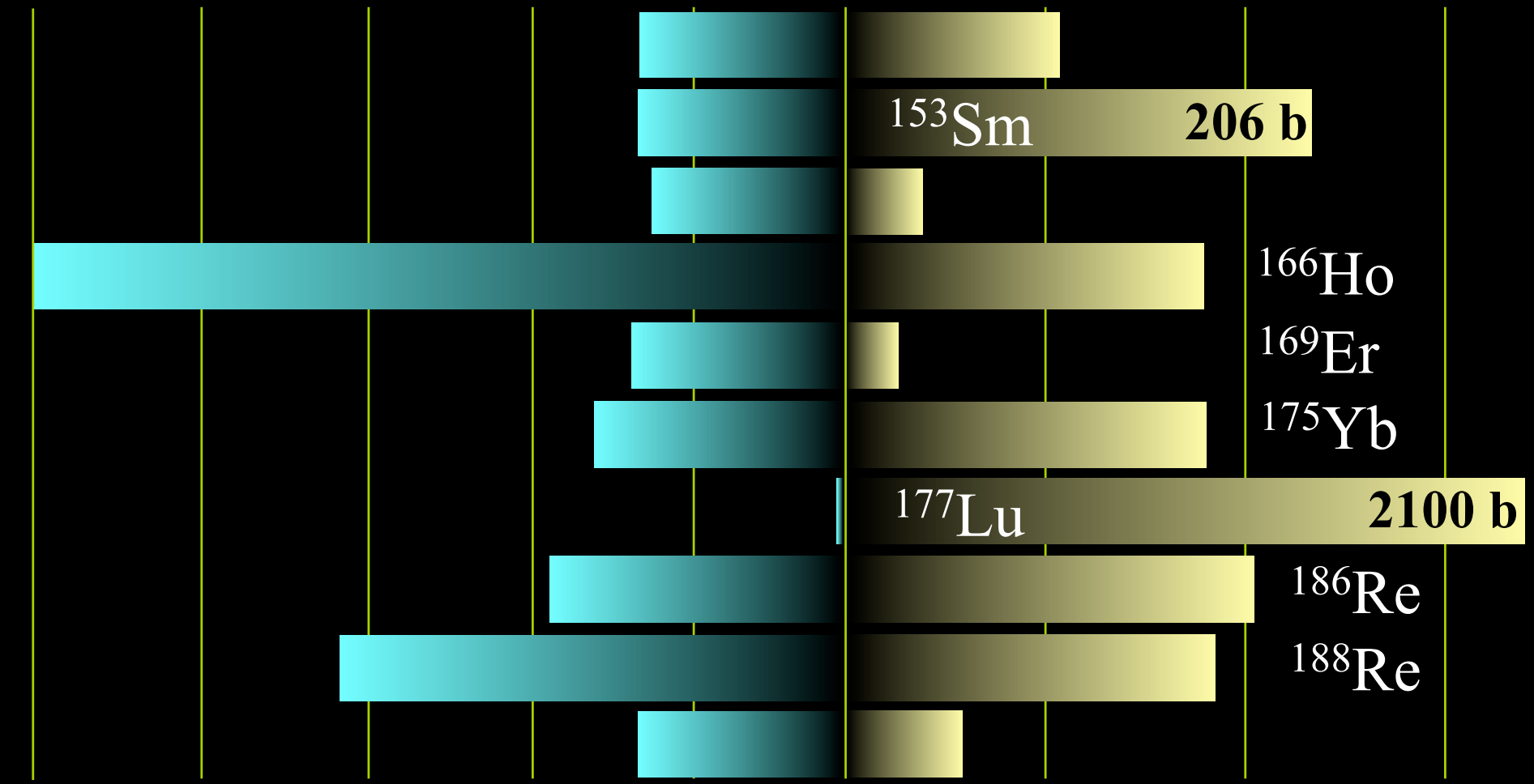
Production yield of radiotherapeutic nuclides
(at reactors)

$$Y \approx \Phi_n \, \sigma \, N(h) \, (1 - e^{-t\lambda})$$

A chemist´s point of view

Φ_n	Thermal neutron flux
σ	Cross section (n_{th},g)
N	Number of atoms of target element
h	Percentage of the target isotope (natural or enriched)
t	Irradiation period
λ	Product isotope decay constant

potential β^- emitters: reactor based direct production



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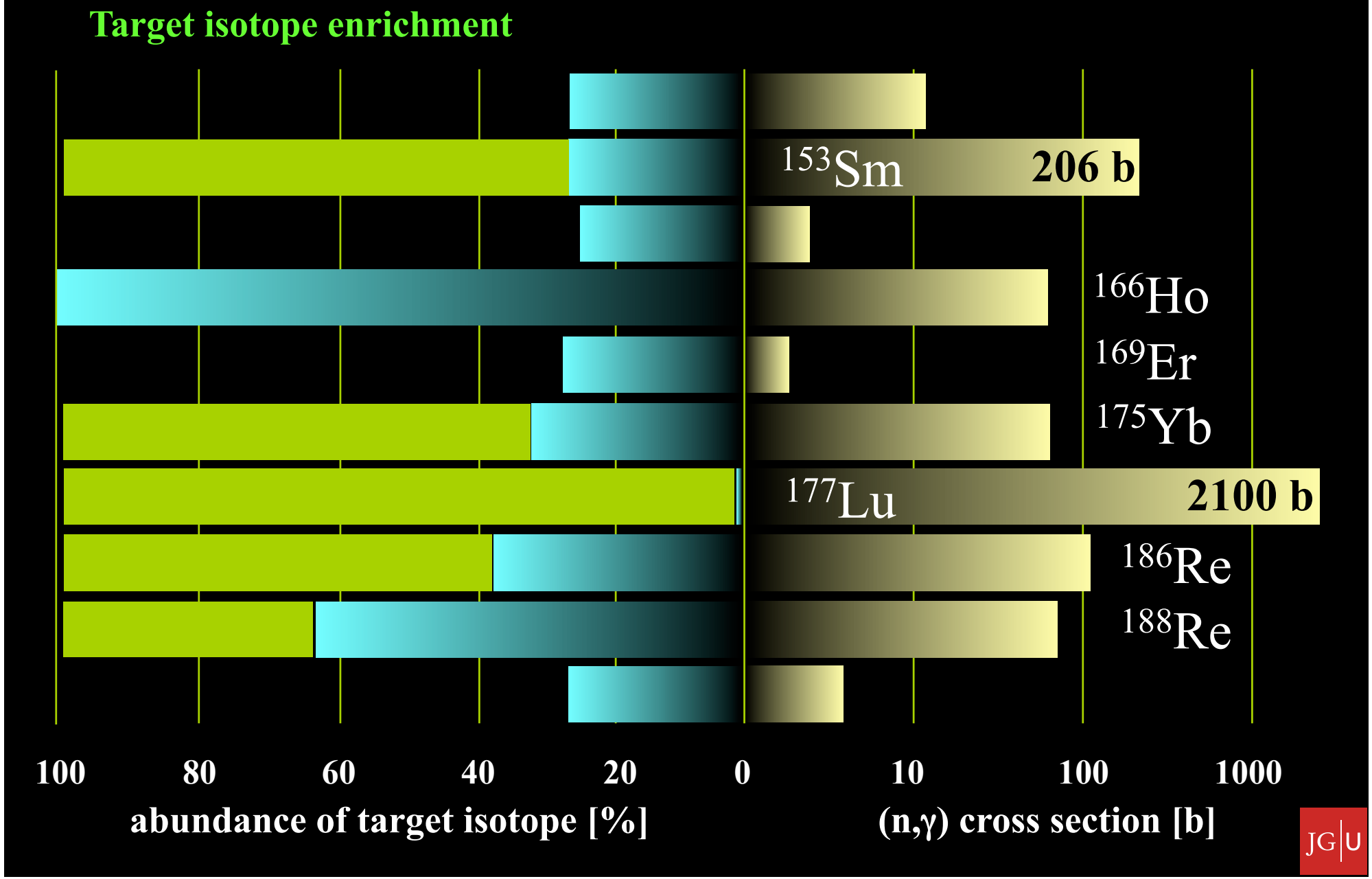
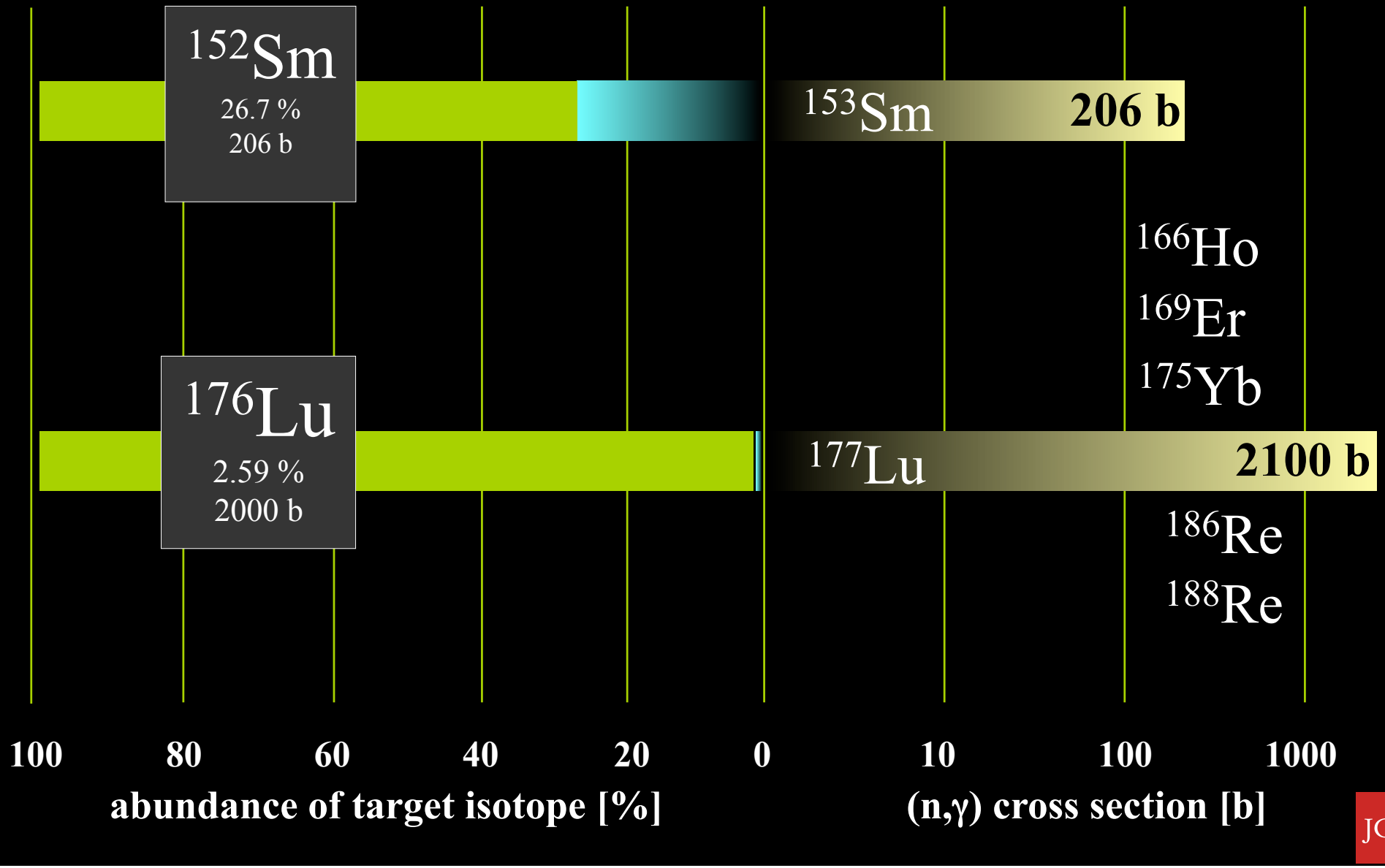


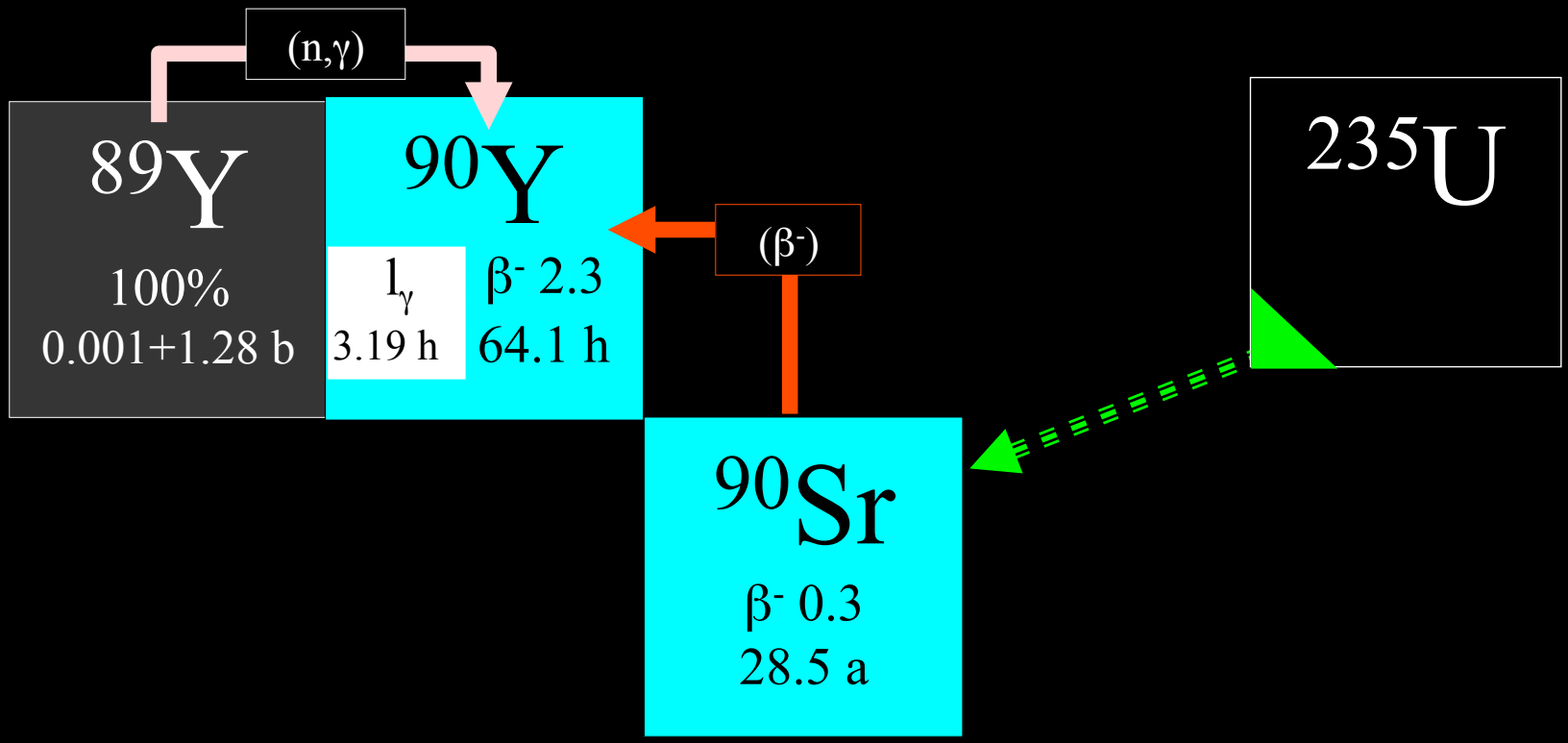
potential β^- emitters: reactor based direct production

Target isotope enrichment



Individual Radionuclides: Production Routes

Reactors: Neutron Capture
vs. neutron-induced alternative pathways



Individual Radionuclides: Production Routes

Reactors: Neutron Capture

Cyclotrons: Charged projectiles

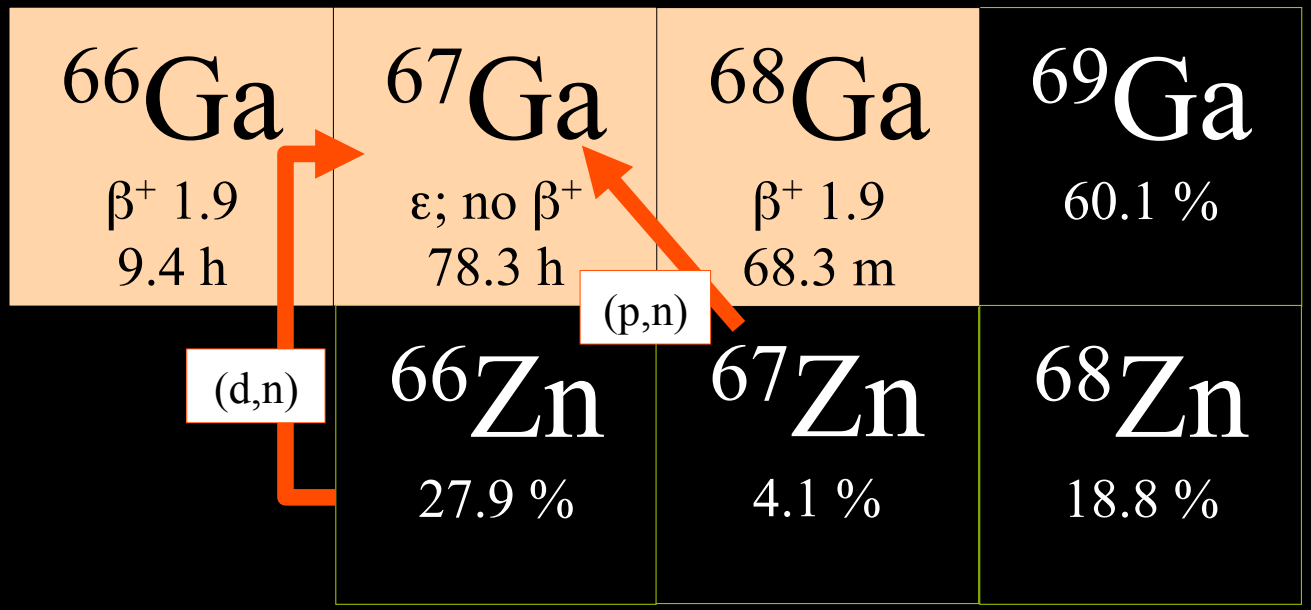
Mostly neutron-deficit nuclides

Radionuclide Generators

Example: potential Auger / conversion electron emitters

^{67}Ga

Different production routes for identic isotopes

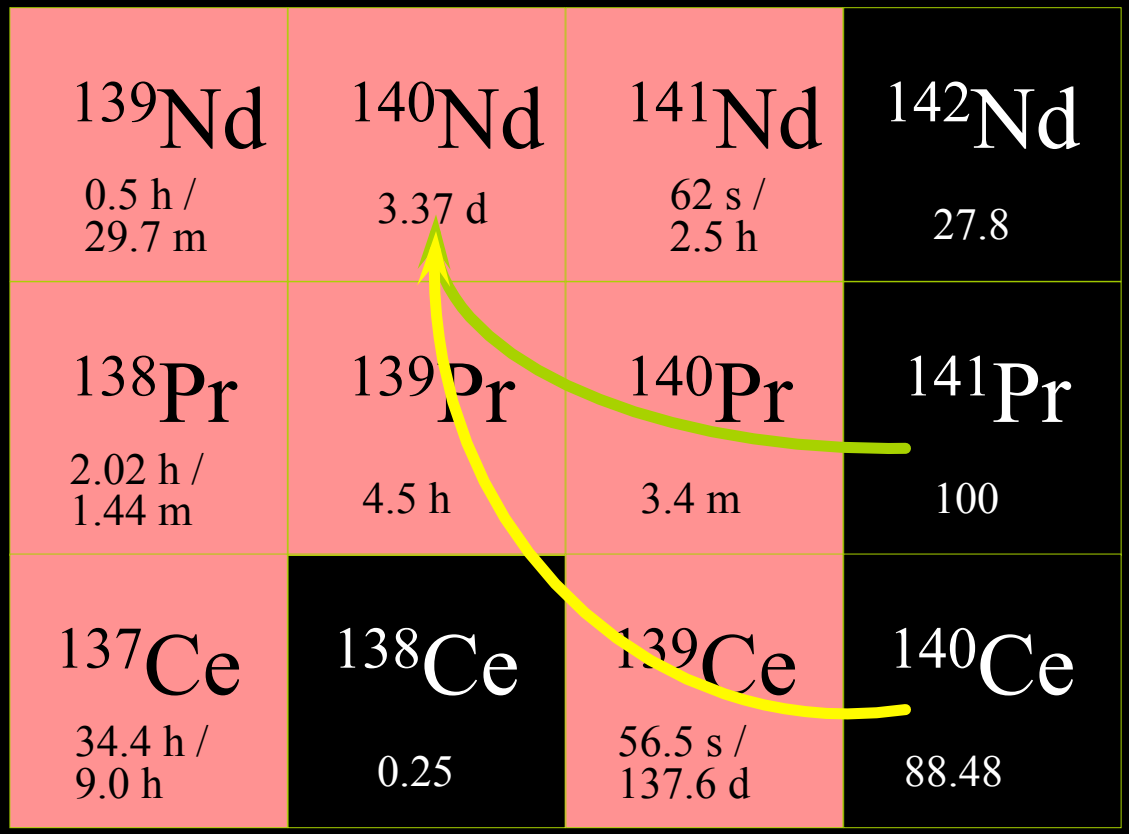


advantage:
radiochemical purification mandatory / possible

Example: potential Auger / conversion electron emitters

^{140}Nd

Different production routes for identic isotopes



^{141}Pr(p,2n)^{140}Nd

^{140}Ce(^{3}He,3n)^{140}Nd

CV28, Jülich
$E_{^3He}$ = 36-10 MeV
$^{nat}CeO_2$, 350 mg
5 MBq / µAh
> 100 MBq batch yields
isotopically pure

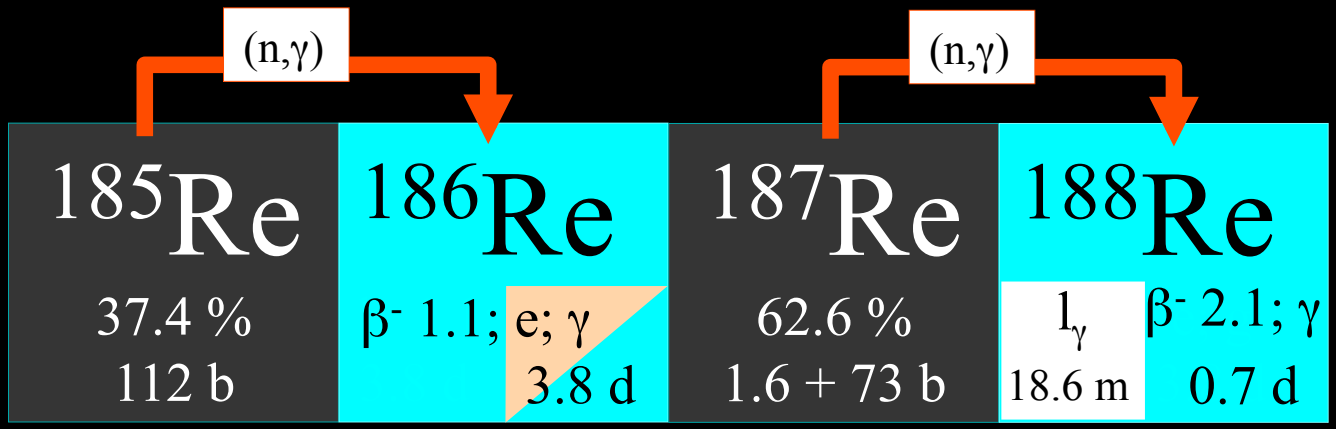
Individual Radionuclides: Production Routes

Different production routes for identic isotopes

Example: β^- emitting radionuclides

Different production routes for identic isotopes

reactor (n,γ)



Example: β^- emitting radionuclides

Different production routes for identic isotopes

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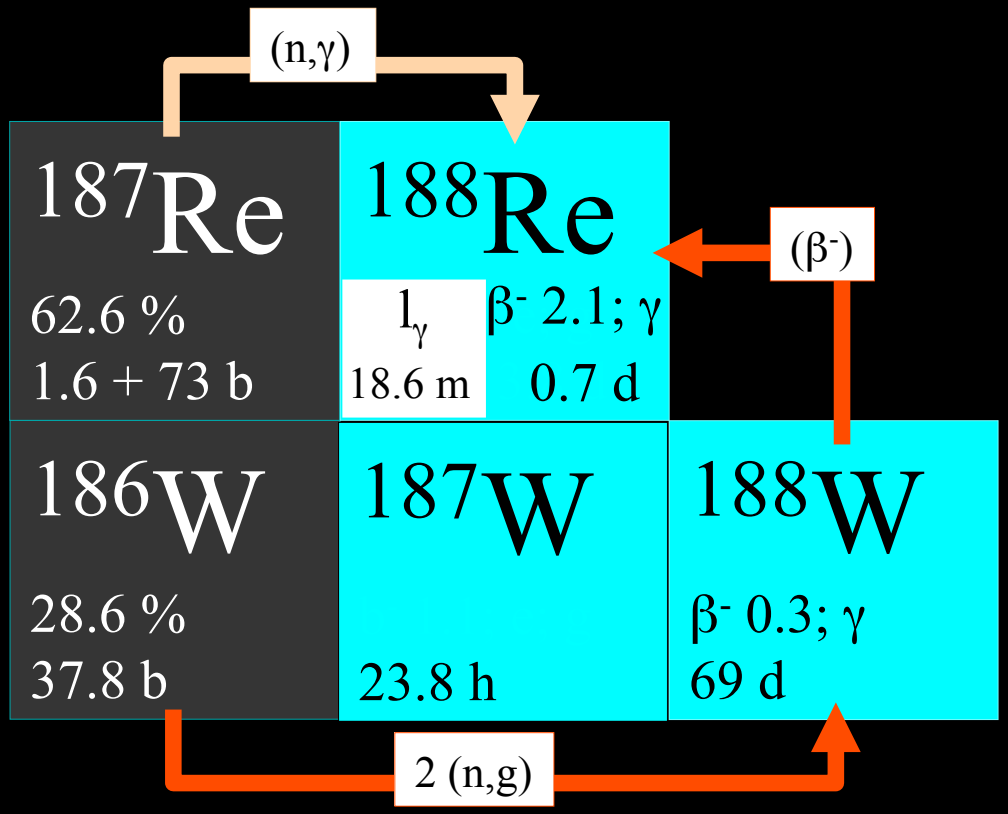

AF Novgorodov, F Bruchertseifer, J Brockmann, NA Lebedev, F Rösch.
Thermochromatographic separation of no-carrier-added ^{186}Re or ^{188}Re from tungsten targets relevant to nuclear medical applications.
Radiochim Acta 88 (2000) 163-167

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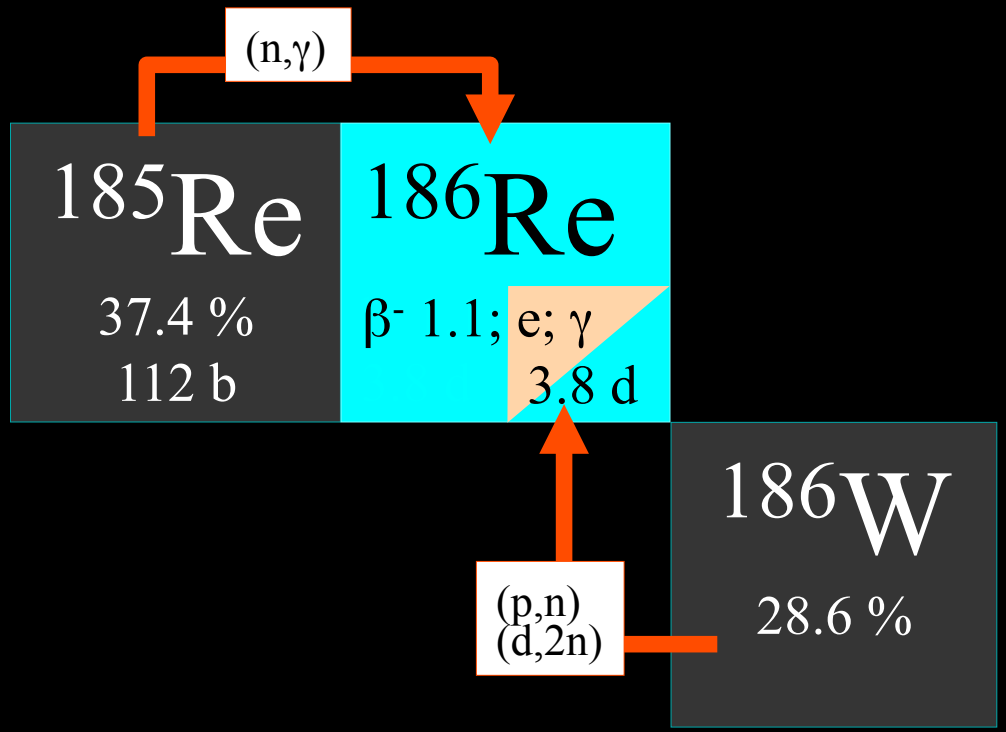
Example: β^- emitting radionuclides

Different production routes for identic isotopes

Cyclotron



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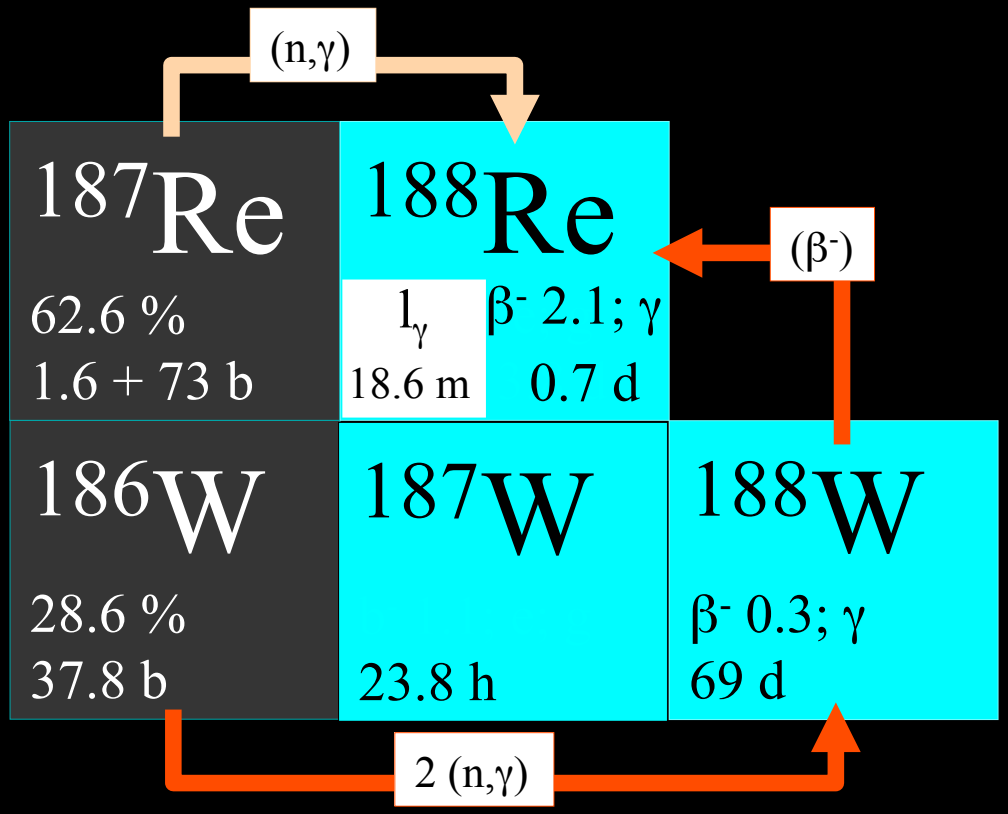

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Individual Radionuclides: Production Routes

Reactors: Neutron Capture

Cyclotrons: Charged projectiles

Radionuclide Generators

real ones vs. (natural) decay chains

α emitting radionuclides: different production routes: Cyclotron / generators (chains) / reactors

Nuclide	t½	Generator / chain	Cyclotron	Reactor
^{225}Ac	10 d	^{233}U-chain, ^{229}Th-chain,	^{226}Ra(p,2n)^{225}Ac	
^{224}Ra	3.66 d	^{228}Th		
^{223}Ra	11.4 d	^{227}Ac-chain, ^{227}Th-chain,		^{226}Ra(n,γ)^{227}Ac
^{213}Bi	45.6 m	^{225}Ac-chain, ^{225}Ac/^{213}Bi-generator		
^{212}Bi	60 m	^{224}Ra-chain, ^{212}Bi/^{212}Pb-generator		
^{211}At	7.2 h		^{209}Bi(α,2n)^{211}At	
^{149}Tb	4.1 h		Ta(p,spall), ^{152}Gd(p,4n)^{149}Tb	

α emitting radionuclides:

Example: ^{225}Ac production routes:

- ^{233}U-stock pile, ^{233}U (160000 y) ⟶ ^{229}Th (7340 y)
- ^{238}U (^{234}Th, ^{234}Pa, ^{234}U) ⟶ ^{230}Th (γ,n) ^{229}Th (7340 y)
- ^{230}Th (p,2n) ^{229}Pa ⟶ ^{229}Th (7340 y)
- ^{230}Th (n,2n) ^{229}Th
- ^{226}Ra multiple (n,γ) process, breeding of ^{229}Th
- ^{226}Ra (γ,n) ^{225}Ra ⟶
- ^{226}Ra (p,2n) ^{225}Ac (E_p = 16.5 MeV)
- ^{238}U (p,spall)
- ^{238}U (p,spall) + ISOL process

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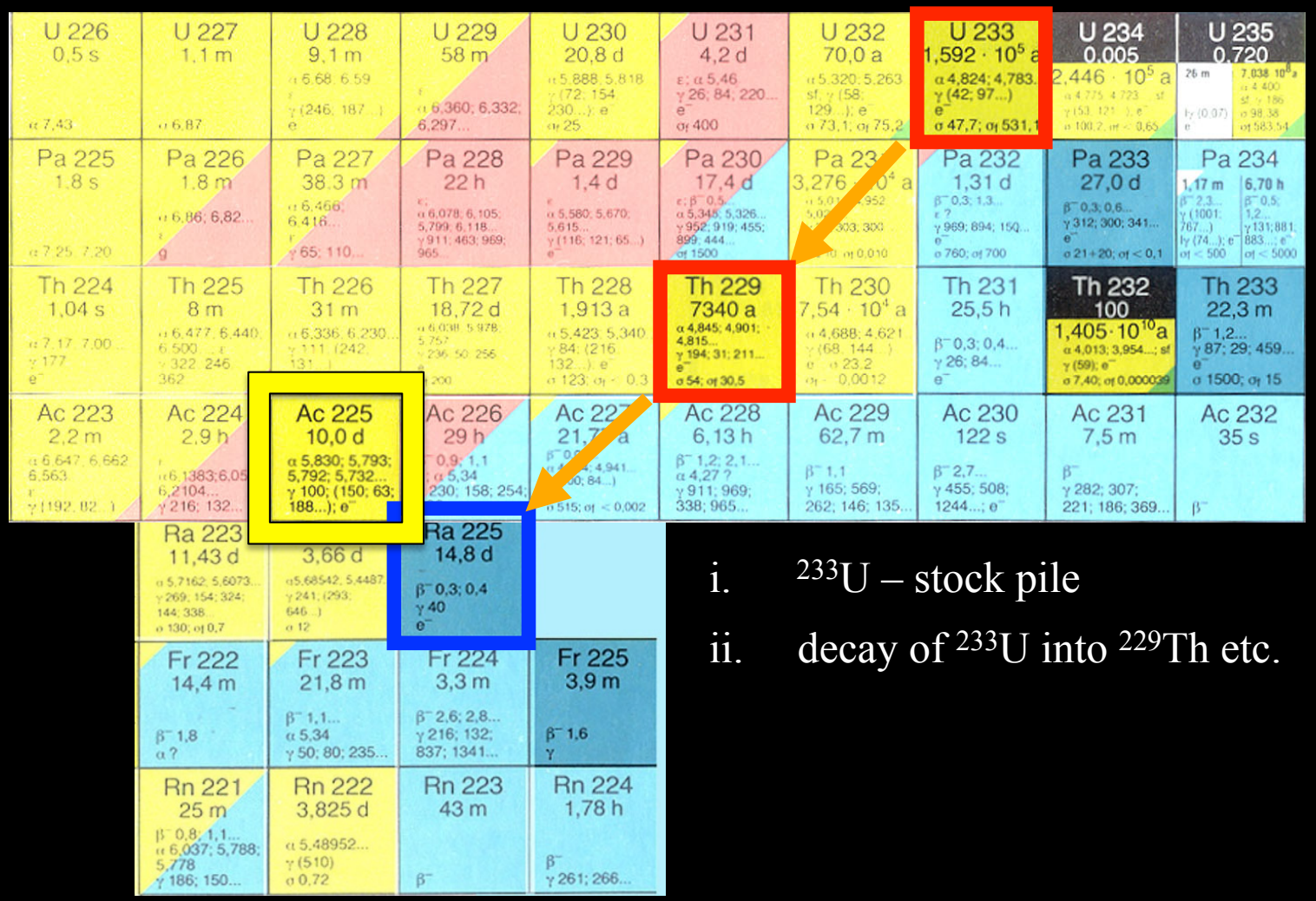
α emitting radionuclides:

Example: ^{225}Ac production routes:



i. ^{233}U – stock pile

ii. decay of ^{233}U into ^{229}Th etc.

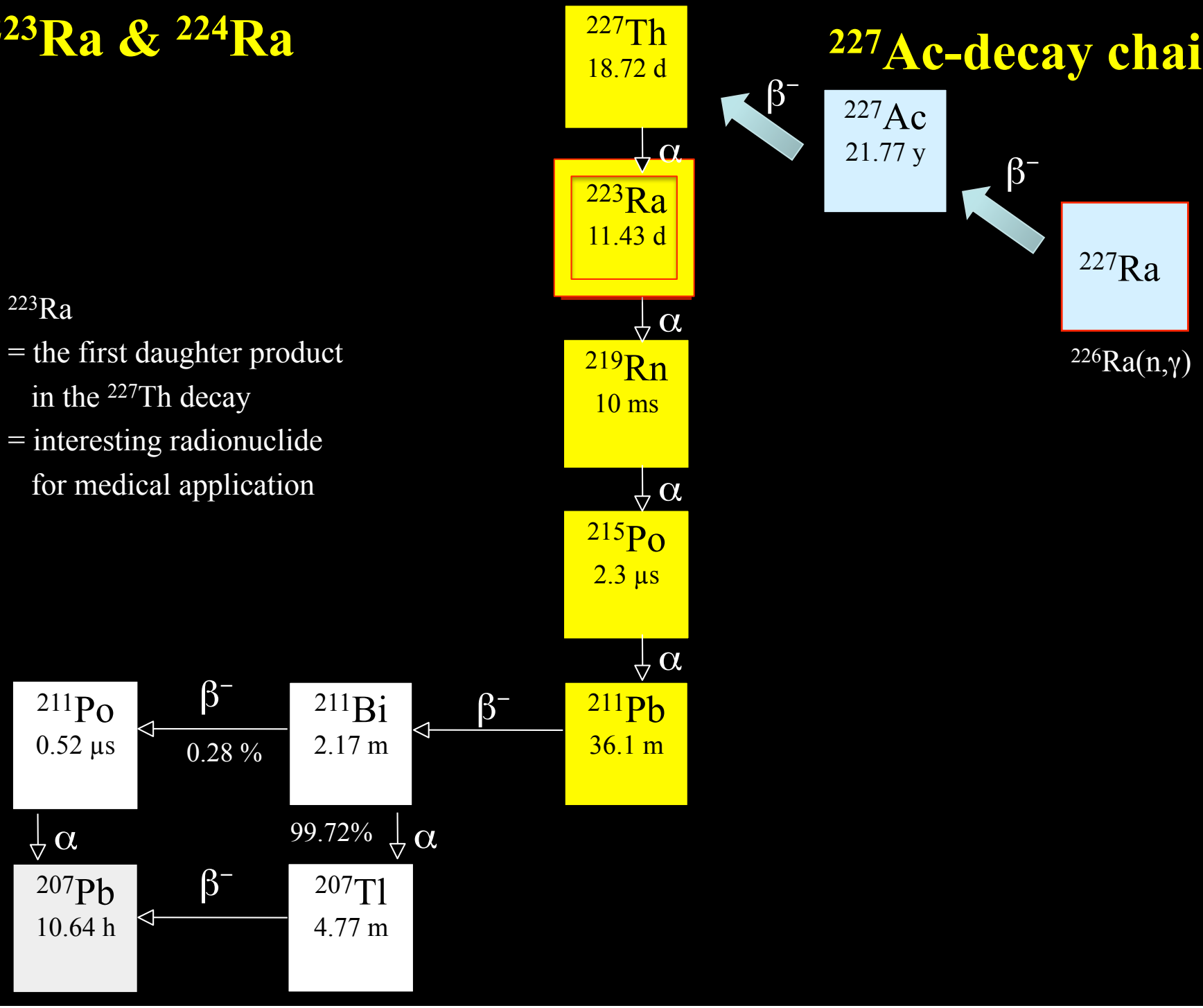
α emitting radionuclides:
Example: ^{223}Ra & ^{224}Ra

+ suitable half-life,
+ availability through generator systems
+ eventually high efficiency (3 effective alpha hits per atom)

- presently used chelators in the immunoconjugates do not work satisfactory with Ra.
- New highly selective ligands needs to be developed

+ Both Ra isotopes are proposed as alternatives to ^{153}Sm for bone metastases treatment

^{223}Ra & ^{224}Ra



^{223}Ra
= the first daughter product
in the ^{227}Th decay
= interesting radionuclide
for medical application

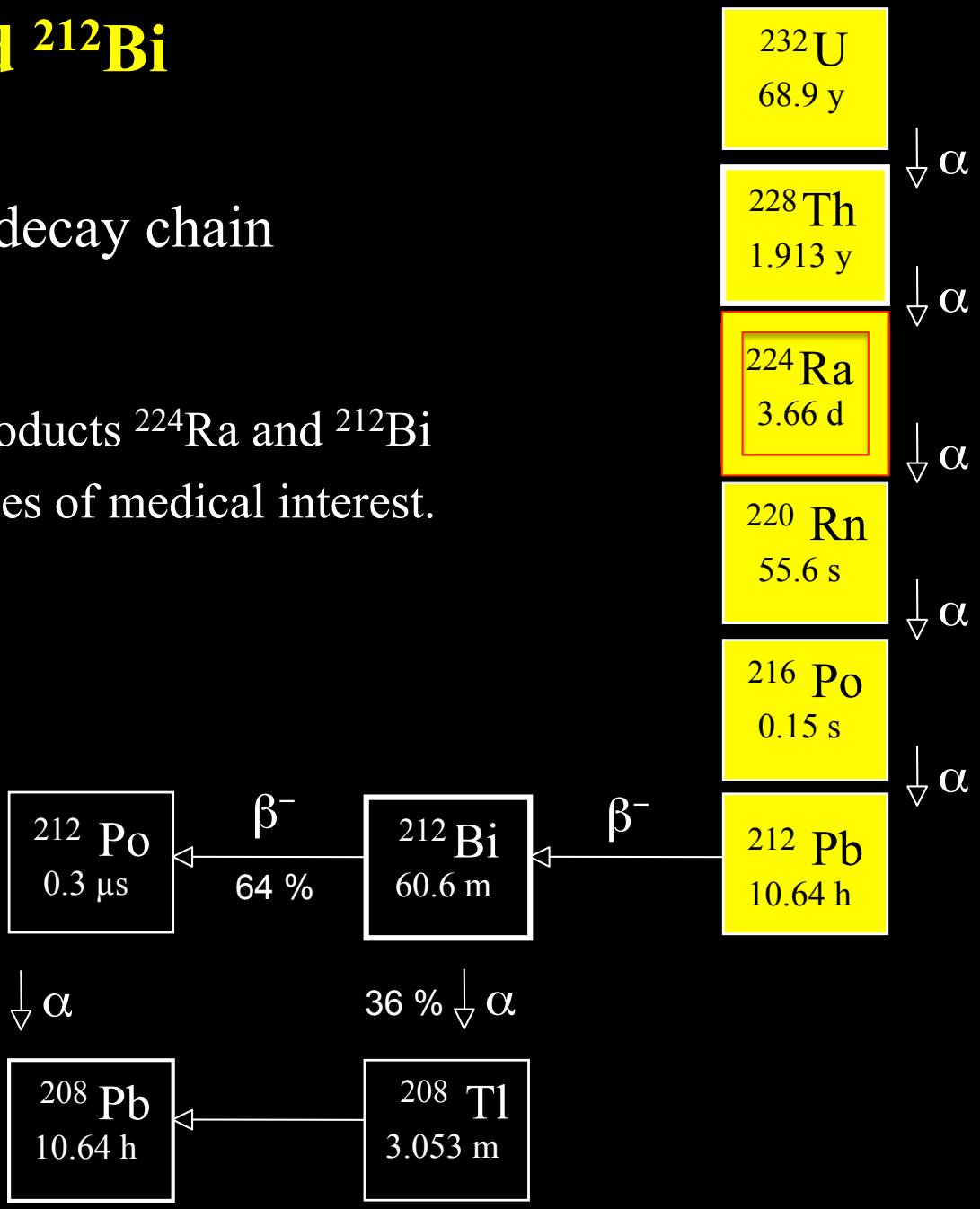
^{224}Ra and ^{212}Bi

^{232}U/^{228}Th decay chain

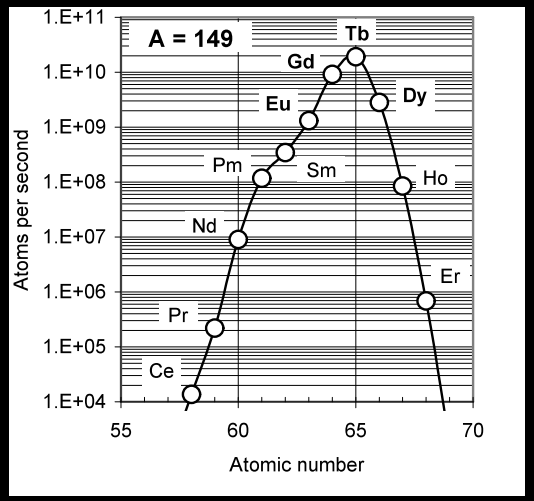
^{227}Ac (n,ß)

^{226}Ra (2n,ß)

The decay products ^{224}Ra and ^{212}Bi are the isotopes of medical interest.



^{149}Tb



Spallation reaction

100 g/cm^2

Ta-target

1 GeV

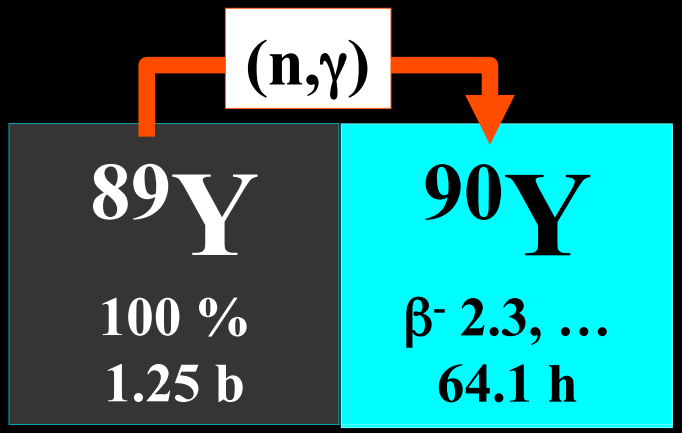
1 µA

Production Batch Activities
vs.
Specific Radioactivity

What is "Specific Radioactivity A_s"?

$$A_s(^*K)^{REALITY} = \frac{A(^*K)}{N(^*K) + N(^{STABLE}K)_i}$$

$A = \lambda N$



Specific Radioactivity A_s

$$A_s(*K)^{REALITY} = \frac{A(*K)}{N(*K) + N(^{ST}\ \ ^{E}K)_i}$$

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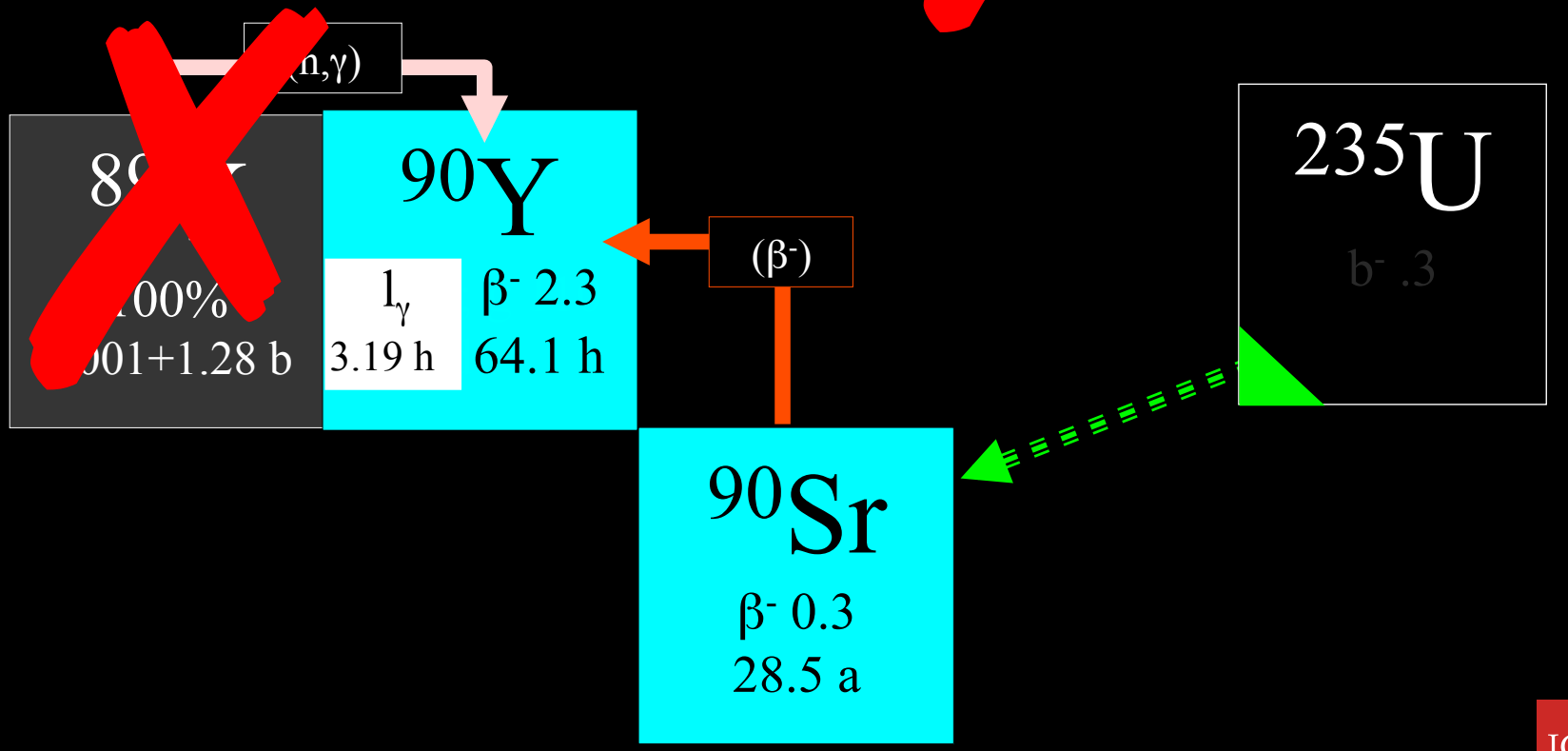

Production Batch Activities
vs.
Specific Radioactivity

The impact of nuclear reaction designs

Specific activity as a function of …

specific activity SA:
radioactivity [Ci] or [GBq] related to the mass [g] or [µmol] of the element
for labelling molecular targeting vectors: max. SA

For radiolanthanides produced by (n,γ) processes (^{153}Sm,^{177}Lu, ...),

SA depends on

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

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

Specific activity as a function of …

potential β^- emitters: reactor based direct production

A_s depends on
- neutron flux,
- neutron capture cross section,
- isotopic enrichment of the target lanthanide isotope,
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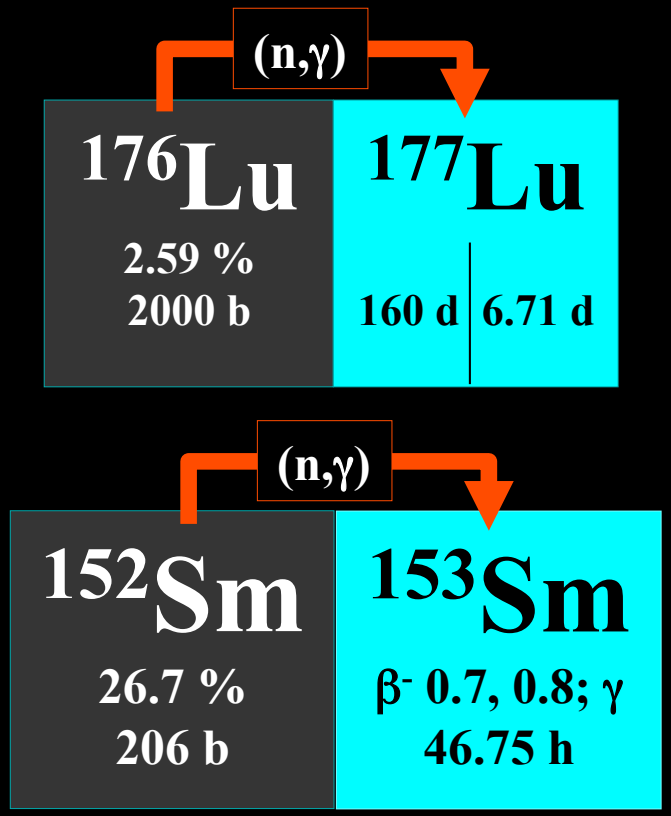

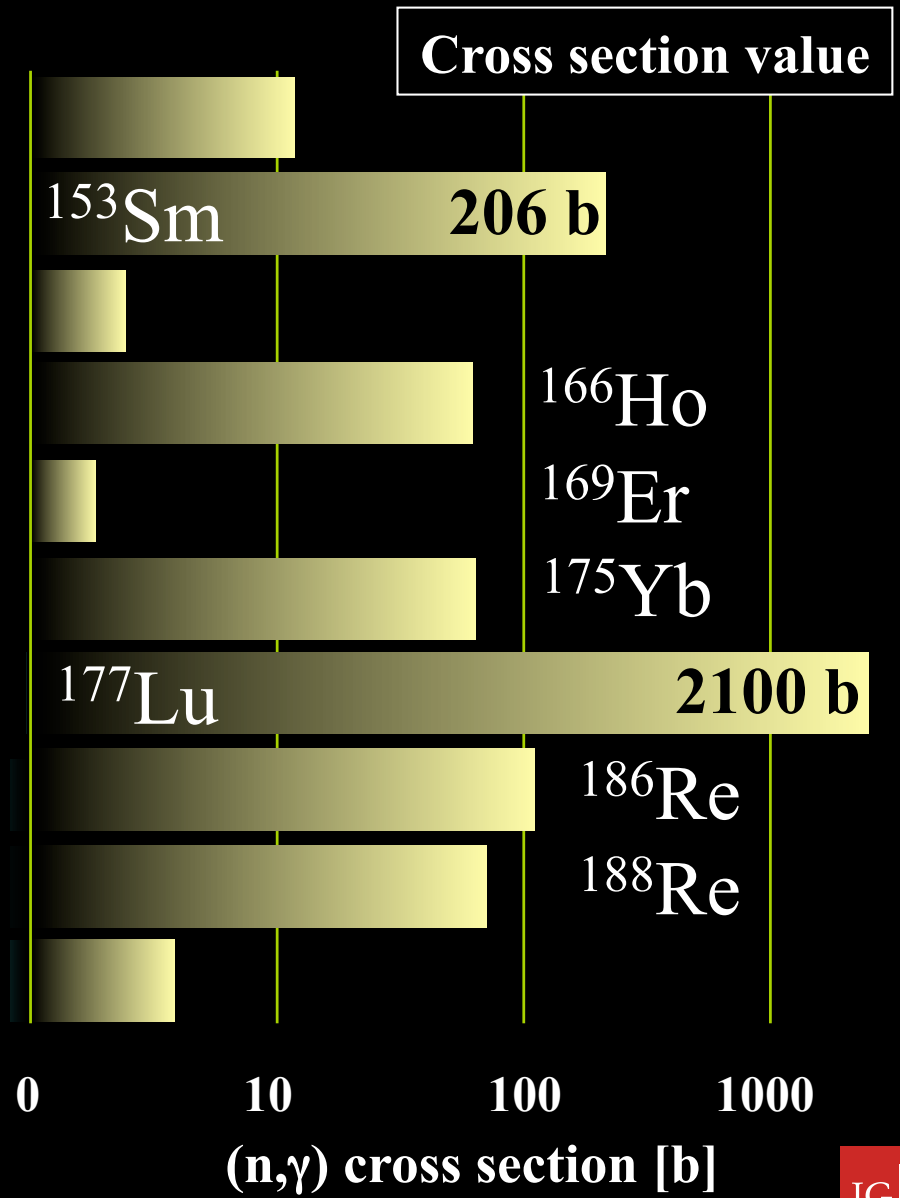

Specific activity as a function of …

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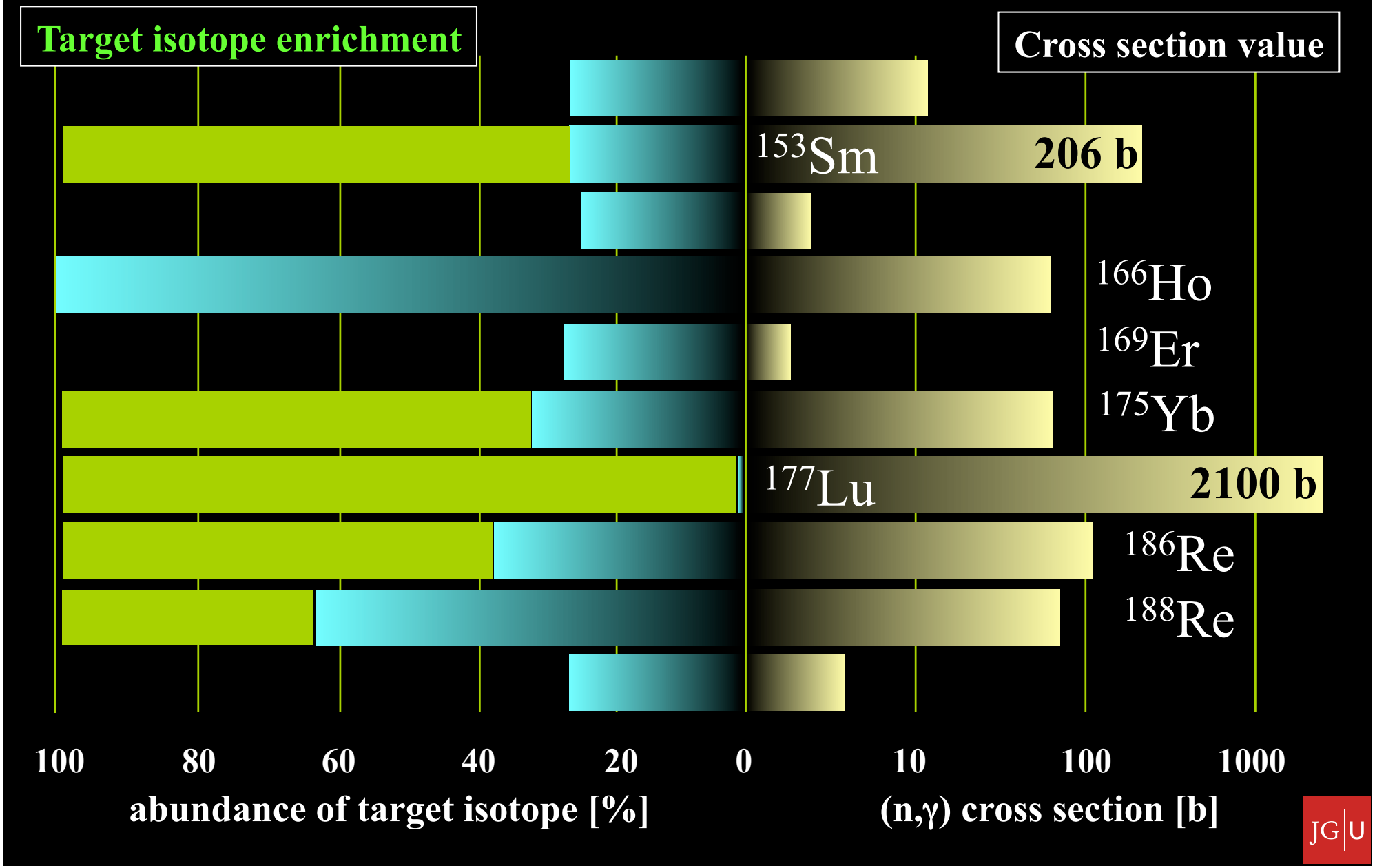


Production Batch Activities
vs.
Specific Radioactivity

The impact of nuclear reaction designs
Generators

High Specific Activity vs. Radiochemistry

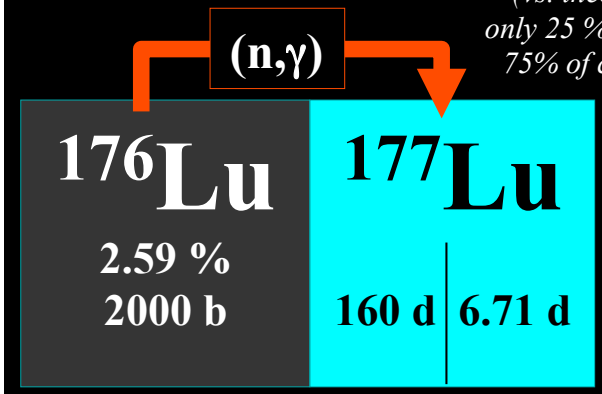
types of reaction	parameters	SA
nuclear reactors (n,γ)		low
nuclear reactors (n,γ)	High σ	medium
nuclear reactors (n,γ)	High flux + high σ	high
nuclear reactors (n,γ)→β^-	+ chemistry	→ nca

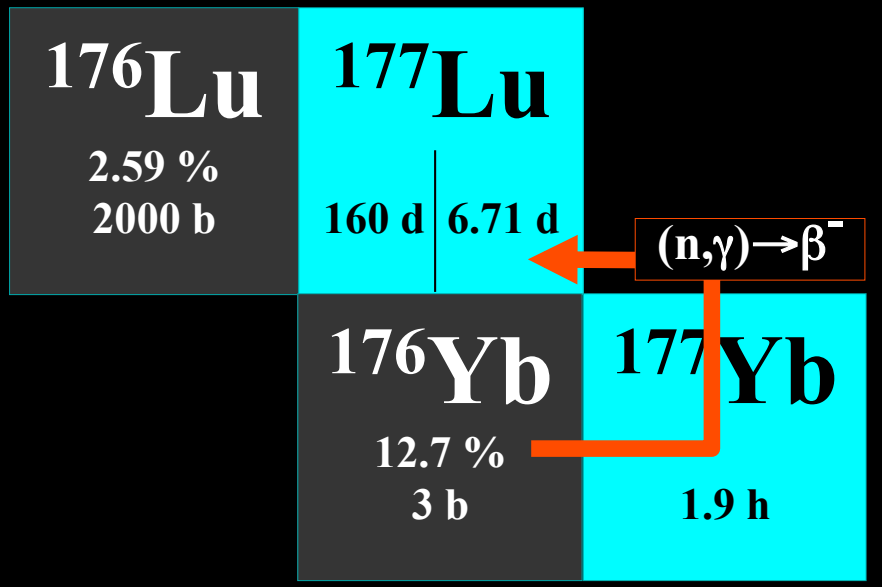
^{177}Lu: nca vs. ca

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

$$^{176}\text{Yb}\ (n,\gamma) \xrightarrow{\sigma = 3\ \sigma} {}^{177}\text{Yb}\ (T_{1/2} = 1.9\ \text{h}) \xrightarrow{\beta^-} {}^{177}\text{Lu}\ (T_{1/2} = 6.68\ \text{d})$$

specific activity
20 – 30 Ci/mg
(vs. theoretical 110 Ci/mg)
only 25 % of hot ^{177}Lu atoms
75% of cold $^{175/176}$Lu atoms





NA Lebedev, AF Novgorodov, R Misiak, J Brockmann, F Rösch.
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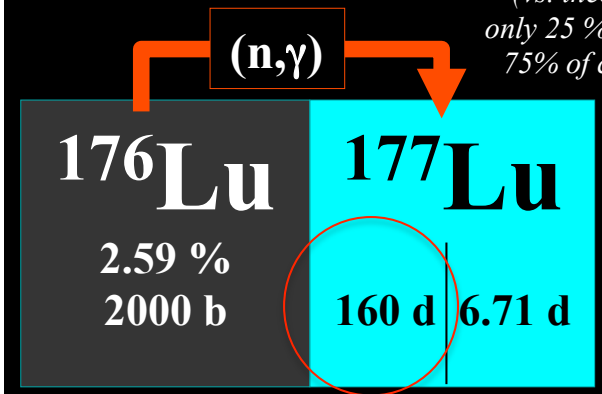
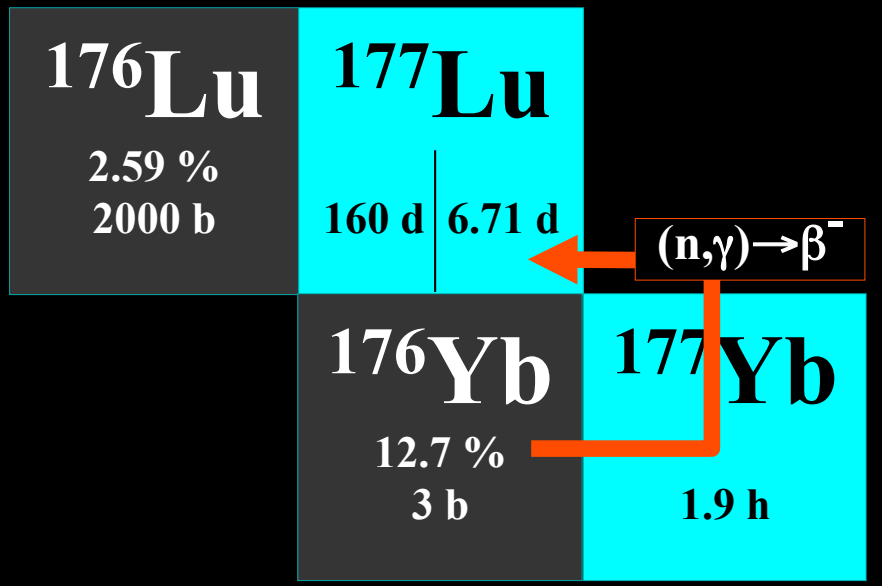


long-lived
radioactive
impurities:
~0.05 % of ^{177m}Lu
waste management;
environment
exposure

specific activity
> 100 Ci/mg
(vs. theoretical 110 Ci/mg)
and highest radionuclide purity



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High specific activity:
No-carrier-added therapeutic radionuclides II:
(n,γ)→β⁻→ processes

target	σ [b]	primary product	T½	secundary product	T½ [d]	$E_{\beta^- max}$
^{142}Ce	0.95	^{143}Ce	33 h	**^{143}Pr**	13.58	0.9
^{148}Nd	2.5	^{149}Nd	1.73 h	**^{149}Pm**	2.212	1.1
^{160}Gd	0.77	^{161}Gd	3.6 min	**^{161}Tb**	6.91	0.55
^{176}Yb	3	^{177}Yb	1.9 h	**^{177}Lu**	6.71	0.5

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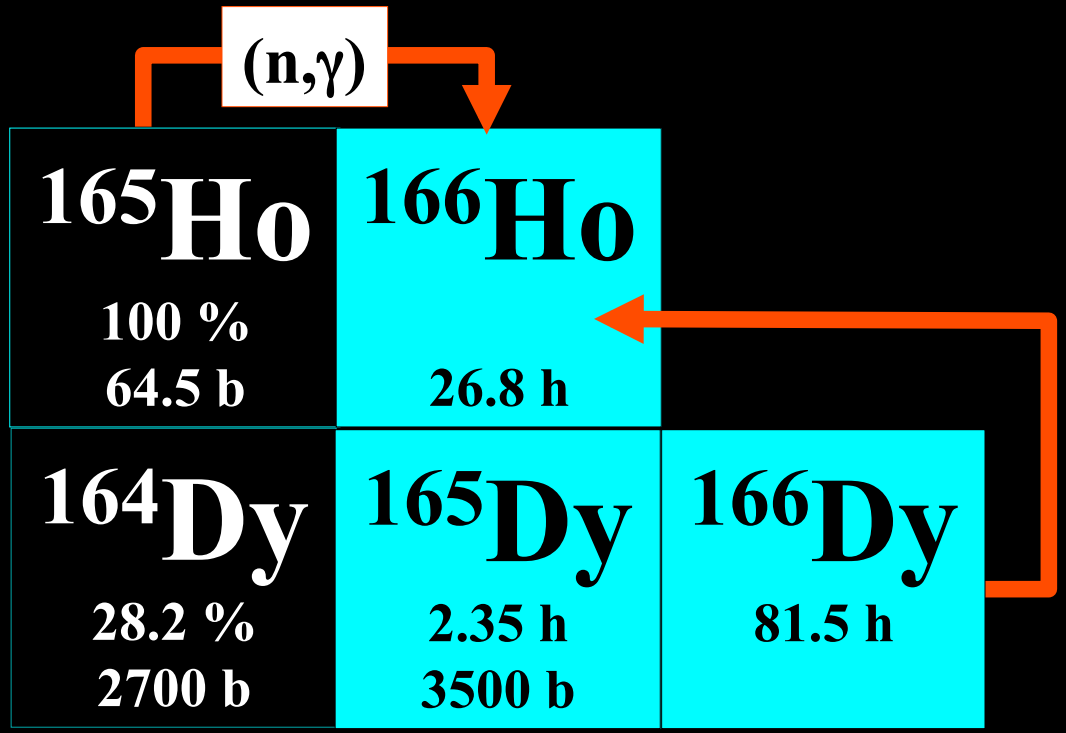
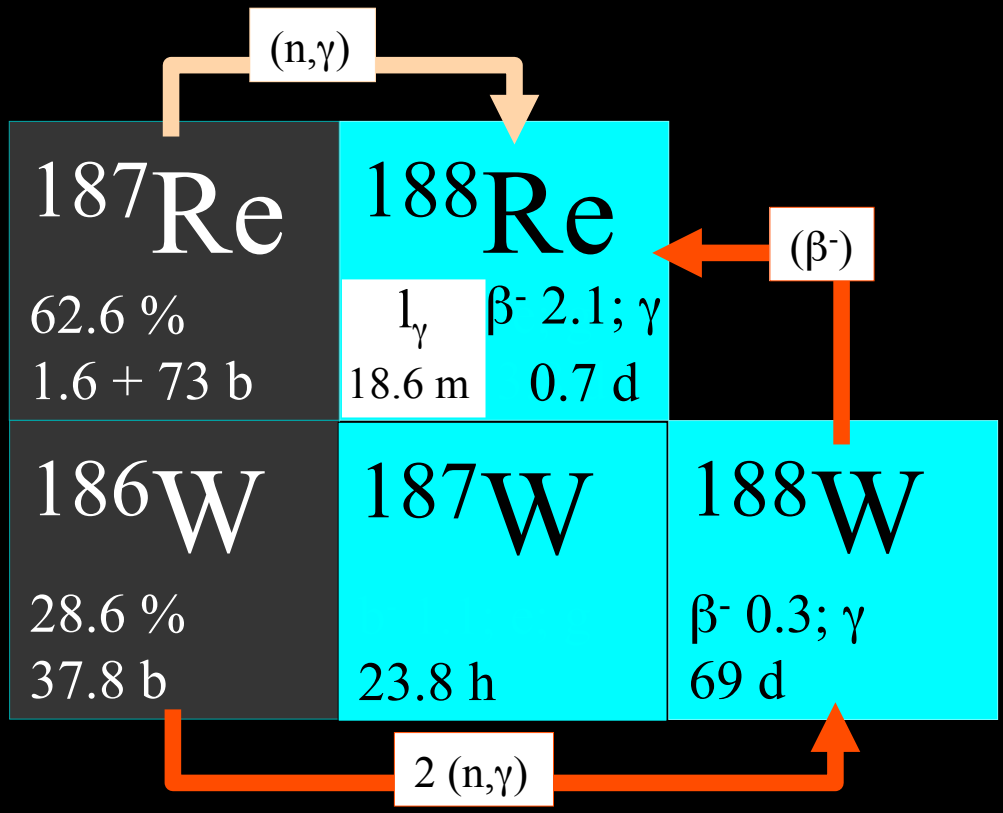
High specific activity = No-carrier-added therapeutic radionuclides: Reactor (n,γ) processes vs generators



$^{164}Dy(n,\gamma) \xrightarrow{\sigma = 2700\ b} {}^{165}Dy(n,\gamma)\ (T_{1/2} = 2.33\ h) \xrightarrow{\sigma = 3500\ b}$

$^{166}Dy\ (T_{1/2}\ 81.6\ h) \xrightarrow{\beta^-} {}^{166}Ho\ (T_{1/2} - 26.80\ h)$

High specific activity = No-carrier-added therapeutic radionuclides: Reactor (n,γ) processes vs generators



Production Batch Activities
vs.
Specific Radioactivity

The impact of nuclear reaction designs
Generators
The impact of radiochemistry

SA ... 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*

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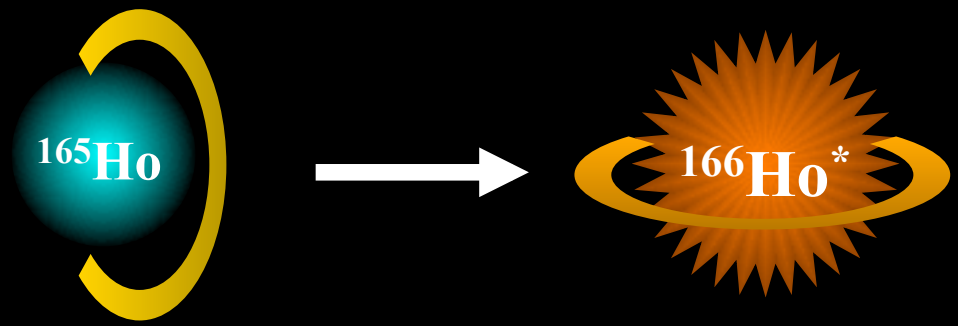
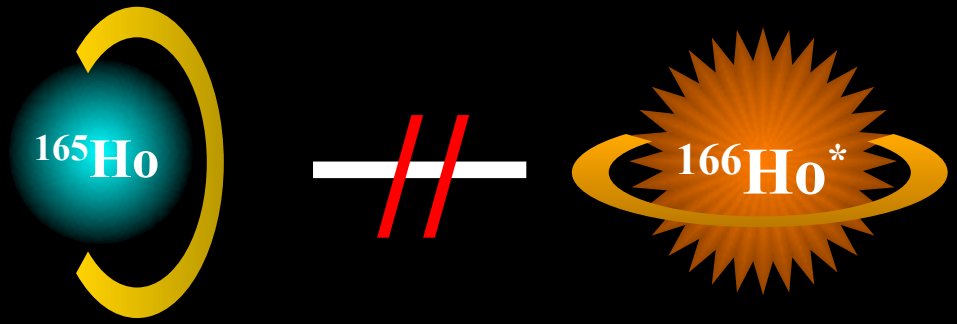
Concept

- prepare and irradiate a chemical compound with the target nuclide bound covalently or by coordination chemistry
- irradiate that stable compound to produce the nuclear reaction product, e.g. in a $^{165}Ho(n,\gamma)^{166}Ho$ process
- the radionuclide undergoes recoil effects or hot atom chemistry *in situ*
- after the end of irradiation, the nuclear reaction product, e.g. ^{166}Ho, exists in a chemical form different to the irradiated target ^{165}Ho compound



- the radioisotope thus can chemically separated from the chemcially unreacted target compound



Production Batch Activities
vs.
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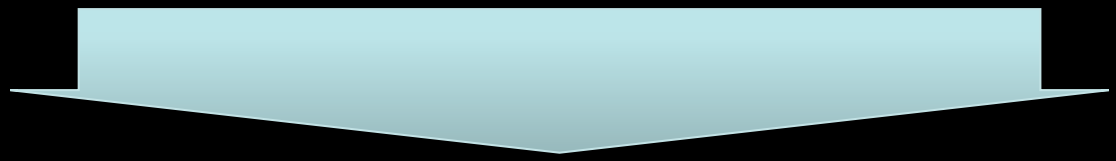

(Radio)chemical Separation

(Radio)chemical Separation

reaction	ΔZ	chemistry	separation
(n,γ)	0	Same element	impossible
(n,γ) + SZILLARD-CHALMERS	0	Same element	impossible ?
(n,γ)→β^-→ processes	+1	Neighbour elements	easy for elements with different valent state / chemistry
(p,xn) etc.	+1		challange for elements of same valent state / chemistry, such as lanthanides Ln^{3+}
(α,xn) etc.	+2	Different elements	„easy“
Generators	-1, -2	Different elements	„easy“

No-carrier-added therapeutic radionuclides:
$(n,\gamma)\rightarrow\beta^{-}\rightarrow$ processes

target	σ [b]	prim. product	t½	sec. product	t½	$E_{\beta^- max}$
^{142}Ce	0.95	^{143}Ce	33 h	^{143}Pr	13.58	0.9
^{148}Nd	2.5	^{149}Nd	1.73 h	^{149}Pm	2.212	1.1
^{160}Gd	0.77	^{161}Gd	3.6 min	^{161}Tb	6.91	0.55
^{164}Dy	1700/1000	^{166}Dy	81.5 h	^{166}Ho	1.117	1.9
^{176}Yb	3	^{177}Yb	1.9 h	^{177}Lu	6.71	0.5

Separation:
macroamount target (several mg)
vs. nca secundary product nuclide

Ion exchange column chromatography

Liquid-liquid exctraction

Thermo-chromatography

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No-carrier-added therapeutic radionuclides: Generators

parent	t½	daughter	t½	decay	
^{90}Sr	28.6 d	^{90}Y	64.1 h	β-	Liquid-liquid exctraction Ion exchange column chromatography
^{166}Dy	3.4 d	^{166}Ho	27 h		Ion exchange column chromatography
^{188}W	69 d	^{188}Re	17 h		Ion exchange column chromatography Thermo-chromatography
^{225}Ac	10 d	^{213}Bi	46 min	α	Ion exchange column chromatography

F Rösch, F F (Russ) Knapp.
Radionuclide Generators.
in A Vértes, S Nagy, Z Klencsár, F Rösch (eds.), *Handbook of Nuclear Chemistry* – Vol. 4,
Radiochemistry and Radiopharmaceutical chemistry in Life Sciences.pp 81-118, 2003, Kluwer Academic Publishers, The Netherlands

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reaction	ΔZ	chemistry	separation
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(n,γ) + SZILLARD-CHALMERS	0	Same element	impossible ?
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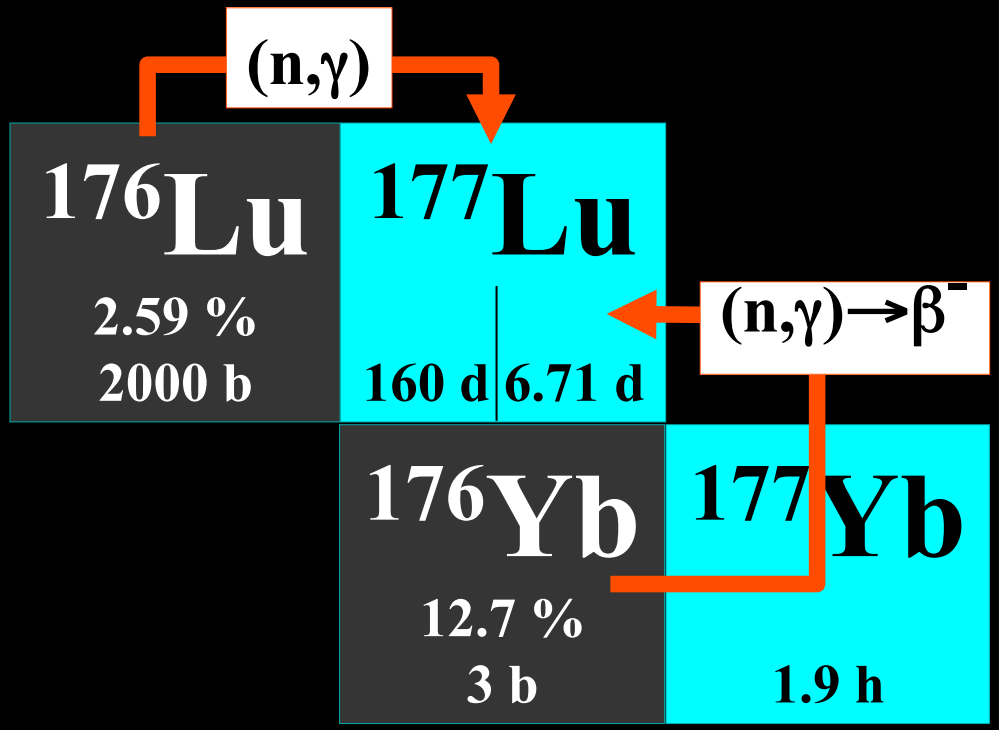
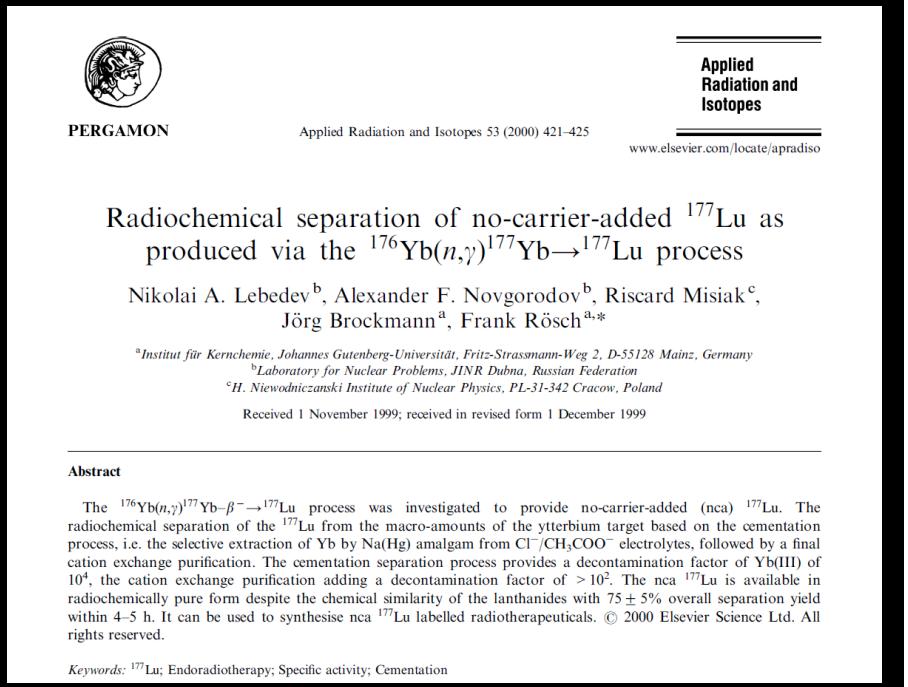
..... chemistry is able to contribute (i) ....

^{177}Lu: nca vs. ca

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

$$^{176}\text{Yb}\ (n,\gamma) \xrightarrow{\sigma = 3\ \sigma} {}^{177}\text{Yb}\ (T_{1/2} = 1.9\ \text{h}) \xrightarrow{\beta^-} {}^{177}\text{Lu}\ (T_{1/2} = 6.68\ \text{d})$$





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Applied Radiation and Isotopes 53 (2000) 421–425

Applied Radiation and Isotopes

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Radiochemical separation of no-carrier-added ^{177}Lu as produced via the ^{176}Yb$(n,\gamma)^{177}$Yb$\rightarrow^{177}$Lu process

Nikolai A. Lebedev[b], Alexander F. Novgorodov[b], Riscard Misiak[c], Jörg Brockmann[a], Frank Rösch[a,*]

[a]*Institut für Kernchemie, Johannes Gutenberg-Universität, Fritz-Strassmann-Weg 2, D-55128 Mainz, Germany*
[b]*Laboratory for Nuclear Problems, JINR Dubna, Russian Federation*
[c]*H. Niewodniczanski Institute of Nuclear Physics, PL-31-342 Cracow, Poland*

Received 1 November 1999; received in revised form 1 December 1999

Abstract

The ^{176}Yb$(n,\gamma)^{177}$Yb–$\beta^-\rightarrow^{177}$Lu process was investigated to provide no-carrier-added (nca) ^{177}Lu. The radiochemical separation of the ^{177}Lu from the macro-amounts of the ytterbium target based on the cementation process, i.e. the selective extraction of Yb by Na(Hg) amalgam from Cl^-/CH_3COO^- electrolytes, followed by a final cation exchange purification. The cementation separation process provides a decontamination factor of Yb(III) of 10^4, the cation exchange purification adding a decontamination factor of $>10^2$. The nca ^{177}Lu is available in radiochemically pure form despite the chemical similarity of the lanthanides with $75 \pm 5\%$ overall separation yield within 4–5 h. It can be used to synthesise nca ^{177}Lu labelled radiotherapeuticals. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: ^{177}Lu; Endoradiotherapy; Specific activity; Cementation

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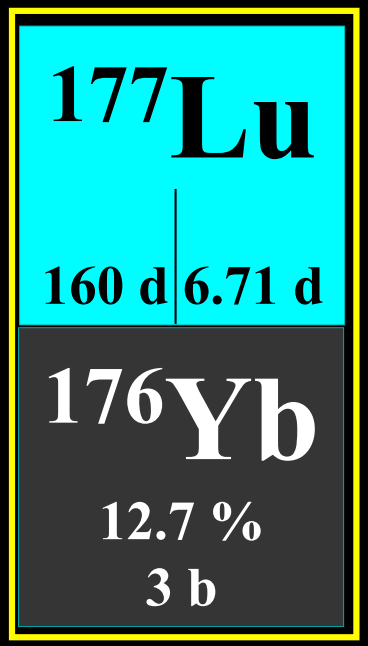
..... but chemistry is able to contribute (i) ....

^{177}Lu: nca vs. ca

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



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

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radiochemical separation of no-carrier-added ^{177}Lu
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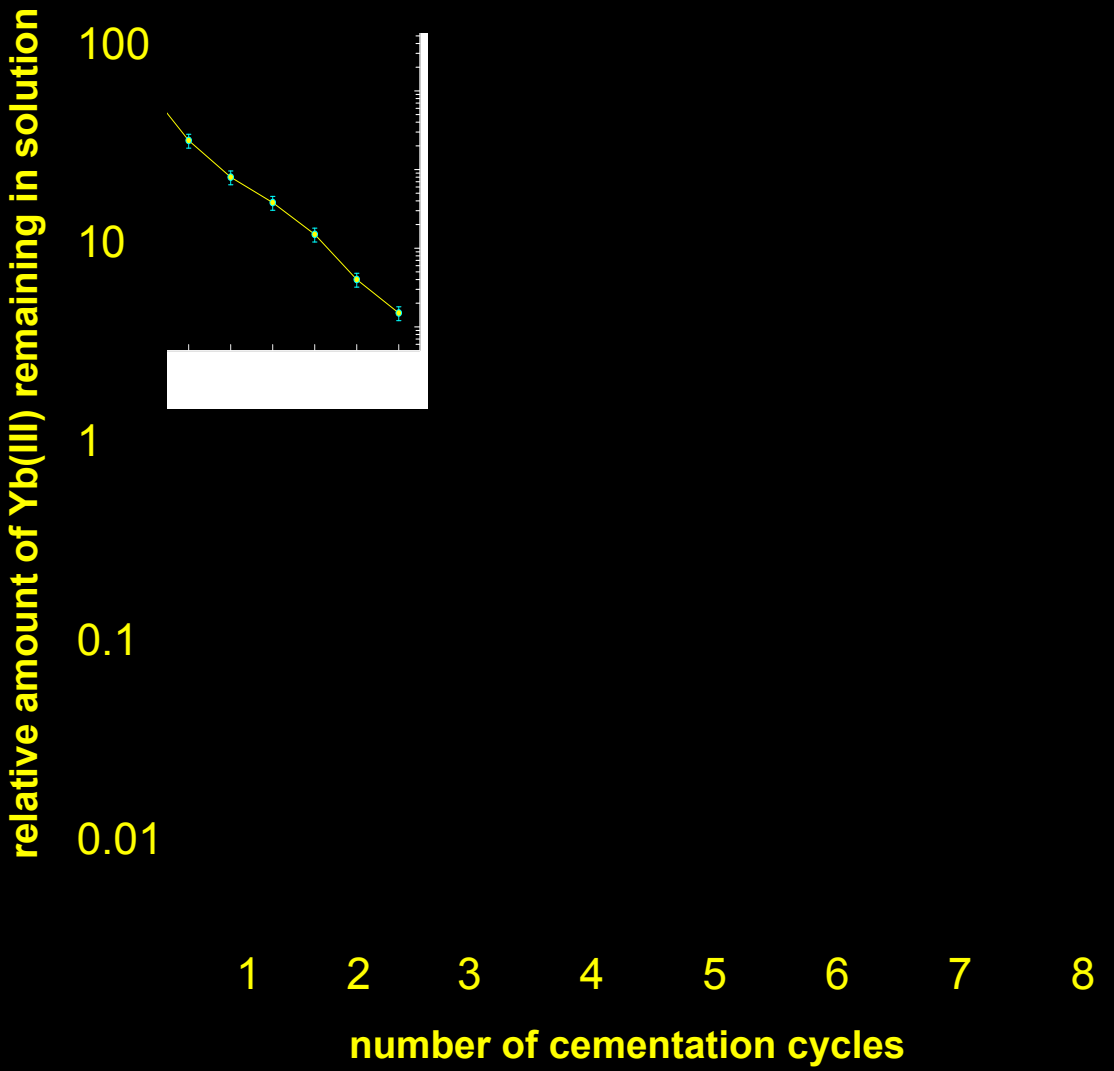


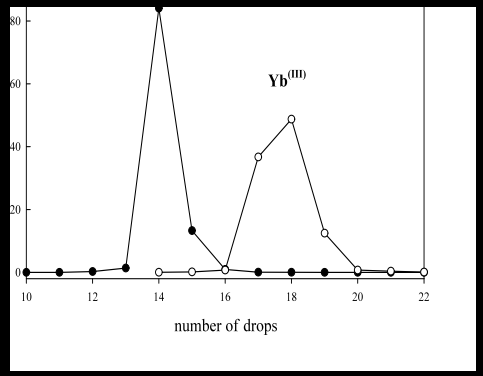
1. Production

94.72% enriched ^{176}Yb
100 mg of $^{176}Yb_2O_3$
F_{th} of $1 \cdot 10^{14}$ cm^{-2}s^{-1},
> 370 MBq per hour
batch yields > 10 GBq

2. Separation (bulk)

Na(Hg) reductive cementation of Yb(III) via extraction
^{177}Lu remaining in solution (100 mg → 20 µg)

radiochemical separation of no-carrier-added ^{177}Lu
as produced via the ^{176}Yb(n,γ)^{177}Yb —1.9h, β$^-$ → ^{177}Lu process



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Na(Hg) reductive cementation
of Yb(III) via extraction
^{177}Lu remaining in solution
(100 mg → 20 µg)

3. Purification
Cation exchange purification
(Aminex A6 2 mm x 80 mm,
0.07 M α-HIB, pH 4.7)
75% yield, 5 h

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

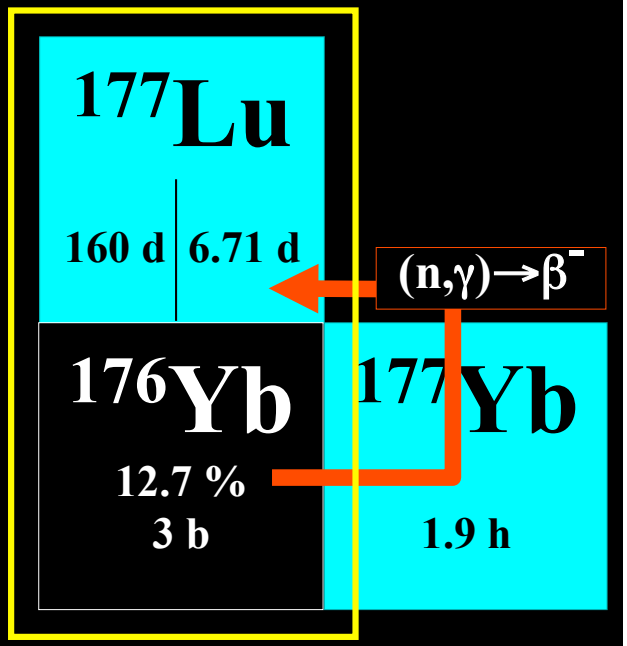
^{177}Lu: nca vs. ca

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

specific activity
> 100 Ci/mg
(vs. theoretical 110 Ci/mg)
and highest radionuclide purity

1. Irradiation of highly-enriched 176Yb
2. Huge batch activities ~ 25 Ci /1000 mg Yb (14 days)
3. radiochemical separation of ^{177}Lu(III) from stable ^{176}Yb(III)
   (~ 25 Ci /1000 mg Yb (14 days))

4. Yb-target must be quantitatively removed by chemical separation



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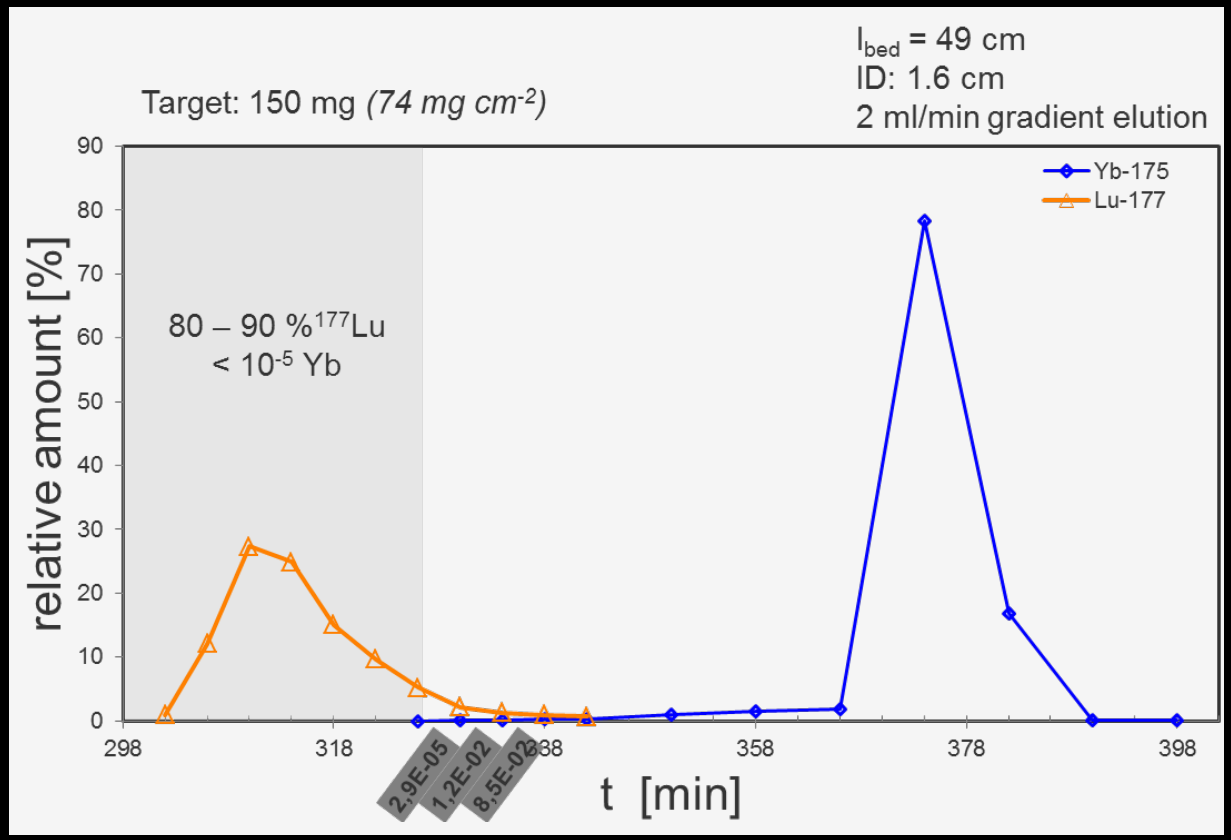
Chromatographic separation
typical elution profile



massive Yb targets (100 – 1000 mg)

column chromatography/ HPLC technique

cation exchanger/ α-HIB;

separation factor Lu(III)/Yb(III) – 1.54

micro before macro

Key parameters:

resin, column dimensions, eluent, Ln-mass

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

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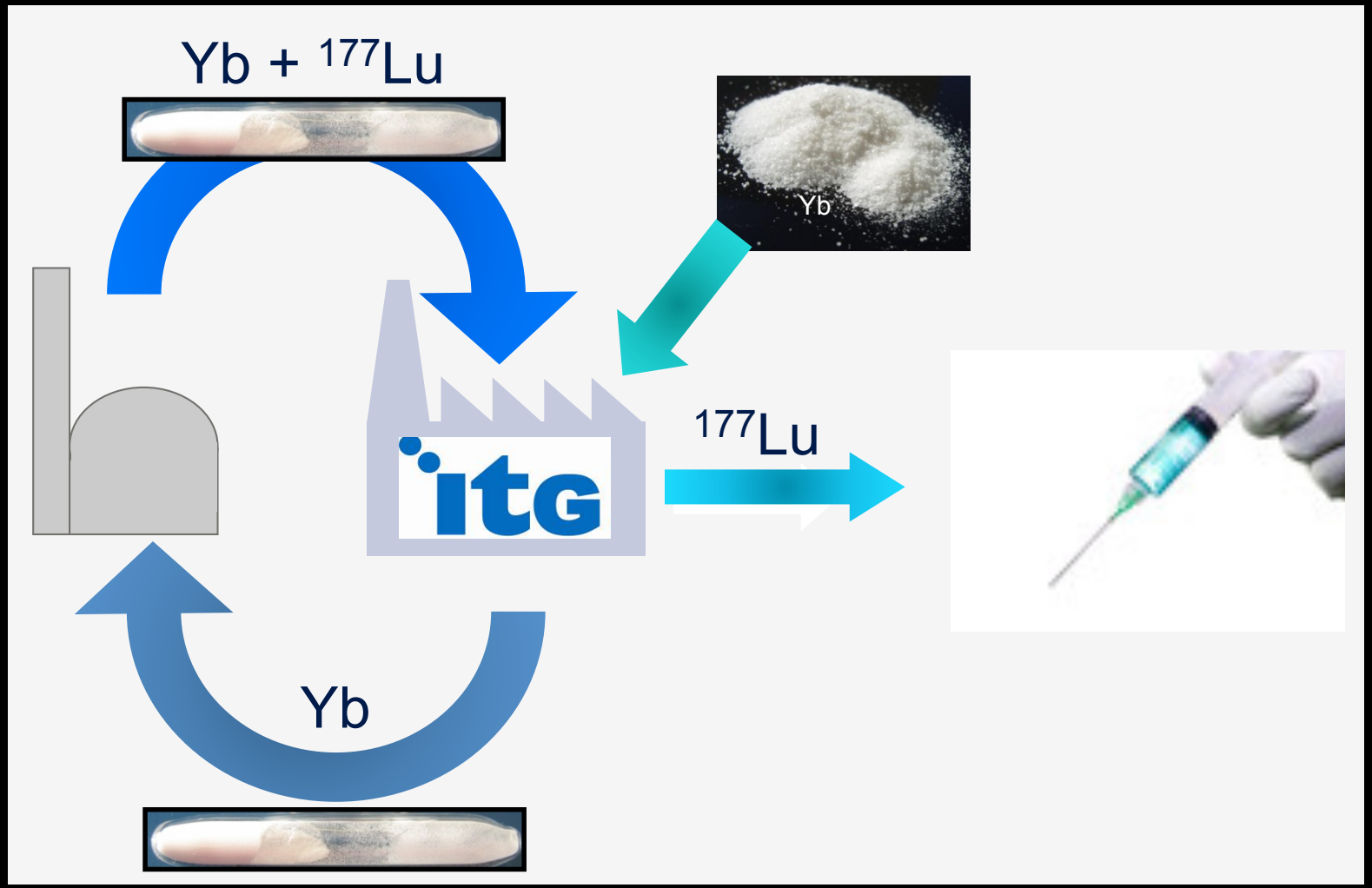

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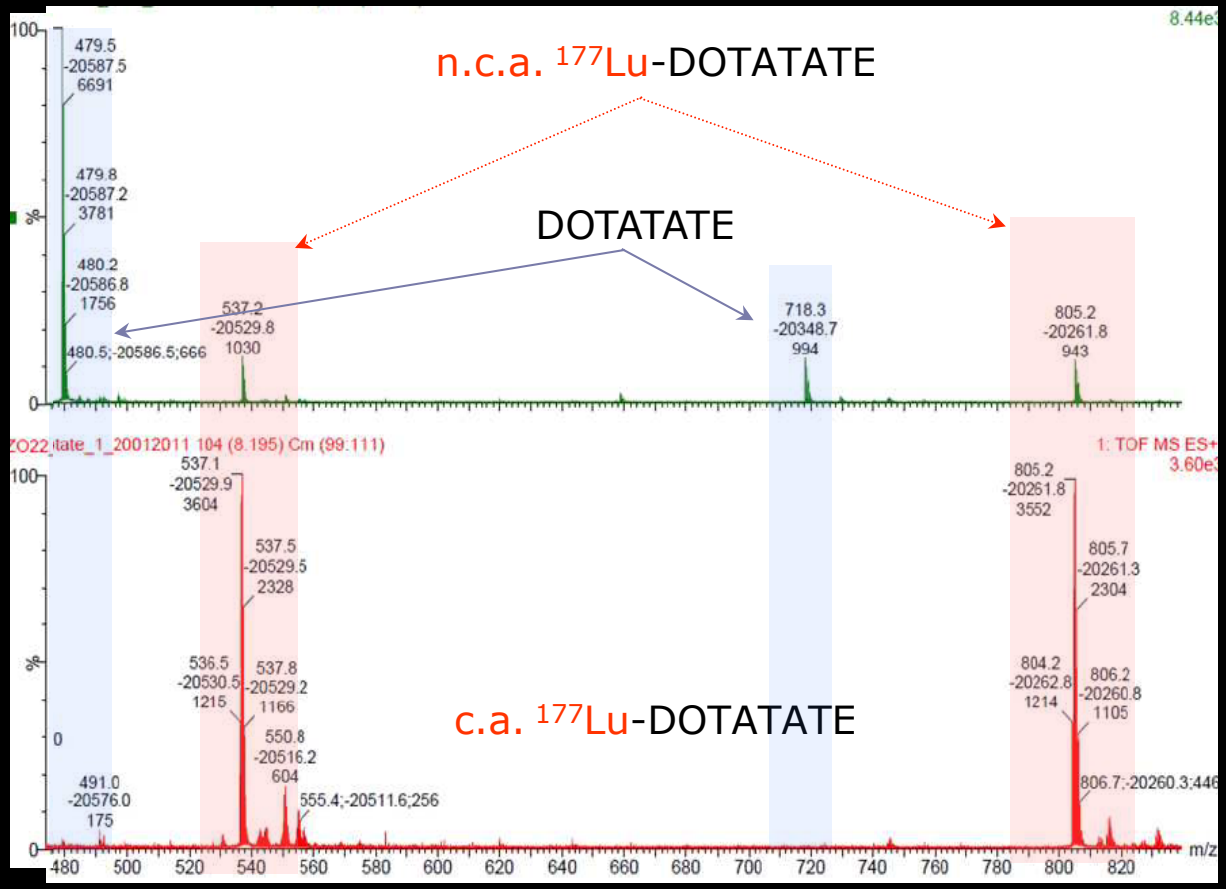
Specific activity/ c.a. vs n.c.a. ^{177}Lu

ESI-TOF-MS for identification of radiolabeled peptide species



1:4 ^{177}Lu to ligand
10 MBq ^{177}Lu-DOTATATE
0.014 nmol

99+ % radiolabeling yield (HPLC)

93% radiolabeling yield (HPLC)

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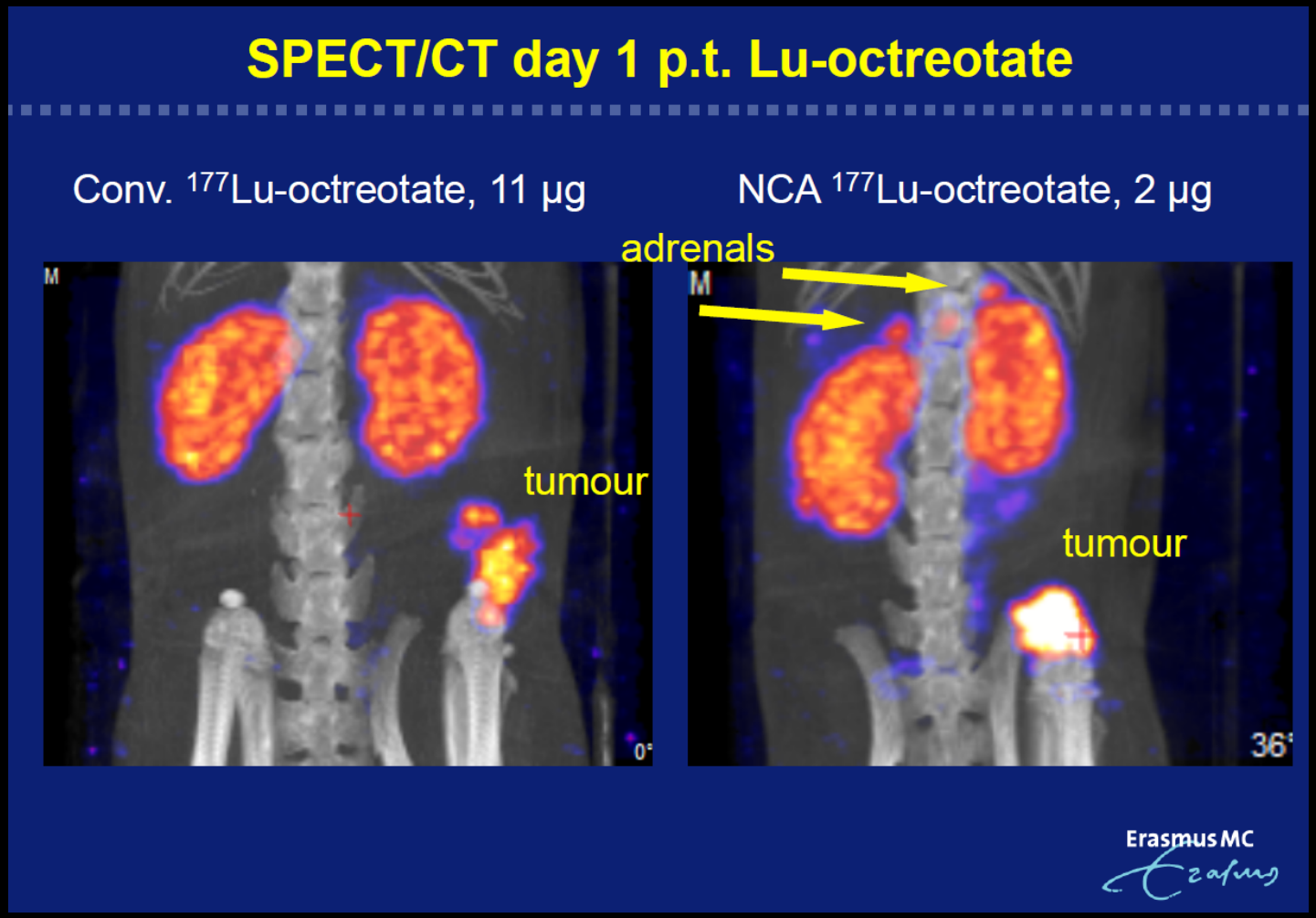

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(n,γ)	0	Same element	impossible
(n,γ) + SZILLARD-CHALMERS	0	Same element	impossible ?
(n,γ)→β^-→ processes	+1	Neighbour elements	easy for elements with different valent state / chemistry
(p,xn) etc.	+1		challange for elements of same valent state / chemistry, such as lanthanides Ln^{3+}
(α,xn) etc.	+2	Different elements	„easy“
Generators	-1, -2	Different elements	„easy“

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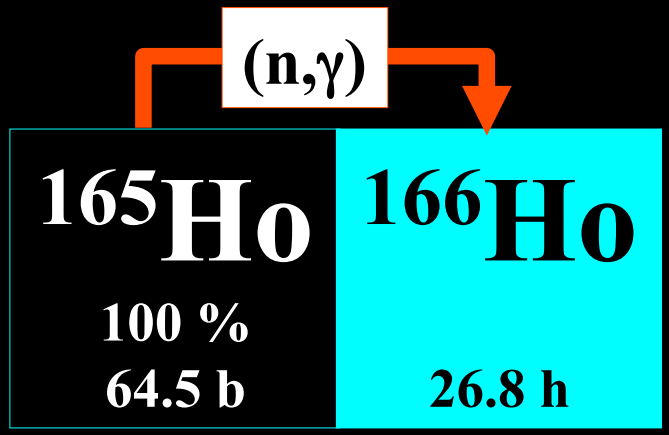
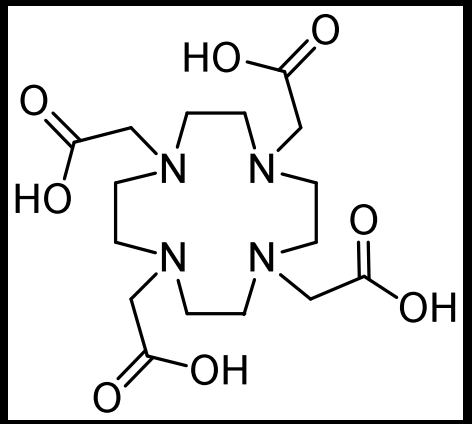
Example

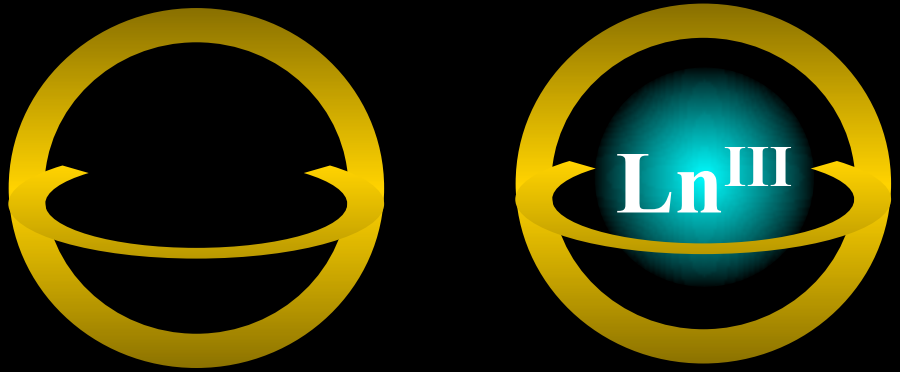
- prepare and irradiate ^{165}Ho-DOTA



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.

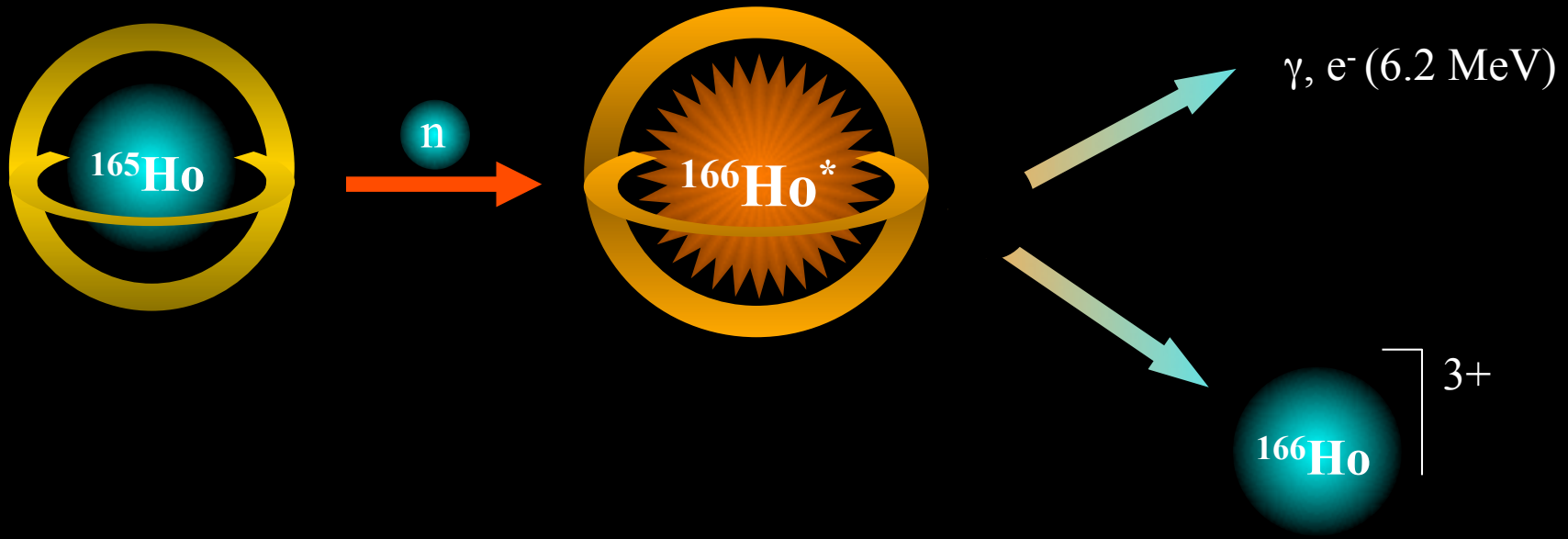




1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid

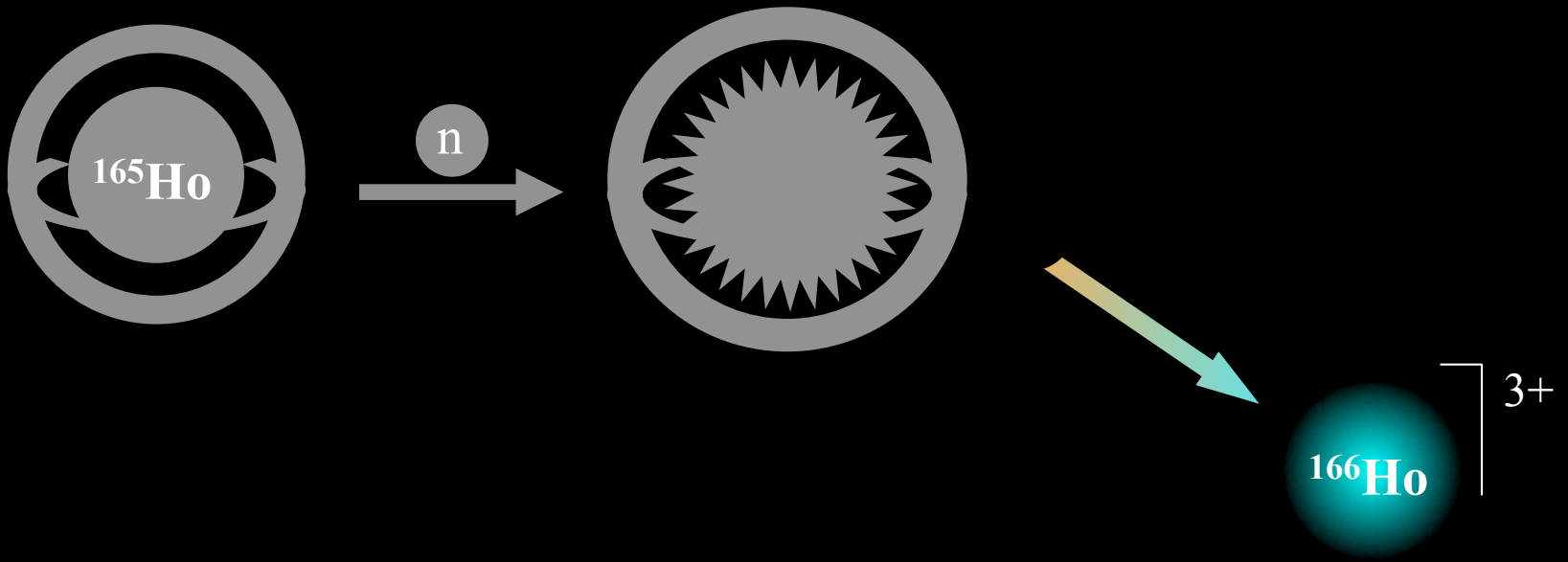
Experiment

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



Experiment

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



- **not** forming ^{166}Ho-DOTA

Experiment

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

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

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Ho-DOTA:

Separation of $[Ho\text{-}DOTA]^-$ from uncomplexed Ho(III)
on a chromatography column 8 × 140 mm, AG 50W-X8, 200 - 400 mesh cation-exchanger K^+-form.
Free $^{166/165}Ho(III)$ quantitatively absorbed on the resin,
while ^{165}Ho-DOTA complex (1:1 stoichiometry) obtained in the eluate.
$^{166/165}Ho(III)$ washed out with 4 M HCl.

Irradiations:

aqueous solution of $K[^{165}Ho\text{-}DOTA]$ (1 mg Ho) evaporated in a polyethylene capsule at < 100° C.
Remained activity of ^{166}Ho negligible.
irradiations at TRIGA II Mainz nuclear reactor at the neutron flux of $4 \cdot 10^{12}$ n cm^{-2} s^{-1},
external temp ~ 21° C, within different periods of 0.5 – 6 h, resulting in 10 – 120 MBq ^{166}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_4^+ -form.
target material $[^{165}Ho\text{-}DOTA]^-$ removed by washing of the column with water.
enriched $^{166}Ho(III)$ eluted with 0.20 M α-HIBA

to determine the amount of stable ^{165}Ho, remained in the obtained ^{166}Ho,
fractions of maximum ^{166}Ho activity in α-HIBA solutions evaporated after 10 half-lives
of the radionuclide irradiated at the same neutron flux.

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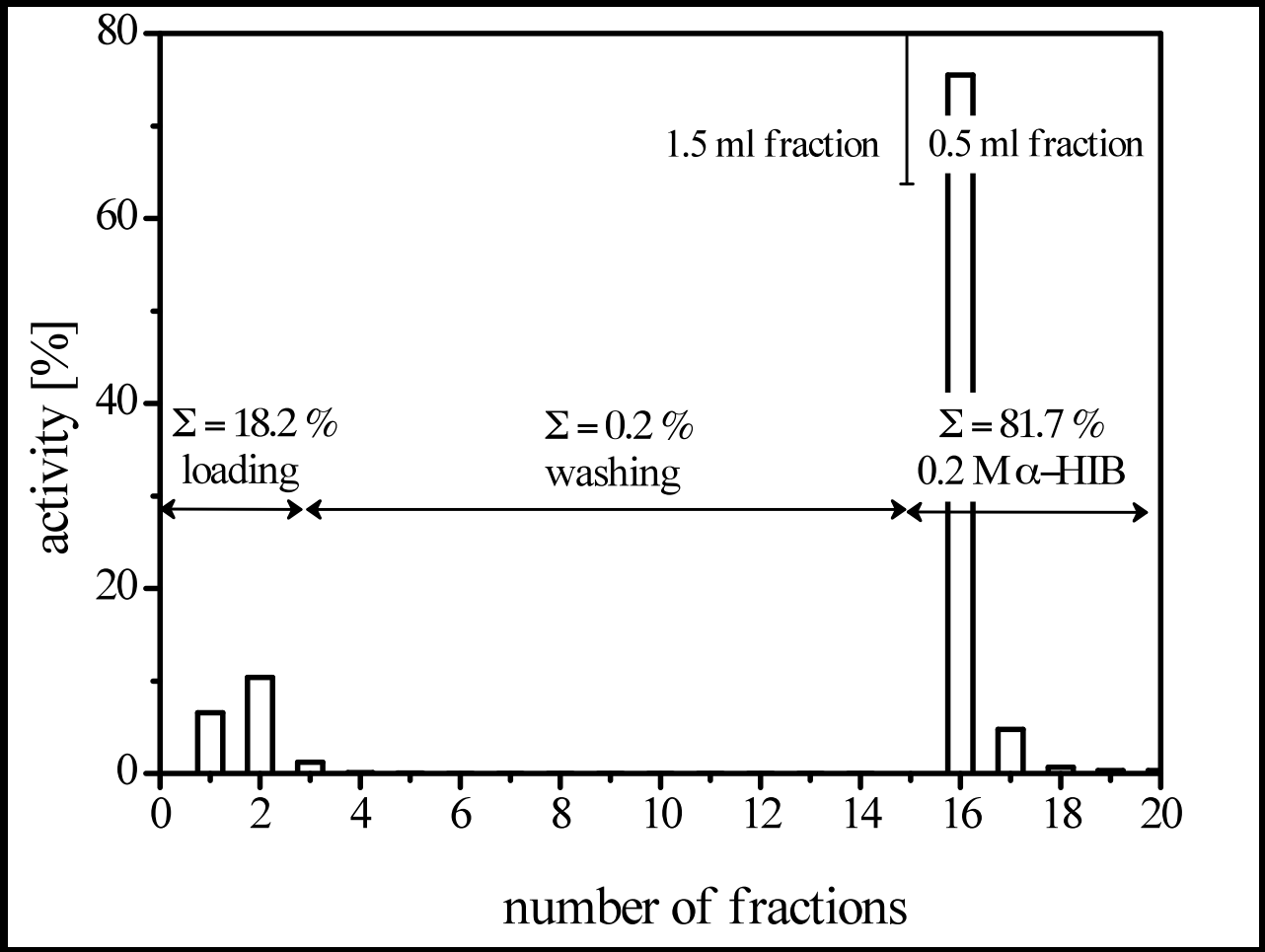
Separation $^{165/166}$Ho-DOTA / $^{166}Ho^{3+}$



Elution profile at a processing of the irradiated target material
chromatography column 4 × 50 mm Bio-Rad AG 50W-X8, minus 400 mesh, NH_4^+-form

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Enrichment factor ξ and retention value R

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

Time of irradiation [h]	Integral flux [neutron/cm^2]	ξ	R [%]
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

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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}Ho-DOTA:
TRIGA II Mainz $4 \cdot 10^{12}$ n cm^{-2} s^{-1}:
k = 750,000 barns

Target material	^{166}Ho experimental SA 6 h irradiation [MBq/mg]	^{166}Ho max. specific activity [MBq/mg] for TRIGA II Mainz
Ho_2O_3	135	886
Ho-DOTA	~ 2000	~ 2200

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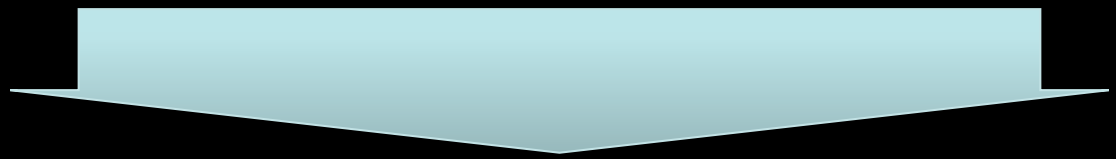
Radionuclides
Chemistry



(Radio)chemical Labelling

Radionuclide valent states

Me^{IV}_{ERT}	Me^{III}_{ERT}	Me^{II}_{ERT}	Me^{I}_{ERT}	X^{I}_{ERT}
	^{47}Sc	^{67}Cu		^{131}I
	^{90}Y			
	^{135}Sm			
	^{177}Lu			
	^{149}Tb	^{223}Ra	^{211}At	
	^{213}Bi	^{224}Ra		
	^{225}Ac			
^{117m}Sn	^{67}Ga			
Coordination chemistry			Covalent binding	

Radionuclide valent states

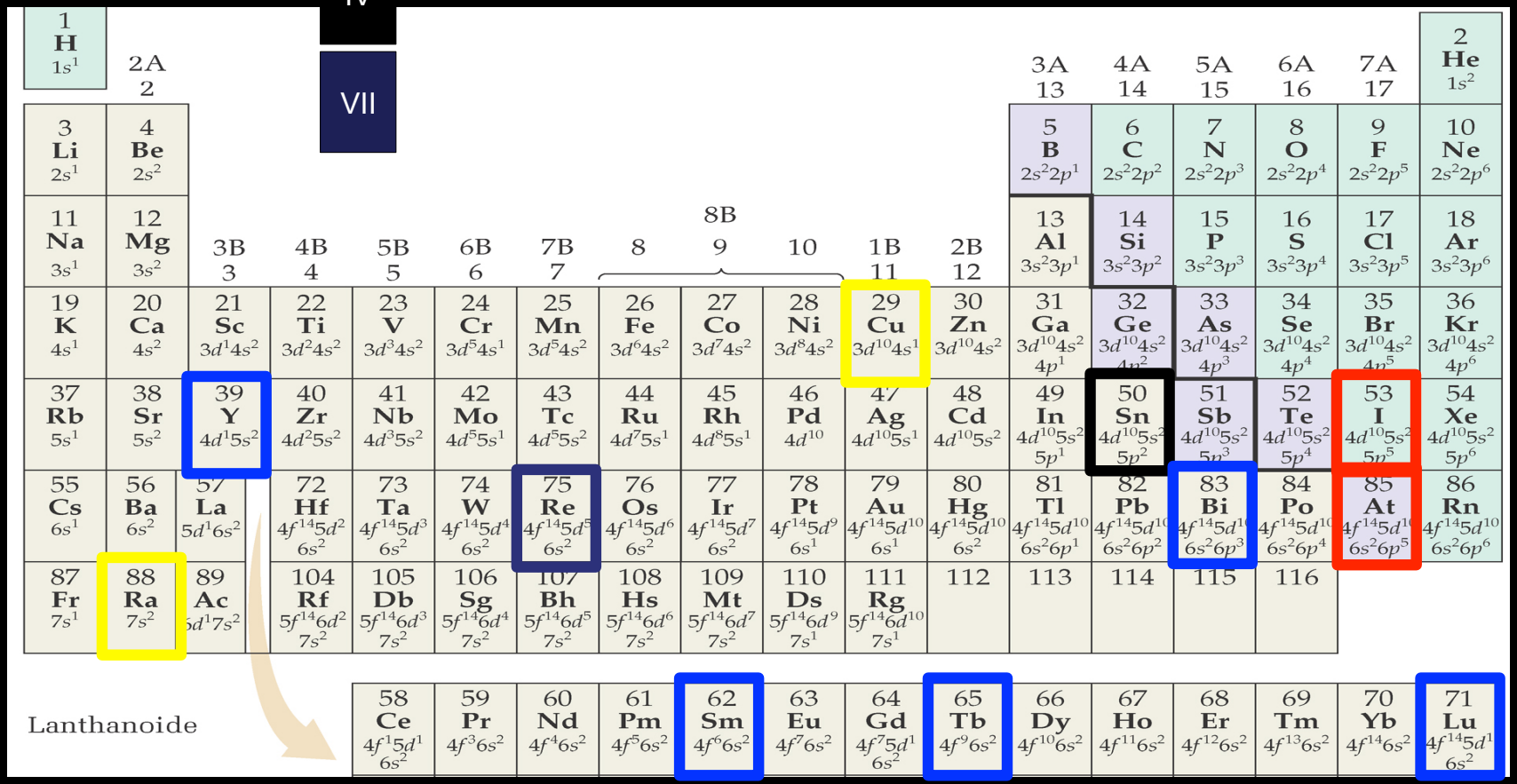
I

II

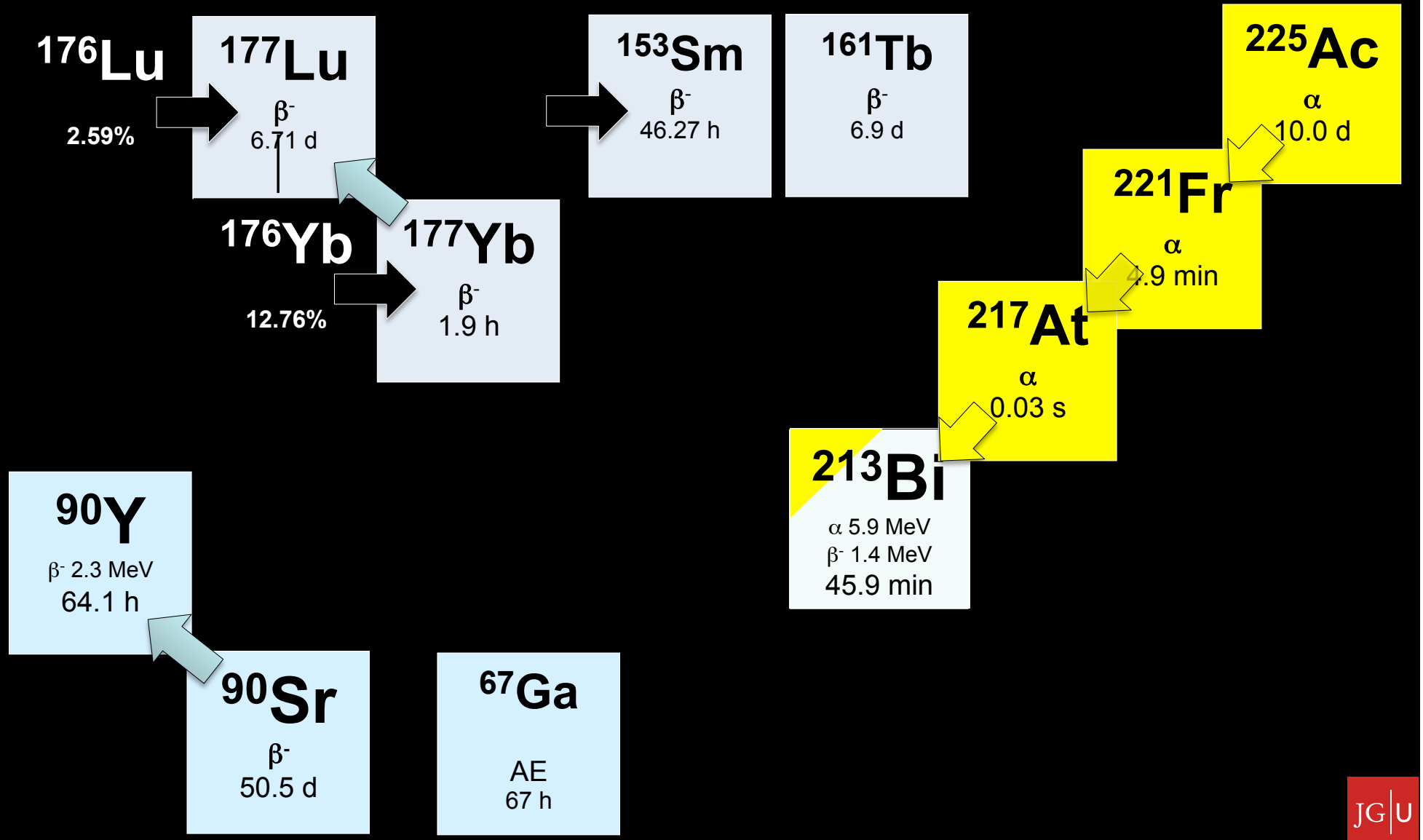
III

IV

VII



Radionuclide valent states Me(III)



Radionuclide valent states (non-III)

VII

^{186}Re
β^-
89.25 h

^{188}Re
β^-
16.98 h

IV

^{117}Sn
IC
13.6 d

II

^{67}Cu
β^-
61.9 h

^{223}Ra
α
11.43 d

^{224}Ra
α
3.66 d

I

^{211}At
α
7.2 h

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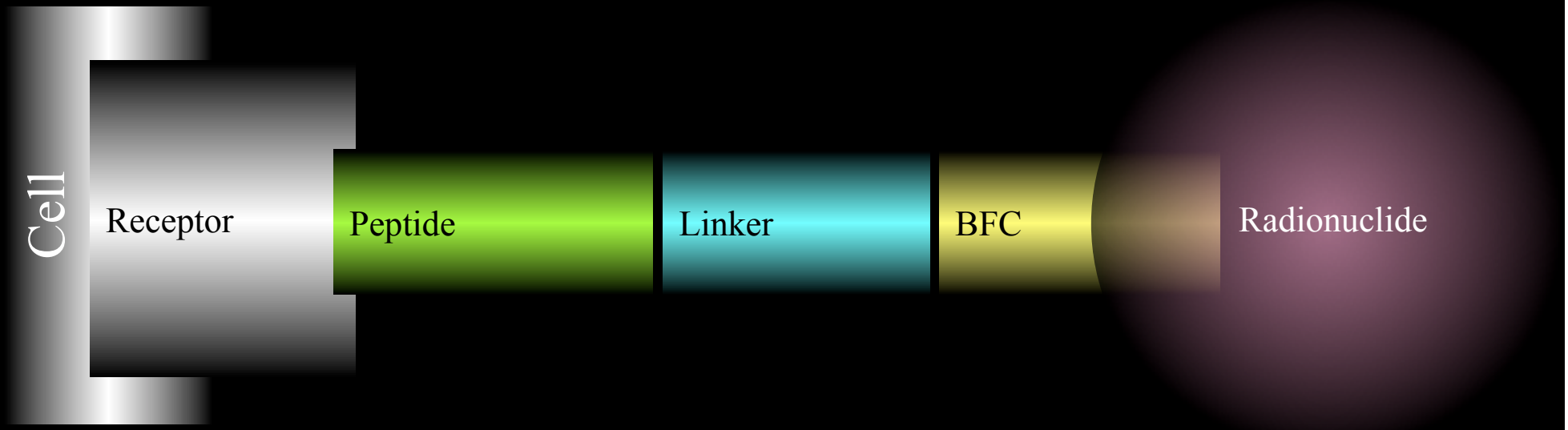
Radionuclides

Chemistry

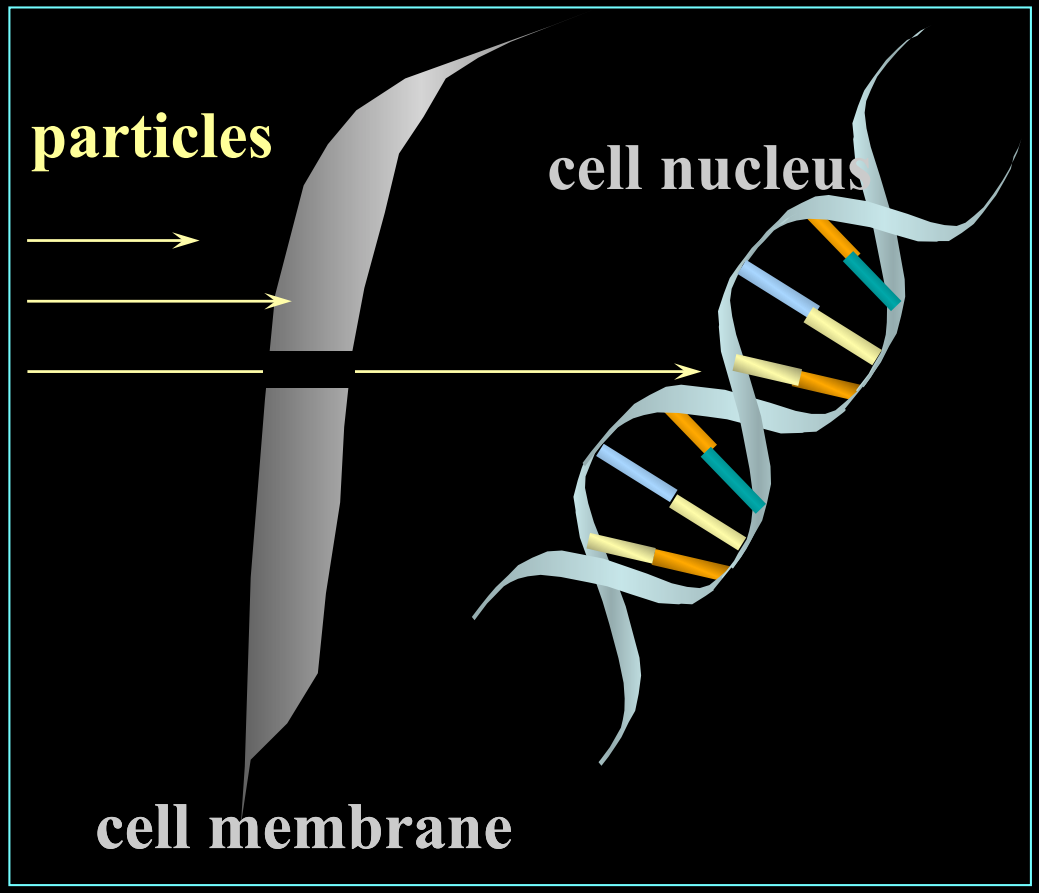
(Radio)chemical Labelling

Chemical strategies for aproaching the tumour cell

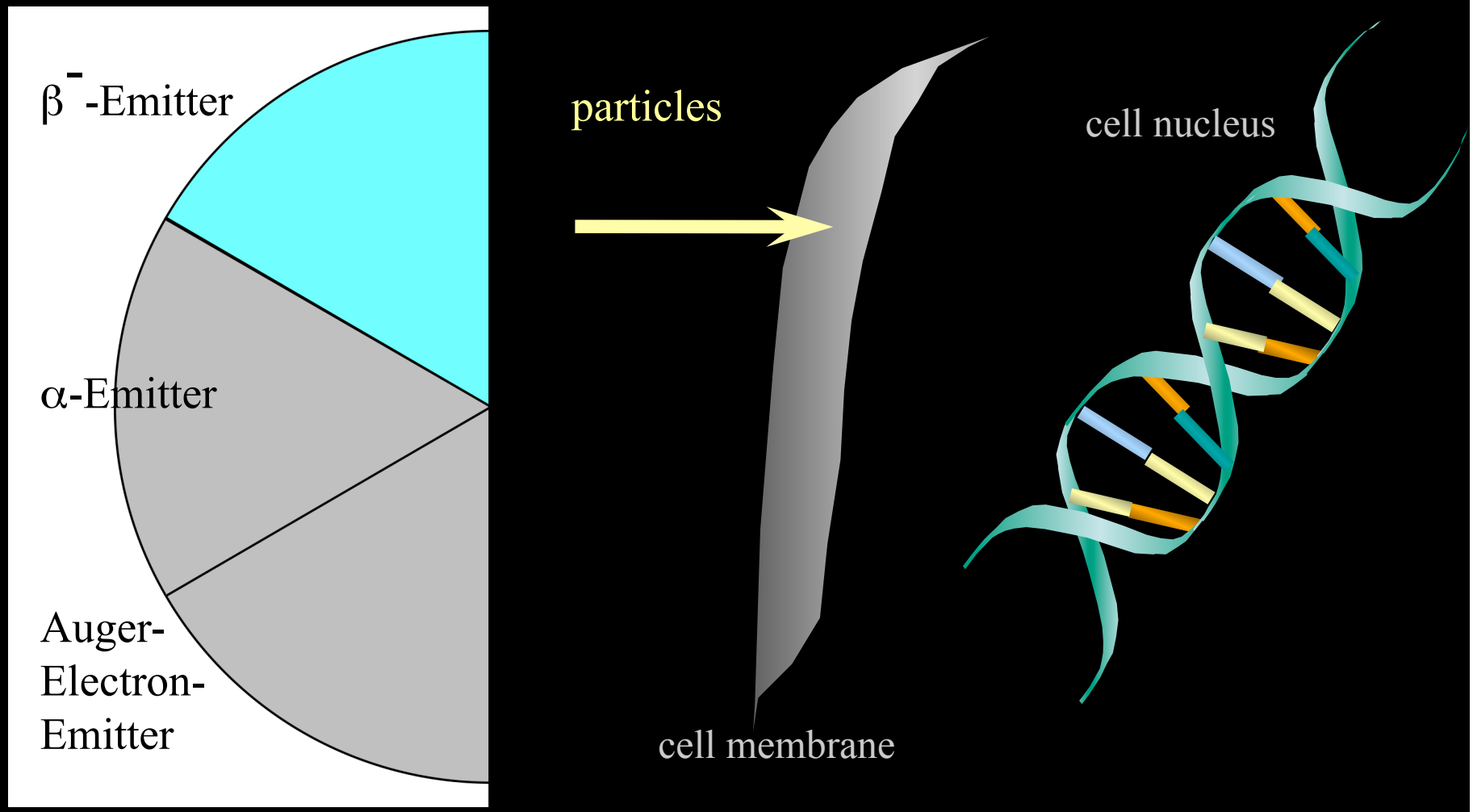


ERT

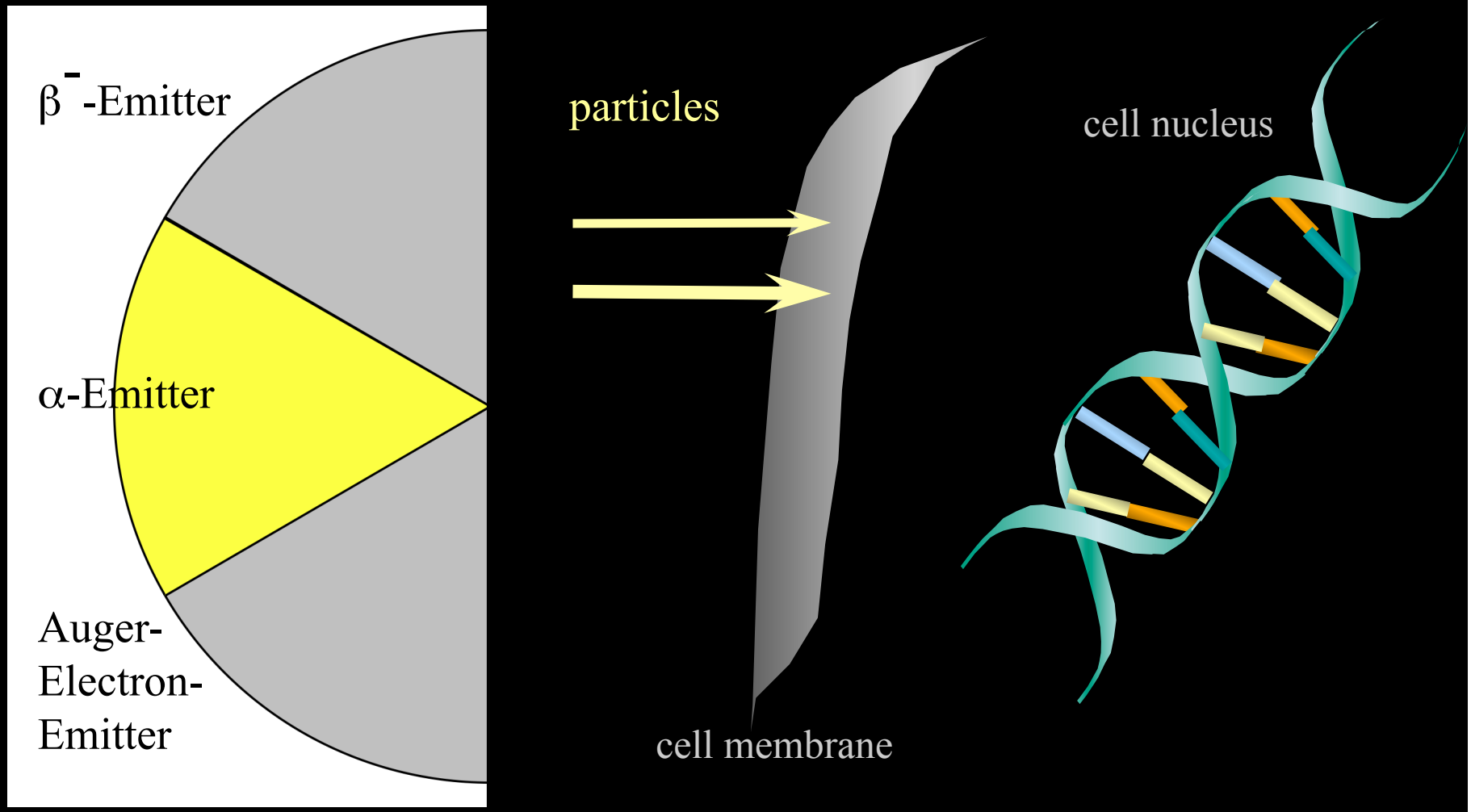
Radionuclide decay characterised by the emission of particles mainly (maximum ratio of non-penetrating / penetrating radiation)



particle range vs.
radiopharmaceutical and pharmacological strategies



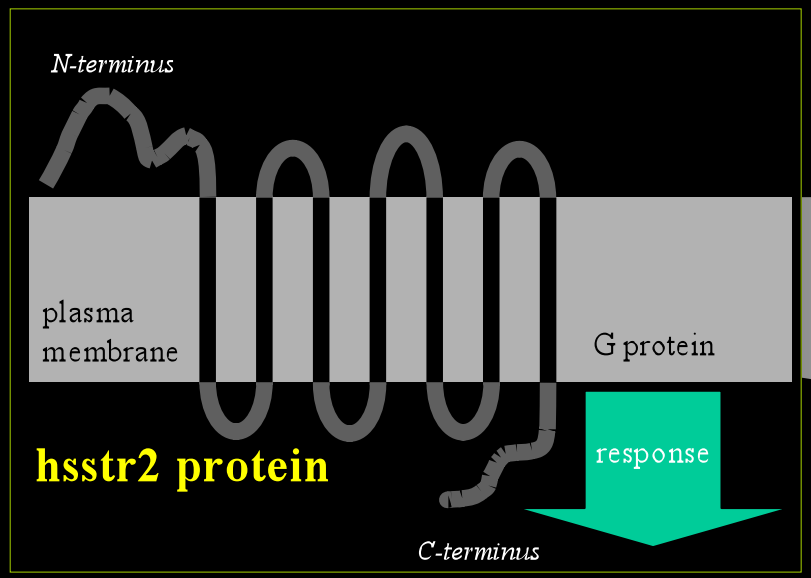
particle range vs. radiopharmaceutical and pharmacological strategies



Chemical strategies for approaching the tumour cell

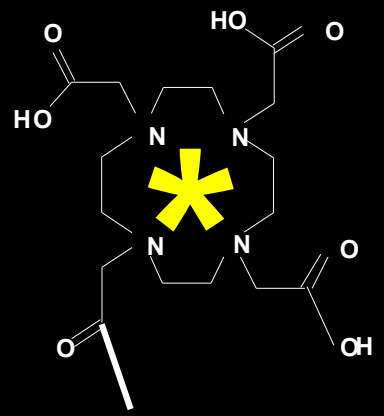
Example:
Somatostatin receptor expressing tumors

Somatostatin receptor
octreotide (SMS 201-995)



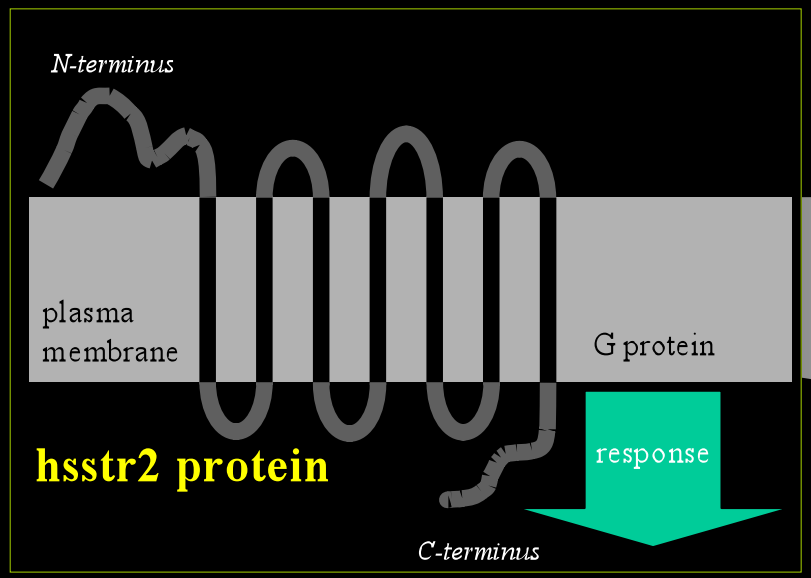
hSSTR1 > 1000 nmol / L
hSSTR2 0.32 nmol / L
hSSTR3 31.6 nmol / L
hSSTR4 > 1000 nmol / L
hSSTR5 7.3 nmol / L

Chemical strategies for approaching the tumour cell



^{68}Ga-DOTATOC

Somatostatin receptor
octreotide (SMS 201-995)

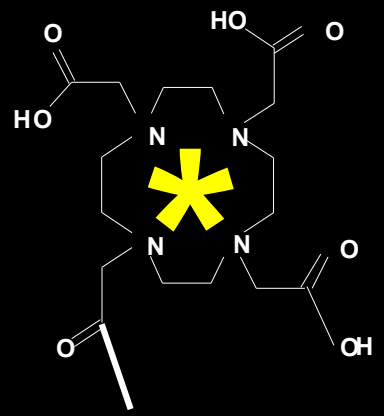


(D)Phe - Cys - Tyr - (D)Trp

Thr(ol) - Cys - Thr - Lys

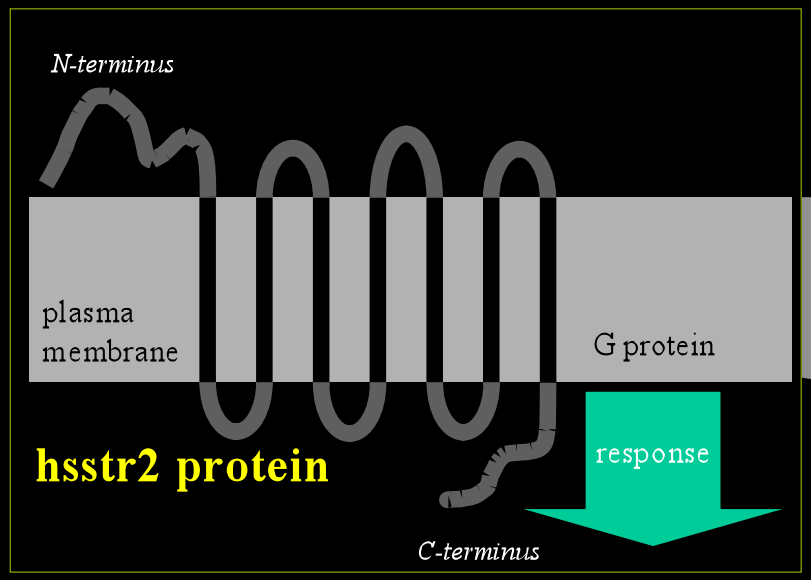
hSSTR1 > 1000 nmol / L
hSSTR2 0.32 nmol / L
hSSTR3 31.6 nmol / L
hSSTR4 > 1000 nmol / L
hSSTR5 7.3 nmol / L

Chemical strategies for approaching the tumour cell

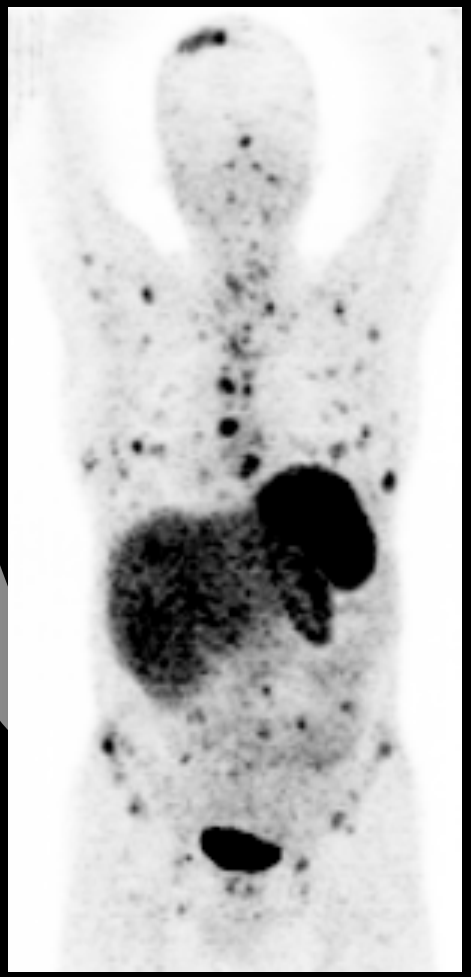


(D)Phe - Cys - Tyr - (D)Trp

Thr(ol) - Cys - Thr - Lys



^{68}Ga-DOTATOC

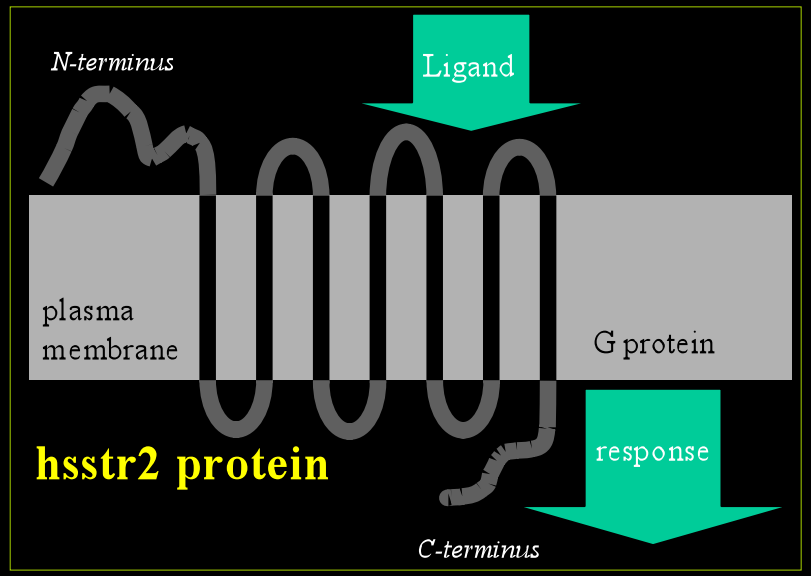


^{177}Lu-DOTATOC

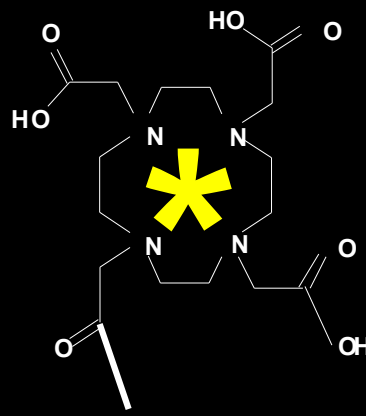
Somatostatin receptor expressing tumors

Somatostatin receptor

octreotide (SMS 201-995)



^{68}Ga-DOTATOC

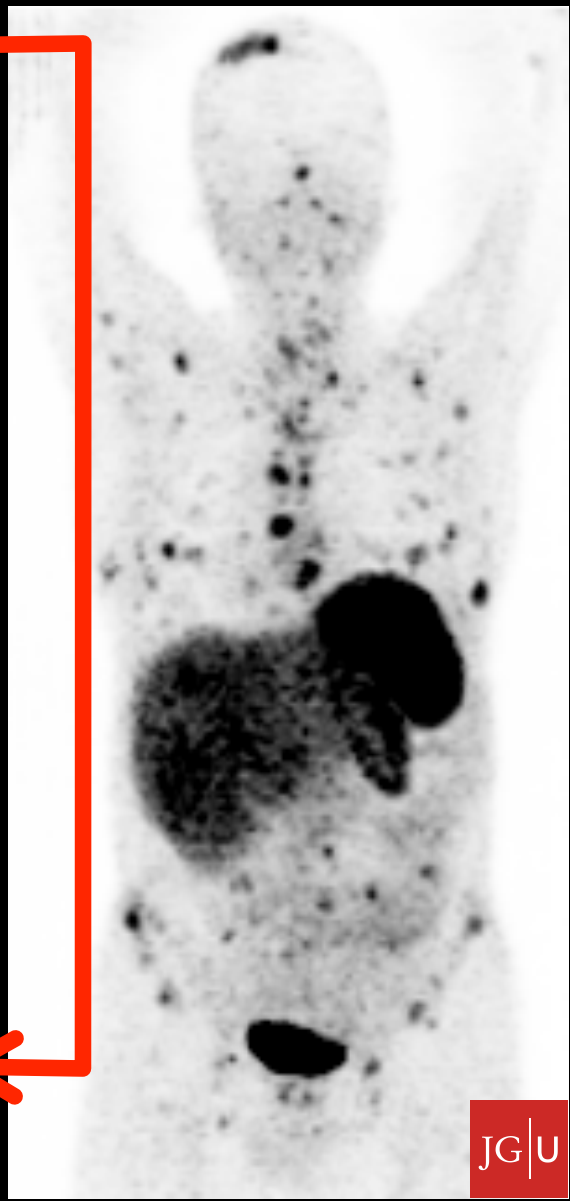


(D)Phe - Cys - Tyr - (D)Trp

Thr(ol) - Cys - Thr - Lys

hSSTR1 > 1000 nmol / L
hSSTR2 0.32 nmol / L
hSSTR3 31.6 nmol / L
hSSTR4 > 1000 nmol / L
hSSTR5 7.3 nmol / L

^{177}Lu-DOTATOC



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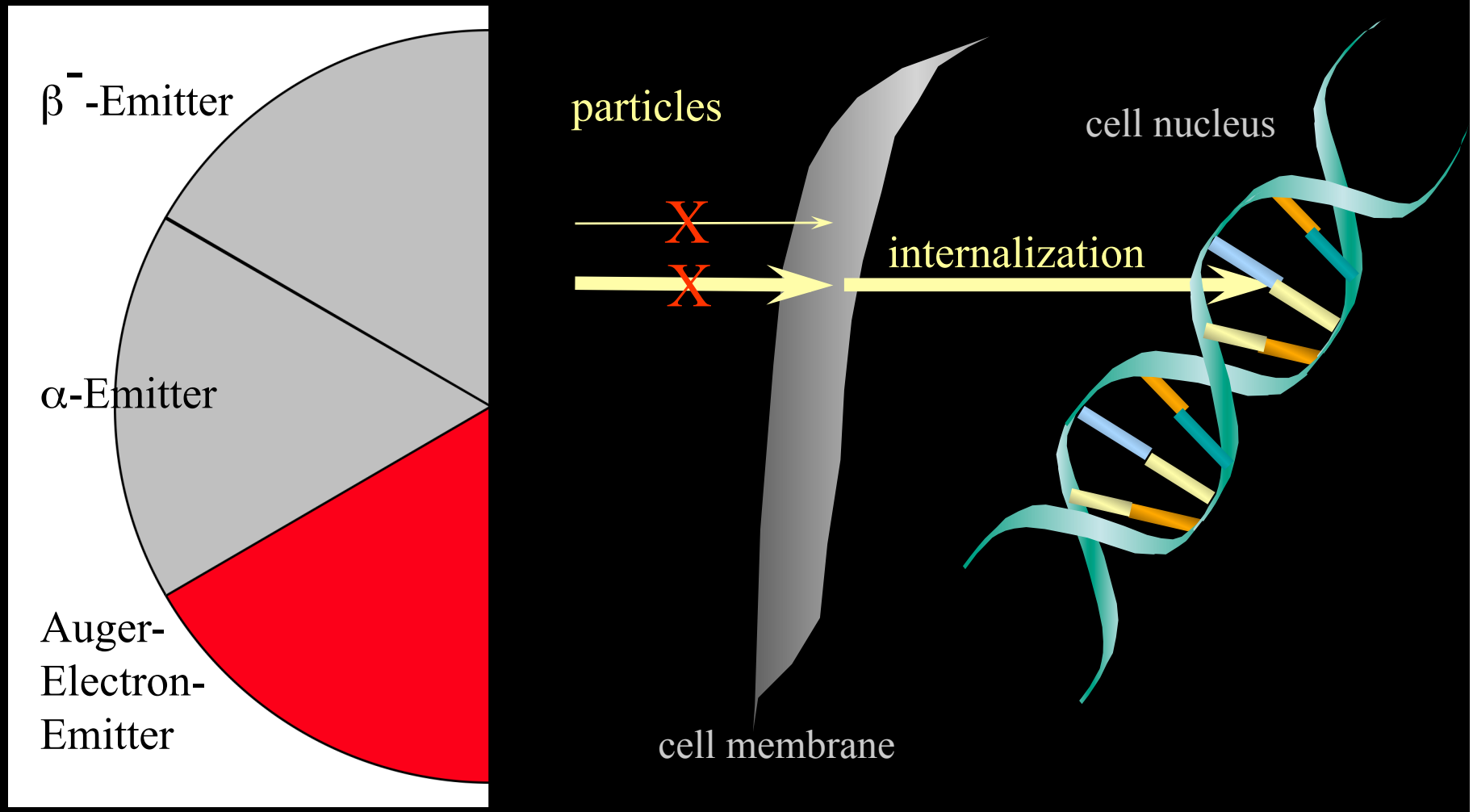
particle range vs.
radiopharmaceutical and pharmacological strategies



Summary

The isotope:
- decay property (photons / particles)
- energy (detection / dosimetry)
- half-life (biological half-life)
- decay products

The access:
- availability
- nuclear reaction (yields / isotopic purity)
- commercial aspects (routine / research)

The labeling:
- chemistry / radiopharmacology
- covalent / organic chemistry
- co-ordination / metal isotopes

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Acknowledgement

KP Zhernosekov[1],
DV Filosofov[2]
SM Qaim[3]

[1]Institute of Nuclear Chemistry, University of Mainz, Germany; ITG Munich, Germany
[2]Joint Institute of Nuclear Research, LJAP, Russian Federation
[3]FZ Jülich, Germany