The Nuclear Astrophysics' Curse on Nuclear Medicine

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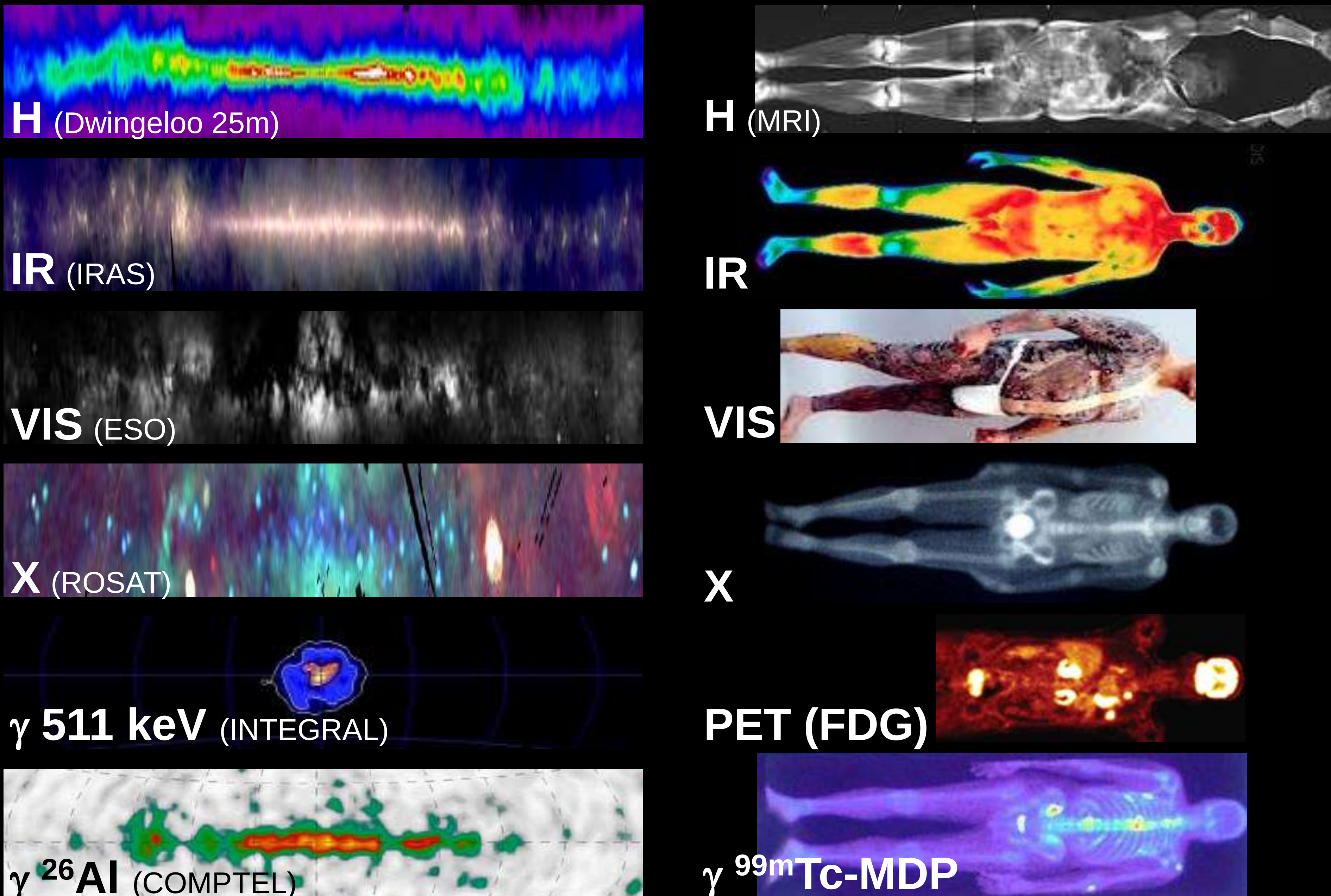
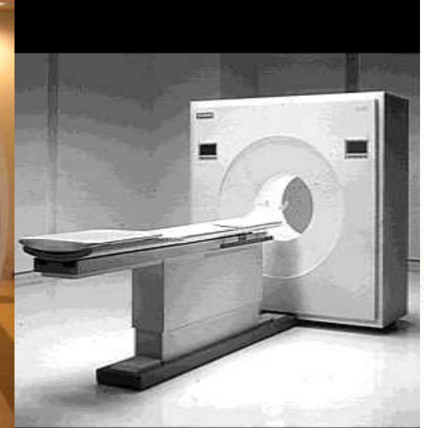
Institut Laue-Langevin, Grenoble

11th Russbach Workshop on Nuclear Astrophysics

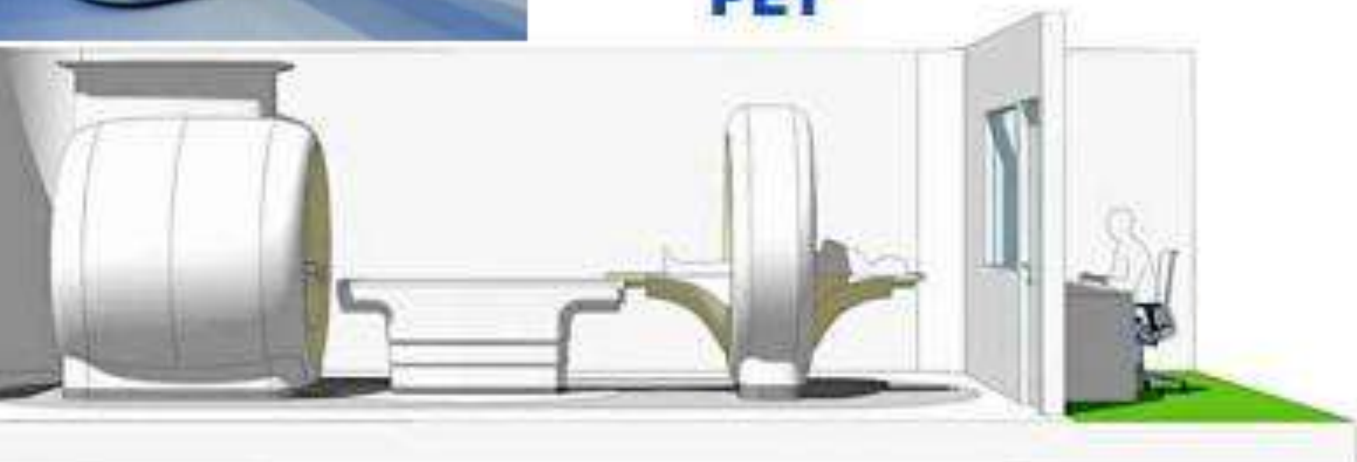
11 March 2014

Different views, different observables

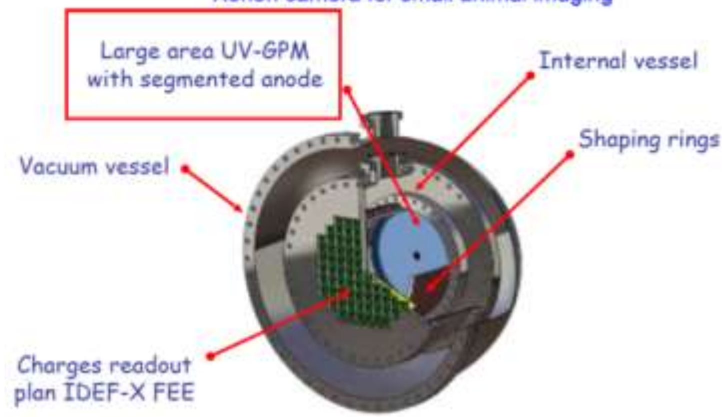




PET



Xenon camera for small animal imaging

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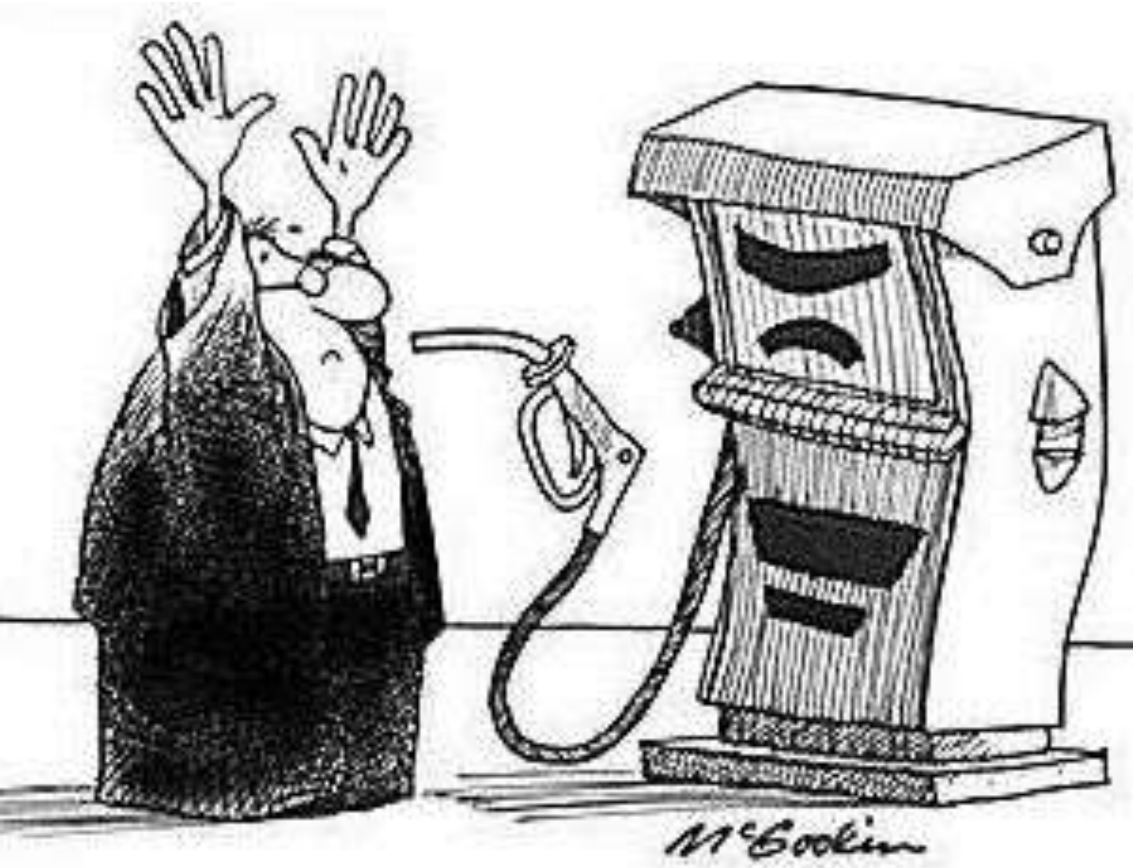
HG KL 414






Don’t forget the fuel!



Radioisotopes: the “fuel” for nuclear medicine

1. What is the optimum fuel for an application ?

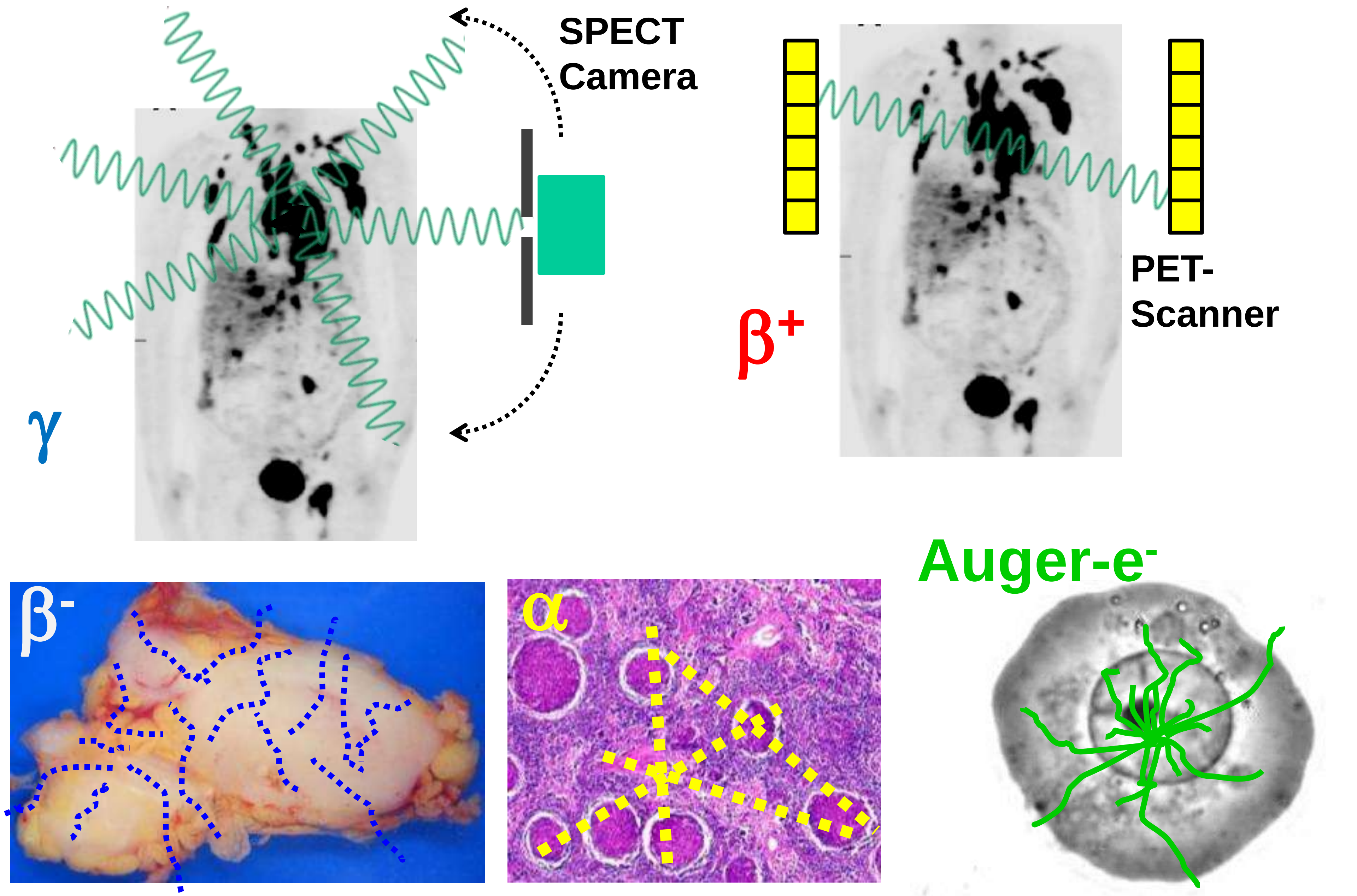
2. Are we using the optimum fuel today ?

3. Where does this fuel come from ?

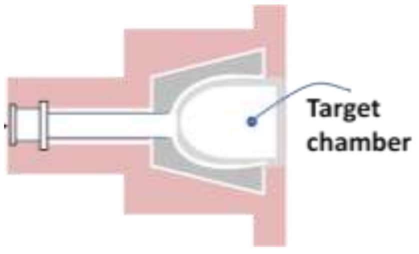
Nuclear medicine needs artificial transmutations.

Nuclear astrophysics: “natural” transmutations in the universe.

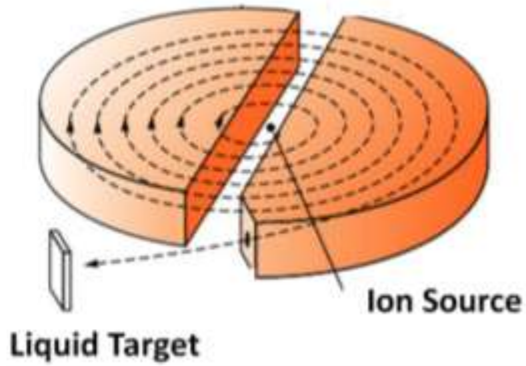
The Nuclear Medicine Alphabet



Cyclotron versus reactor production

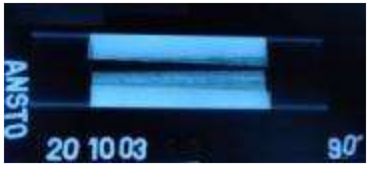


$H_2{}^{18}O$ water
(liquid target)

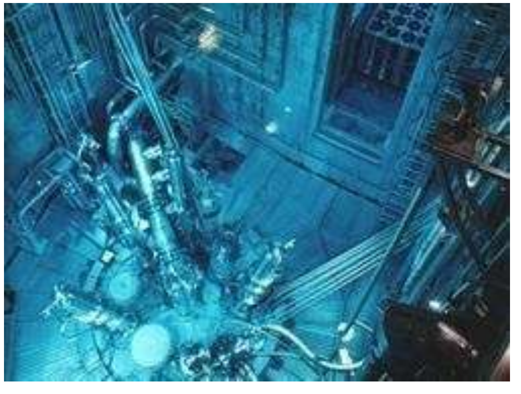


Cyclotron irradiation
$^{18}O(p,n)^{18}F$
produces [^{18}F]fluoride

Transformation into FDG
by automated synthesis
modules in shielded hot cell



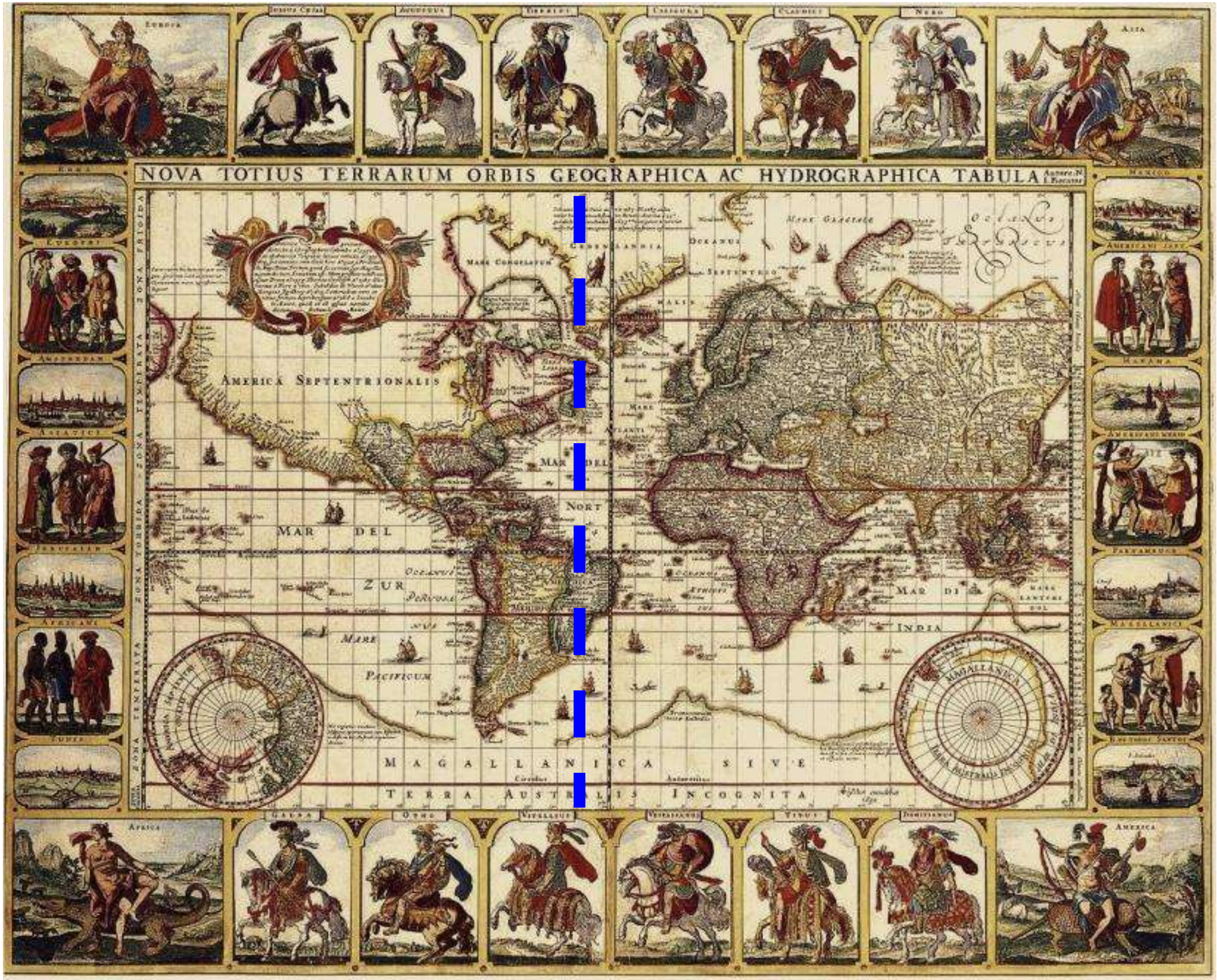
^{235}U
(foil in Al capsule)



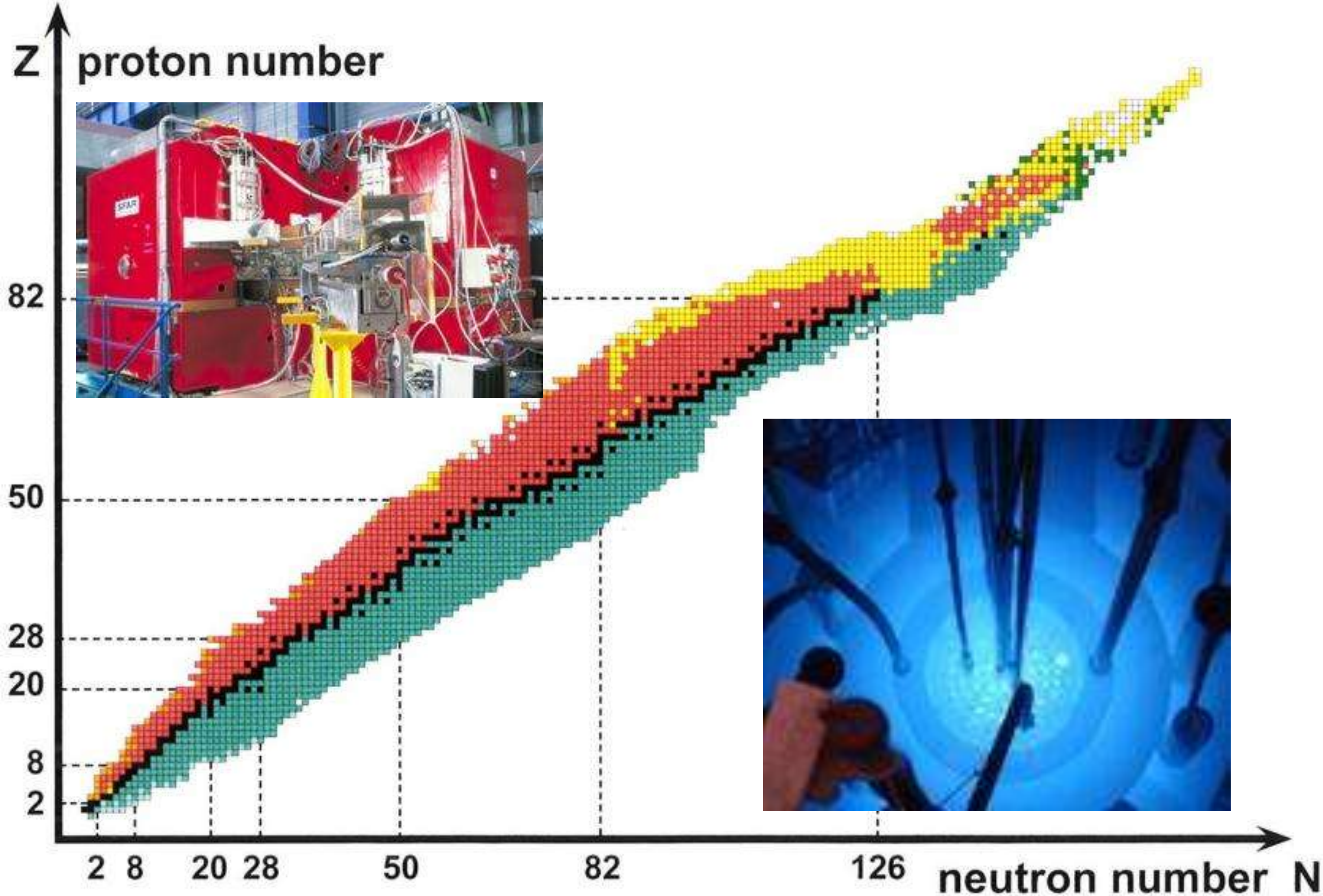
Reactor irradiation
$^{235}U(n,f)$
produces many fission products

Radiochemical separation
of Mo
in shielded hot cells

The Tordesillas meridian



The Tordesillas meridian of radioisotope production

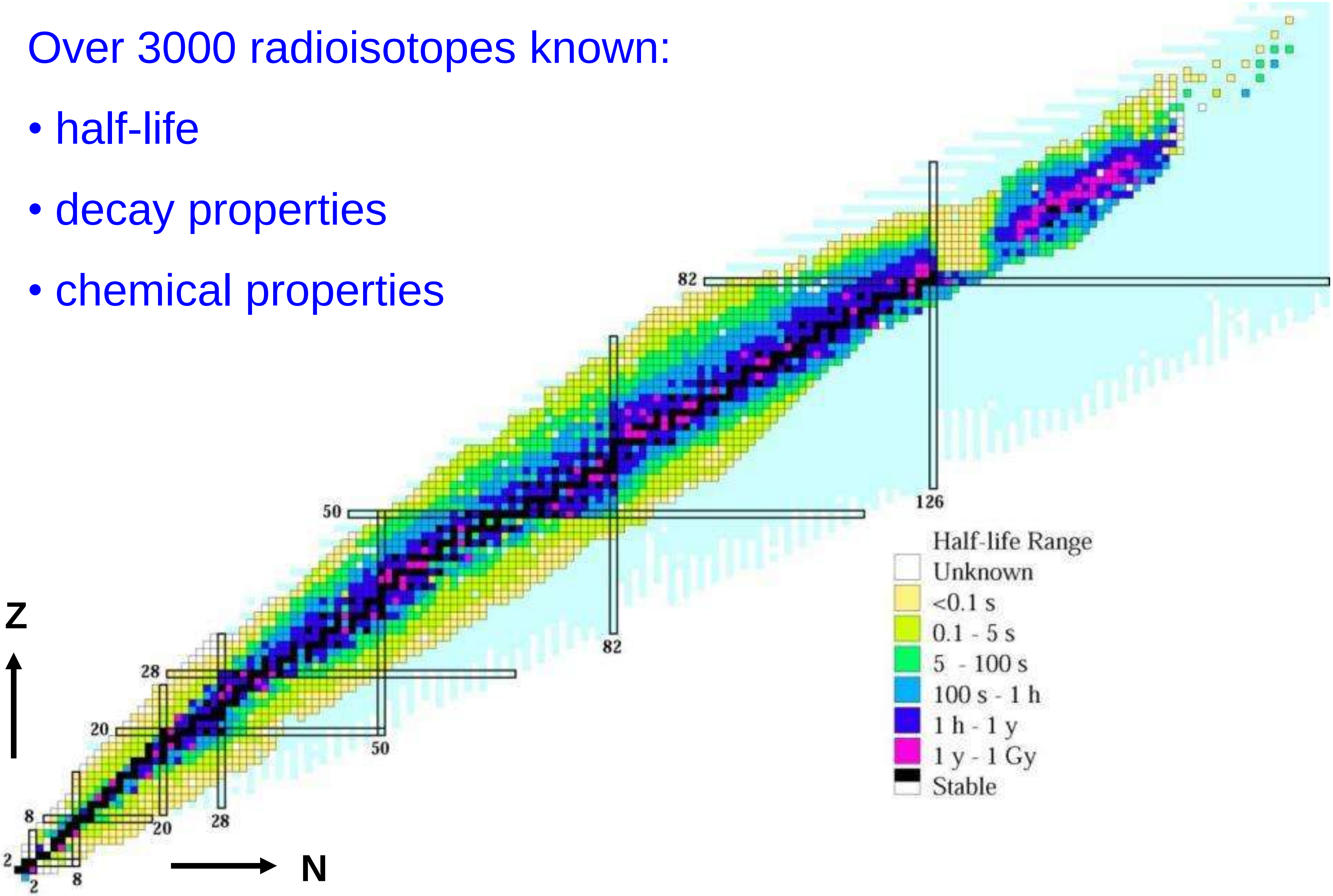


Reactor vs. cyclotron

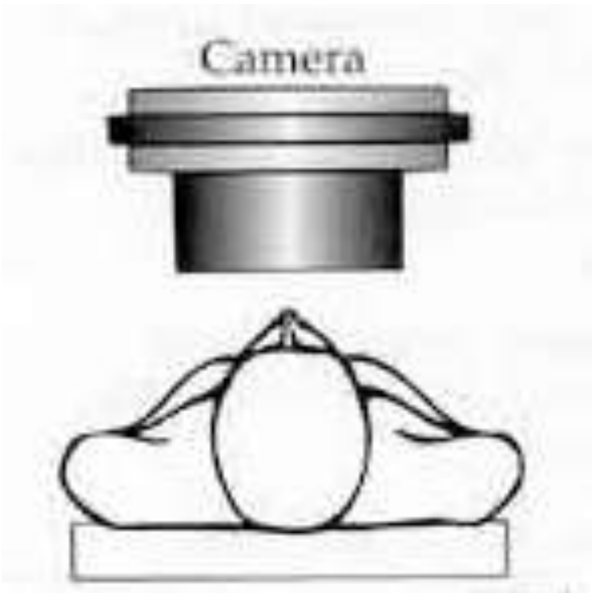
The quest for the optimum isotope

Over 3000 radioisotopes known:

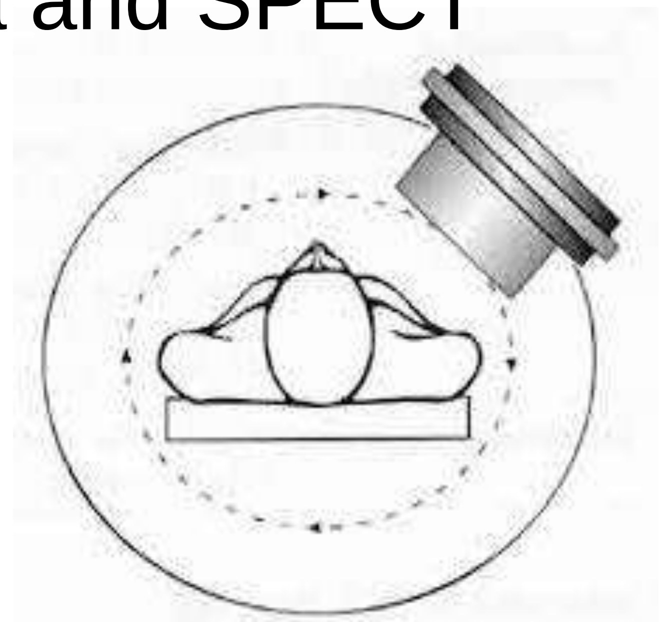
- half-life
- decay properties
- chemical properties



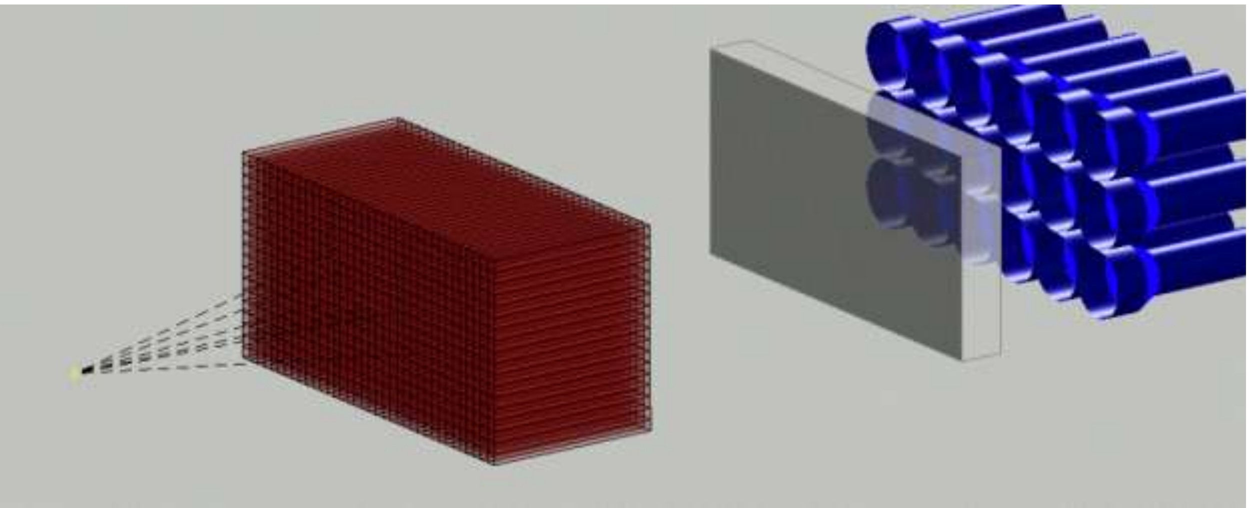
Gamma camera and SPECT



2D: planar scan



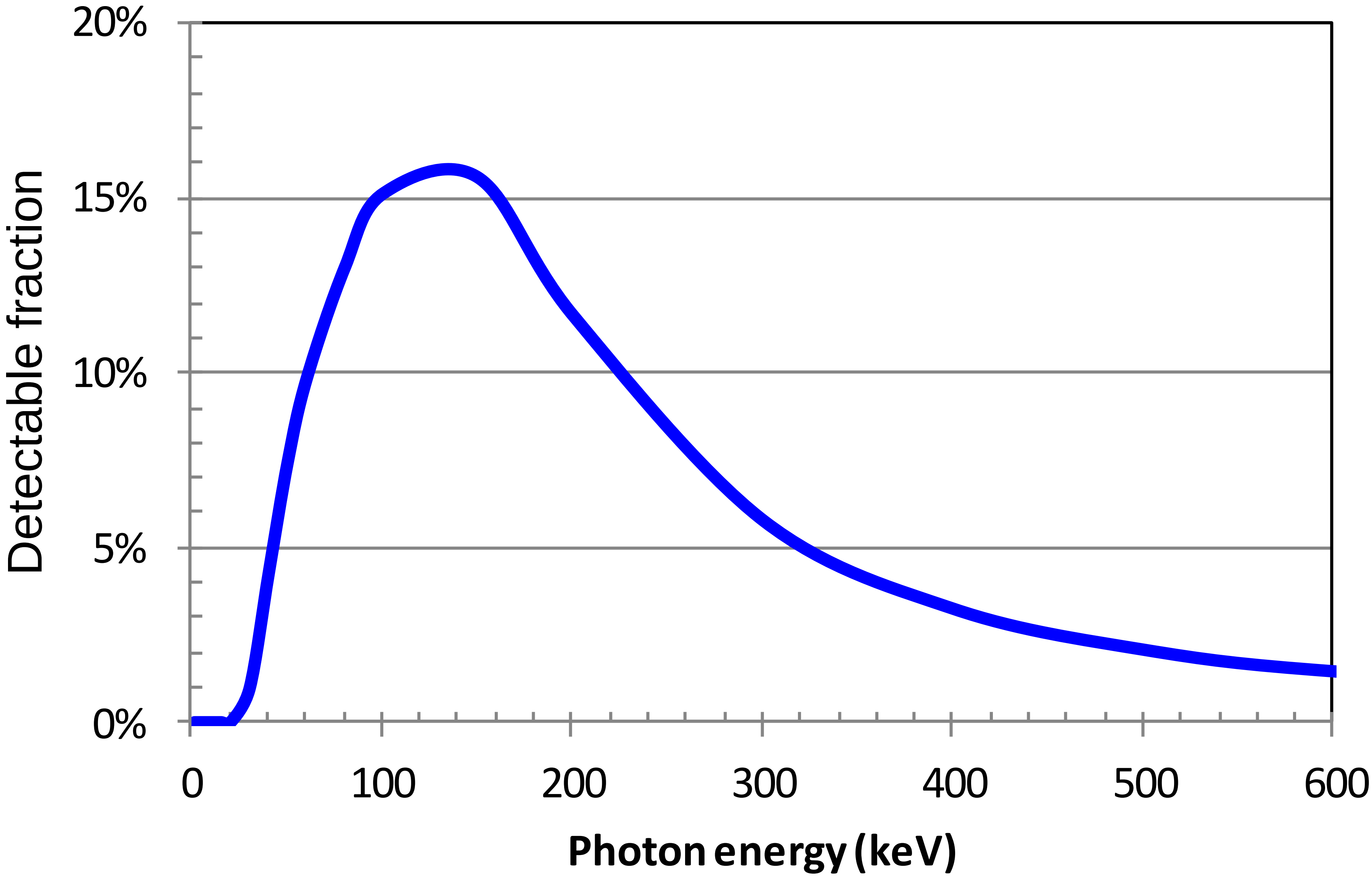
3D: SPECT: Single Photon Emission Computer Tomography



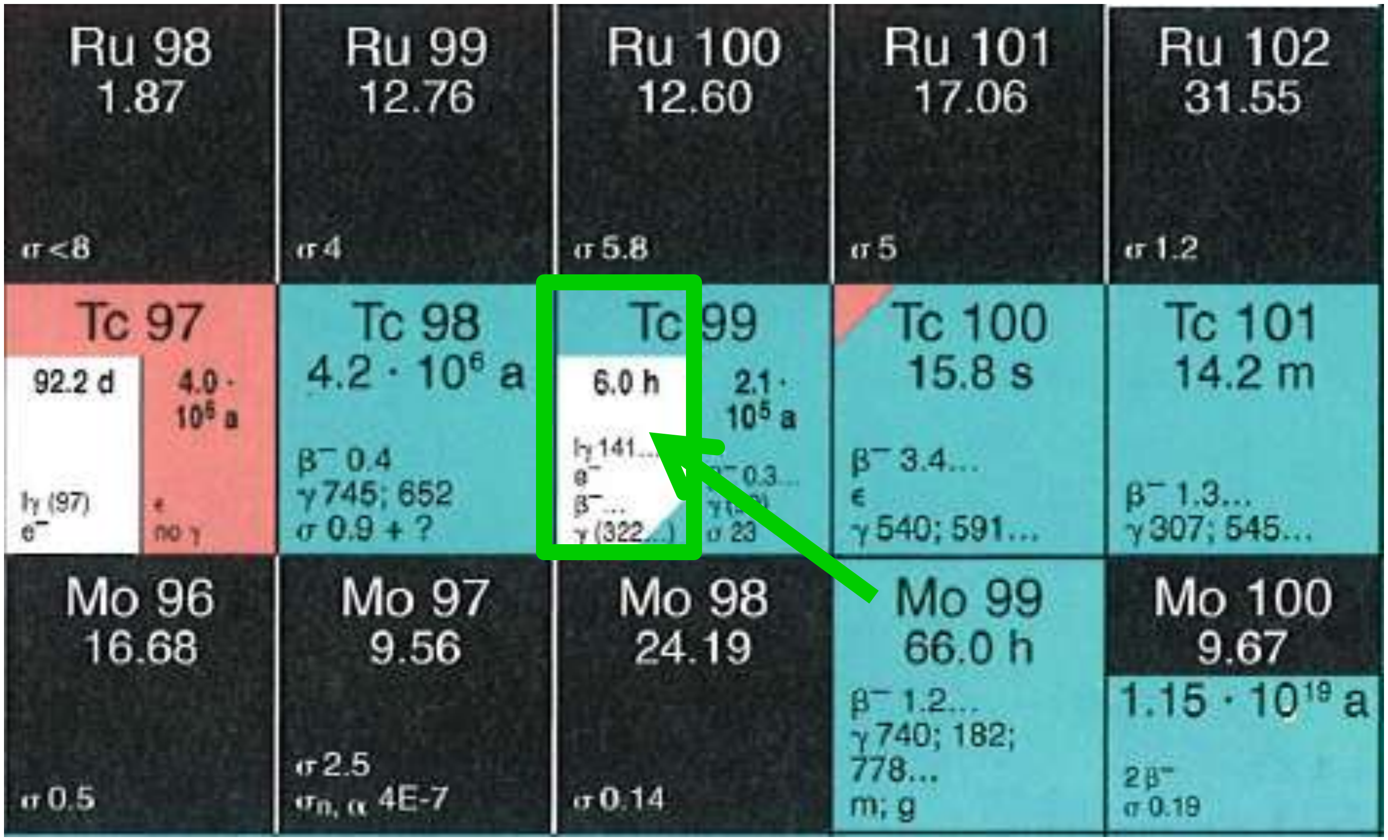
E_γ > 60 keV

E_γ < 300 keV

Ideal gamma ray energy for SPECT

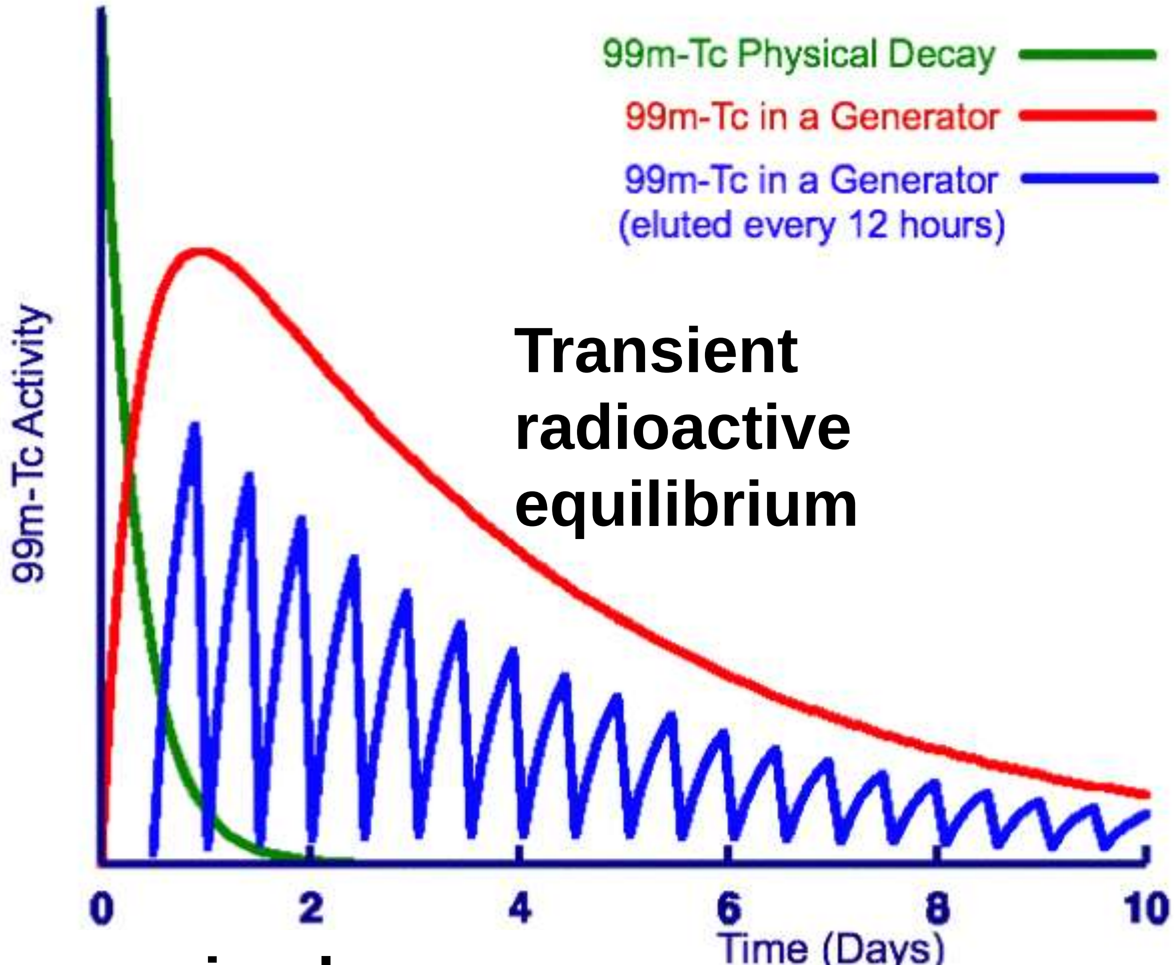


^{99m}Tc: ideal for SPECT and gamma cameras



- IT with 89% 140.5 keV gamma ray, $T_{1/2}$ = 6 h
- decays to quasi-stable daughter
- ^{99m}Tc fed in 88% of β^- decays of ^{99}Mo, $T_{1/2}$ = 66 h
- produces nearly carrier-free product

$^{99}Mo/^{99m}Tc$ generator

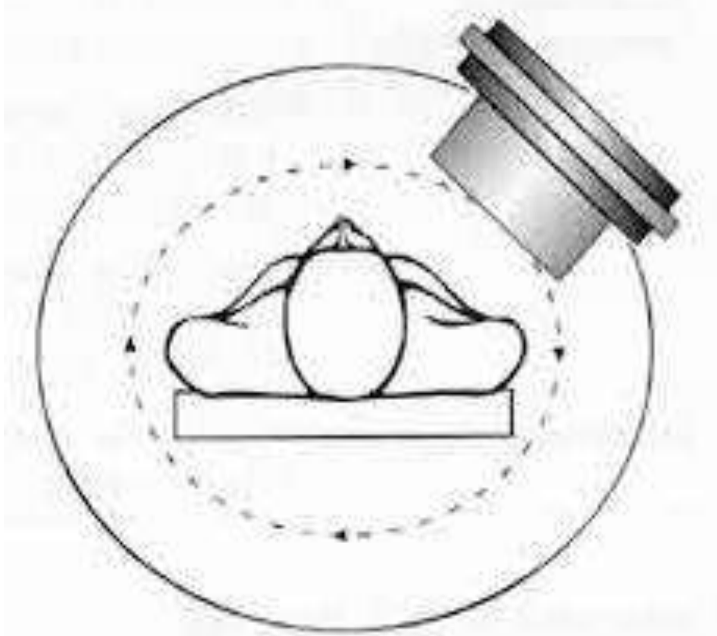


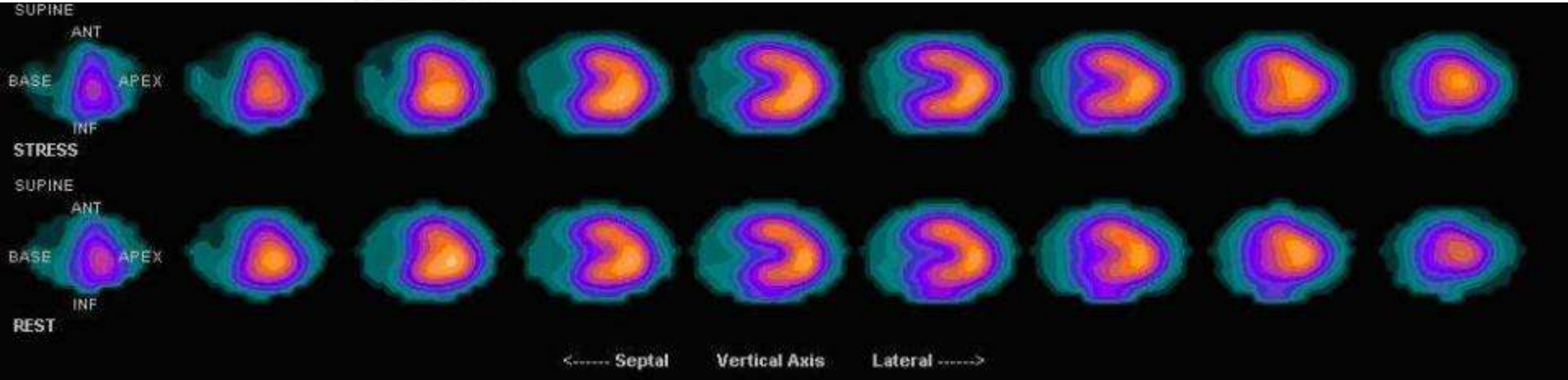
Transient radioactive equilibrium

- **simple**
- **reliable**
- **portable**
- **self-shielded**

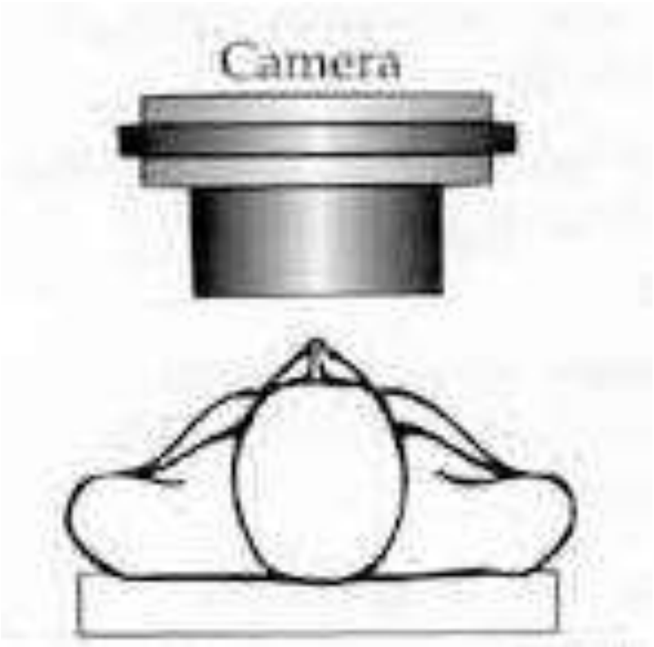
Ischemic heart disease

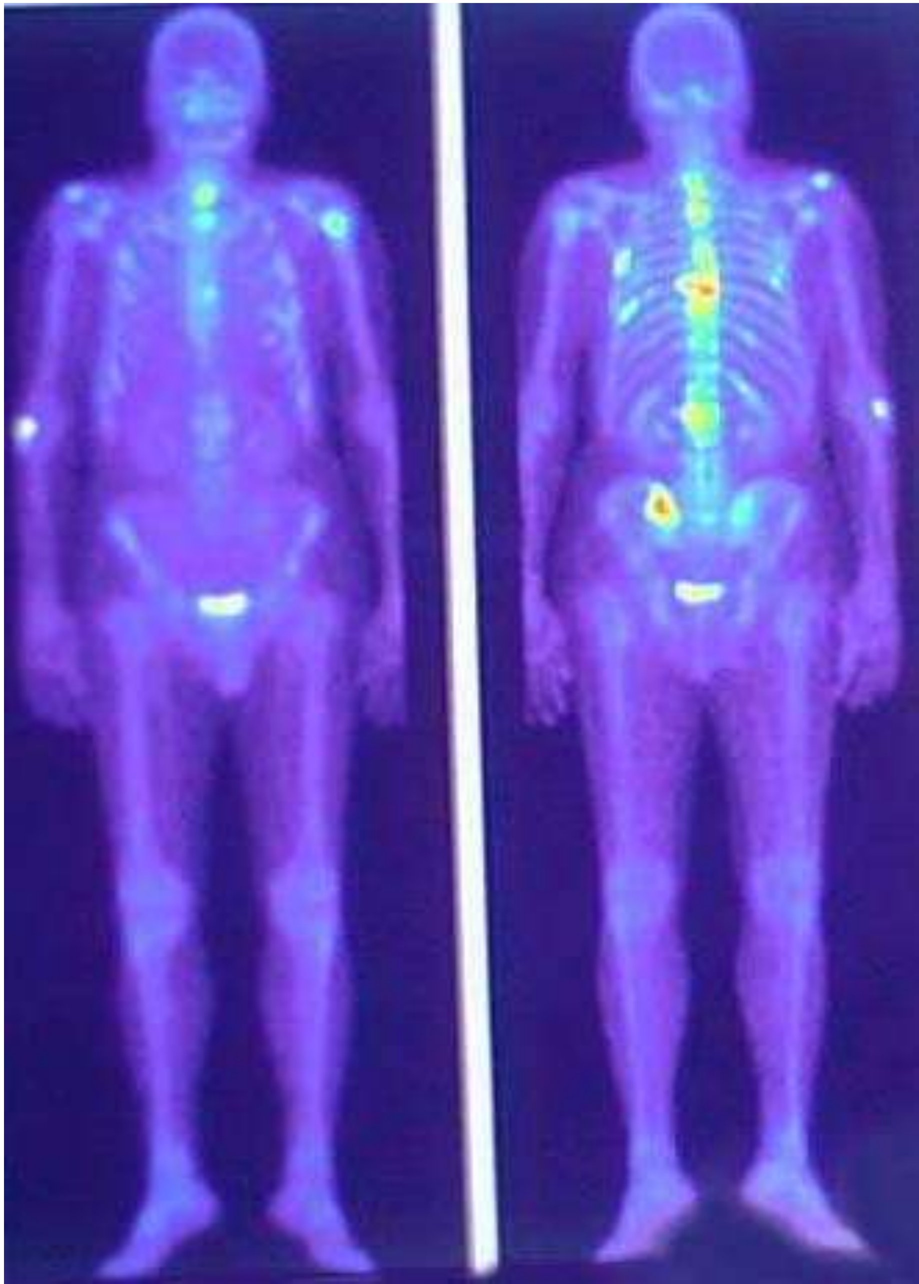
- diagnose by ECG and cardiac stress test with SPECT
- treatment by medication, angioplasty or bypass surgery





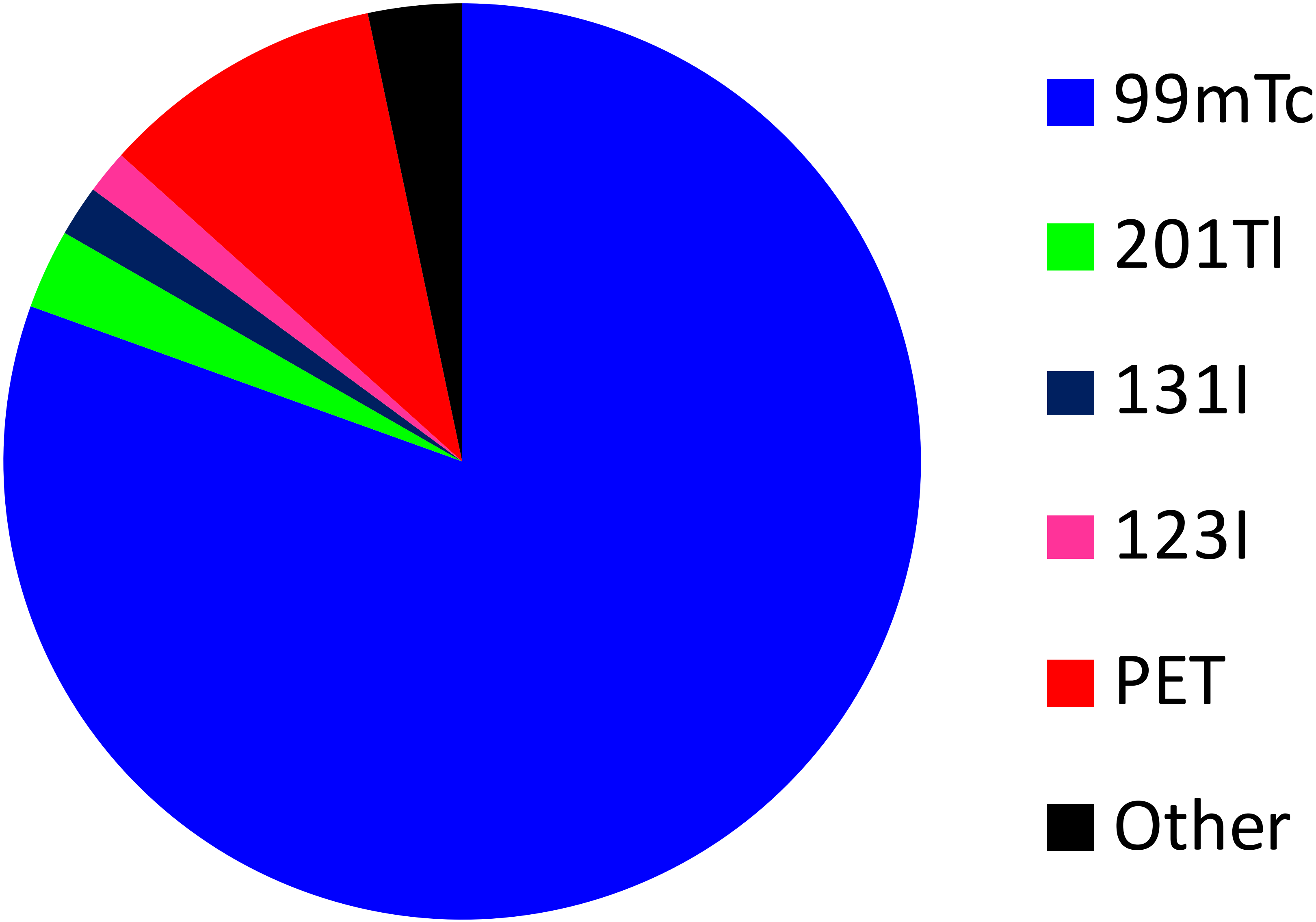
Bone metastases from (prostate) cancer





- planar or SPECT scan for bone metastases
- differentiate between local and generalized disease
- decide on treatment options: surgery or brachytherapy versus systemic therapy

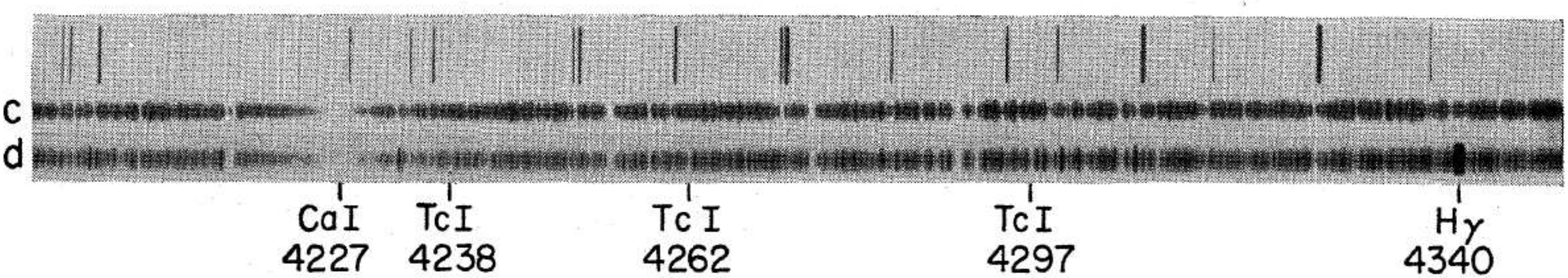
The leading radioisotopes for nuclear medicine



Dose Datamed 2 project; update by NuPECC working group.

Technetium (^{99}Tc): "proof" of the s-process

stars (Ca55, Fo55). The presence of technetium in the atmospheres of *S*-type stars, observed by Merrill (Me52), and also to a lesser extent in carbon and *M*-type stars, affords conclusive evidence that nuclear activity involving neutron capture is currently going on in the interiors of these stars. This element is being both



P.W. Merrill, Science 1952;115:484.
B²FH 1957.

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

Recognizing the prospects of "new" radioisotopes ?

DATE: December 4, 1958

TO: Addressees Below

FROM: Daniel M. Schaeffer, Head
BNL Patent Office

SUBJECT: P-701 and P-702 - PREPARATION OF CARRIER-FREE MOLYBDENUM AND OF TECHNETIUM FROM FISSION PRODUCTS

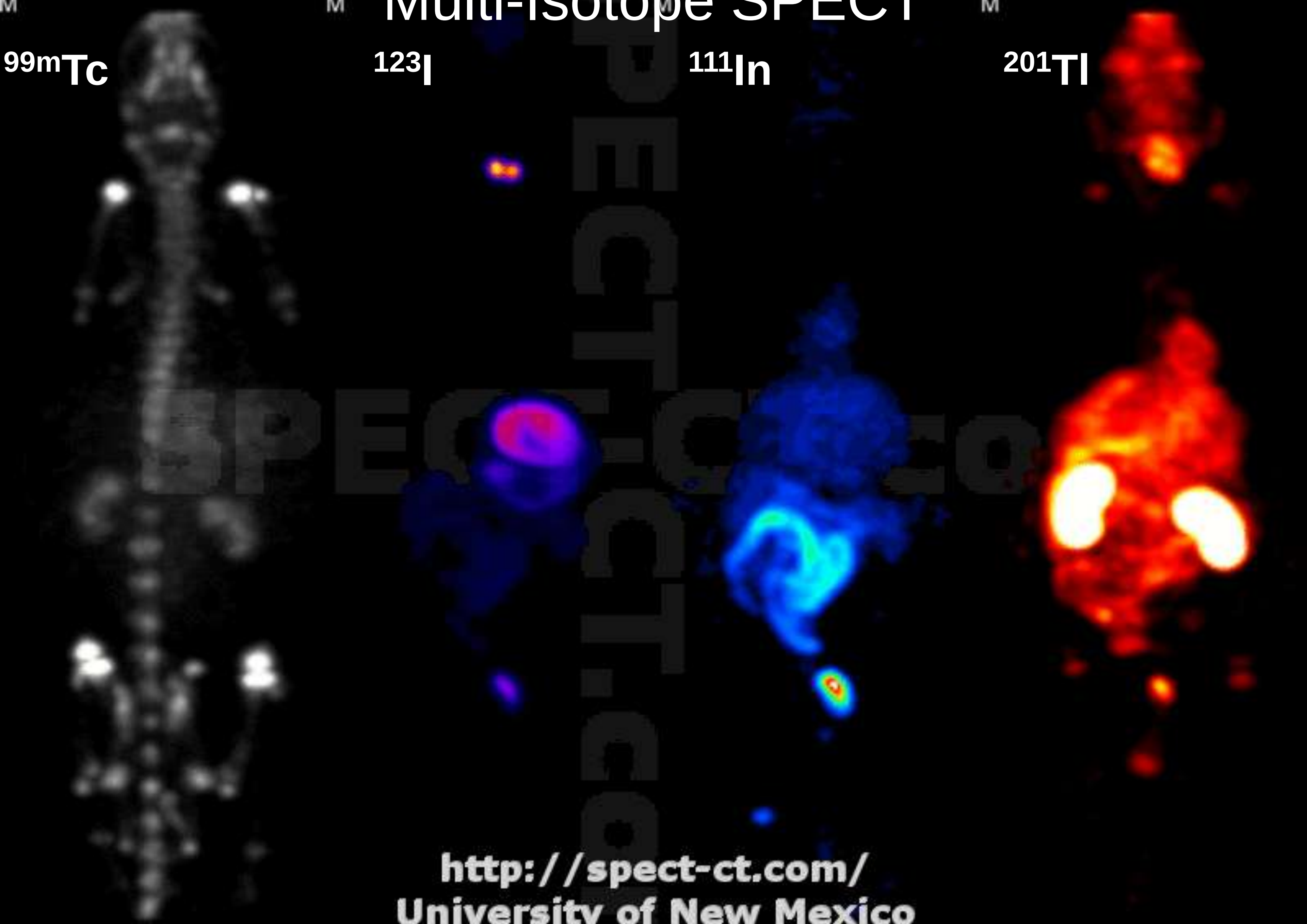
The New York Patent Group has carefully studied the information available relative to the above-identified item. The AEC does not at present desire to prepare a patent application on this item for the following reason:

"The method of producing carrier-free molybdenum-99 from fission products is disclosed in U. S. Patent Application S.N. 732,108, Green, Powell, Samos & Tucker (BNL Pat No. 58-17). It is noted that molybdenum-99 may be separated from its radioactive daughter, technetium-99, by absorption of a solution of molybdenum-99 on alumina and subsequent elution of its daughter

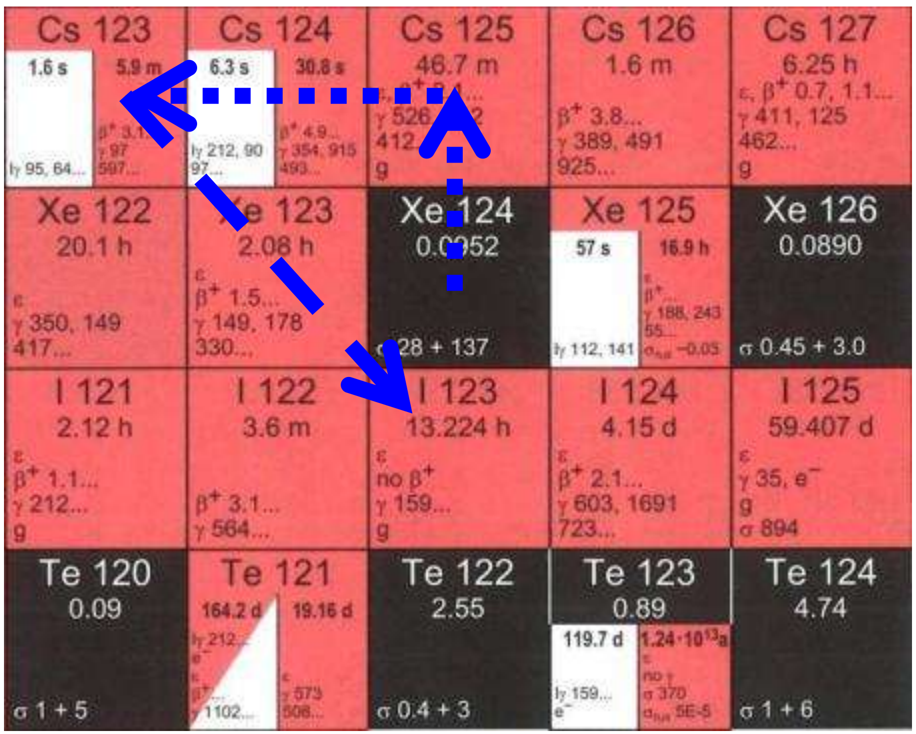
with .1 nitric acid. While this method is probably novel, it appears that the product will probably be used mostly for experimental purposes in the laboratory. On this basis, no further patent action is believed warranted."

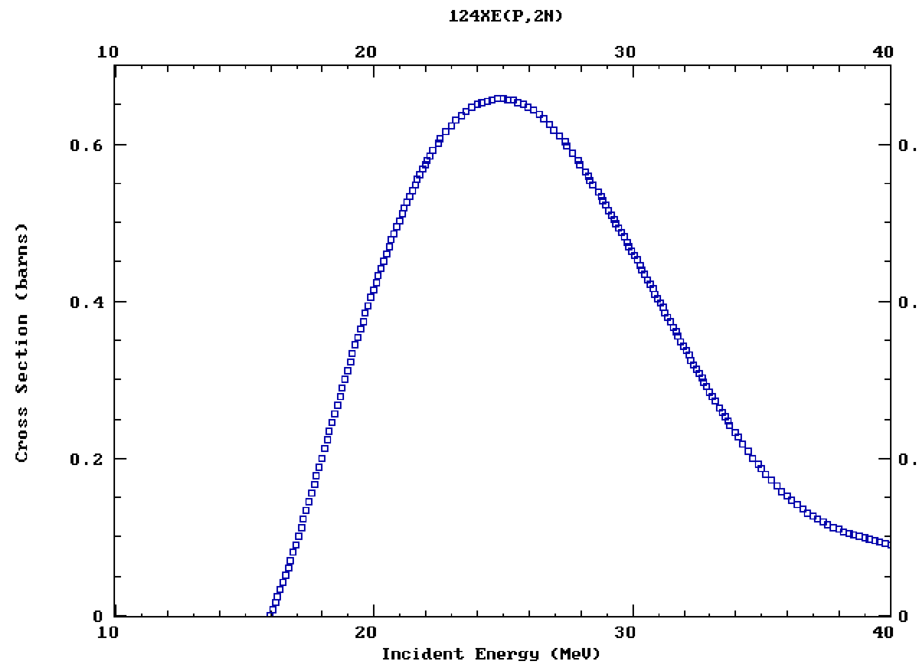
believe that this attitude is significant. We are not aware of a potential market for technetium-99 great enough to encourage one to undertake the risk of patenting in hopes of successful and rewarding licensing. We would recommend against filing on the Tucker, Greene and Murrenhoff separation process."

Multi-Isotope SPECT



Production of ^{123}I by ^{124}Xe(p,2n)^{123}Cs(β^+)^{123}Xe(β^+)^{123}I

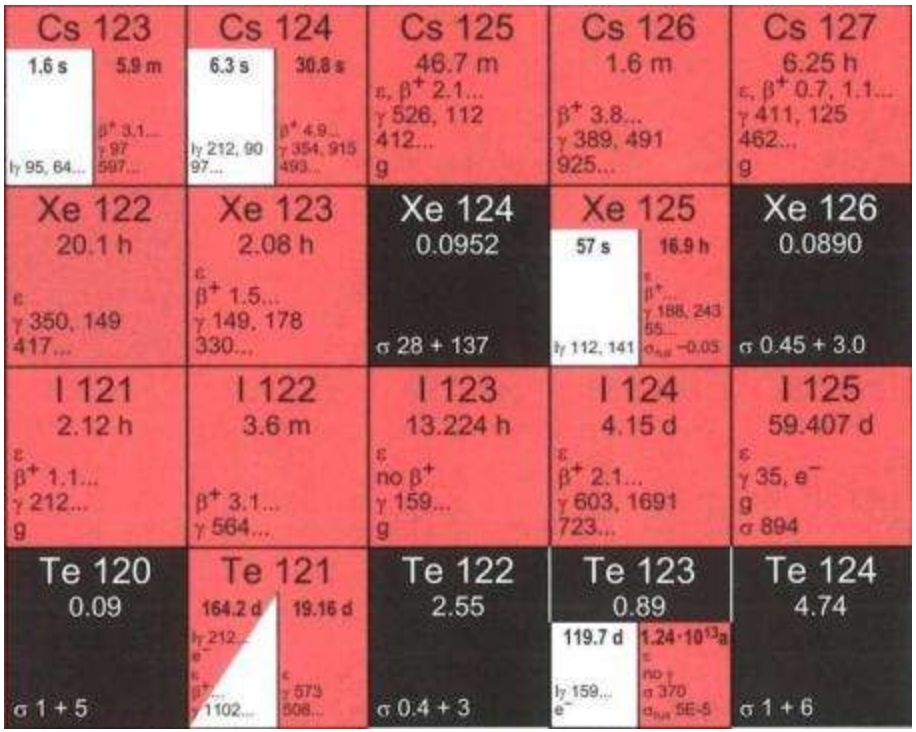


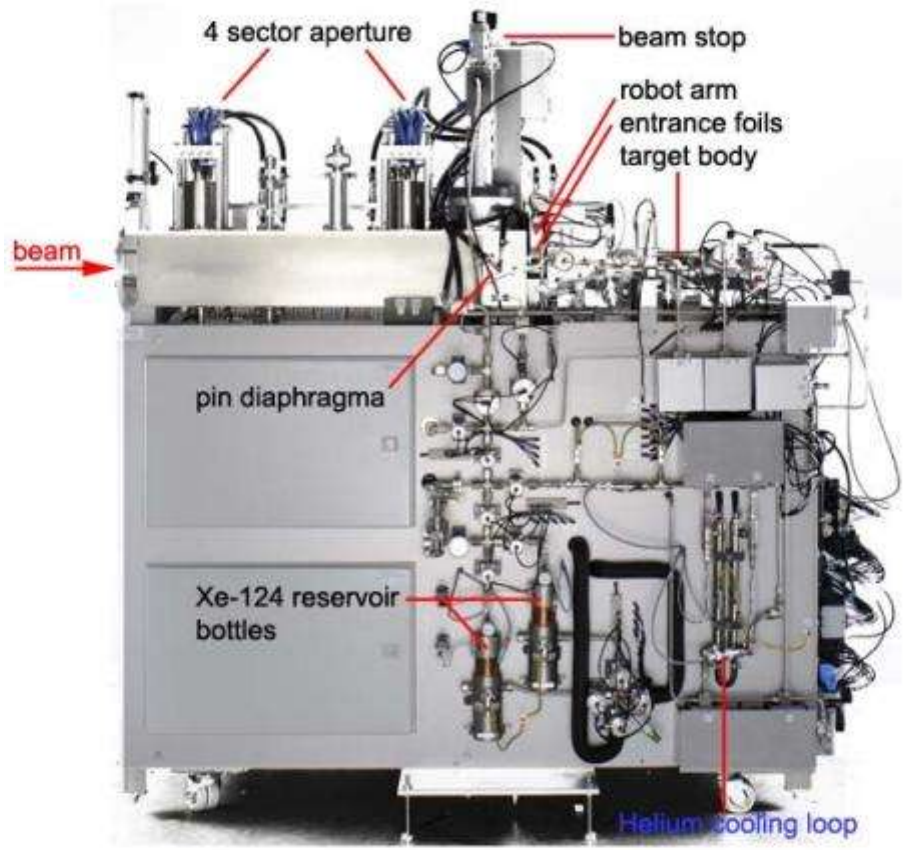


Question

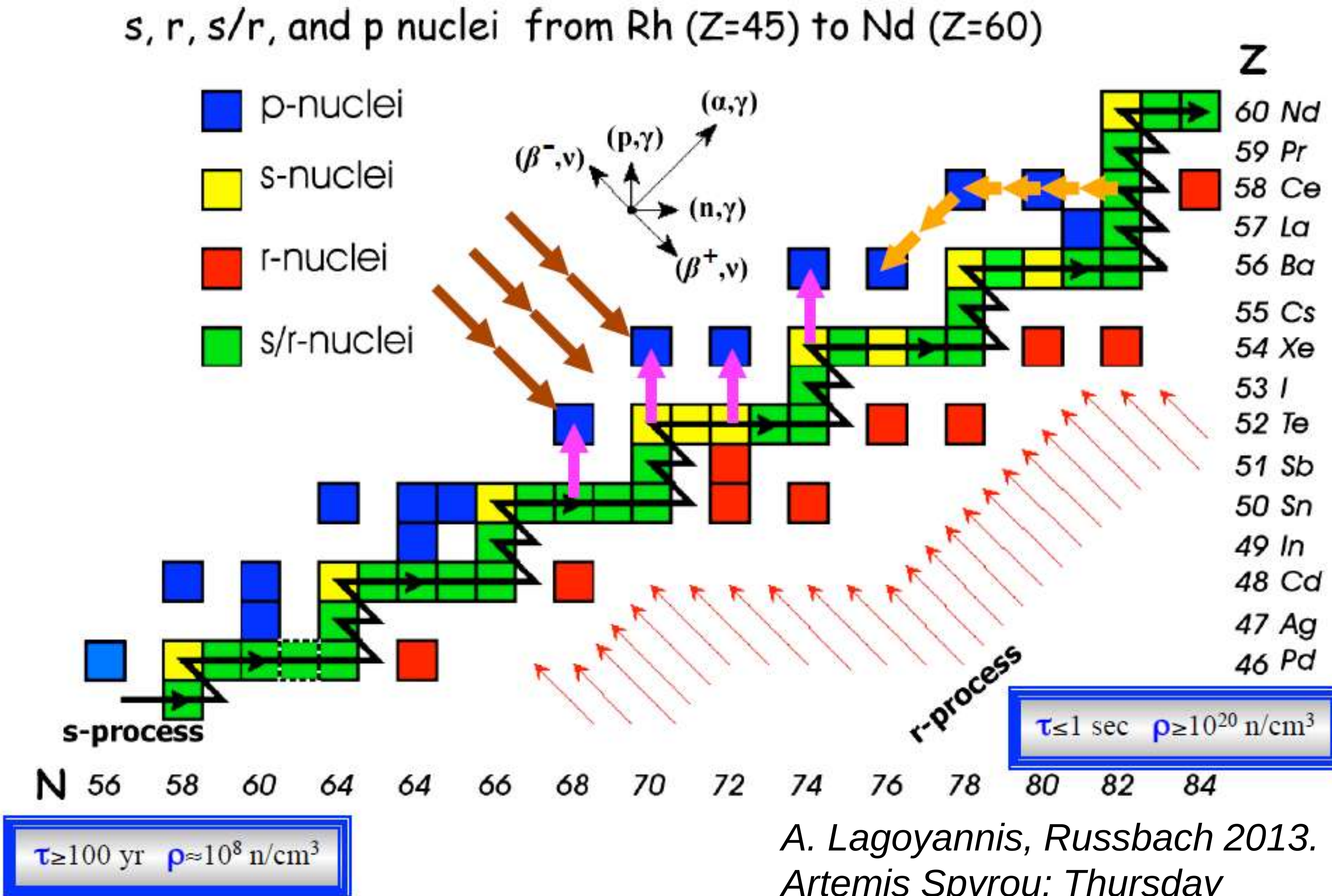
Why is ^{124}Xe so rare ?

$^{124}Xe/Xe = 9.5E\text{-}4$



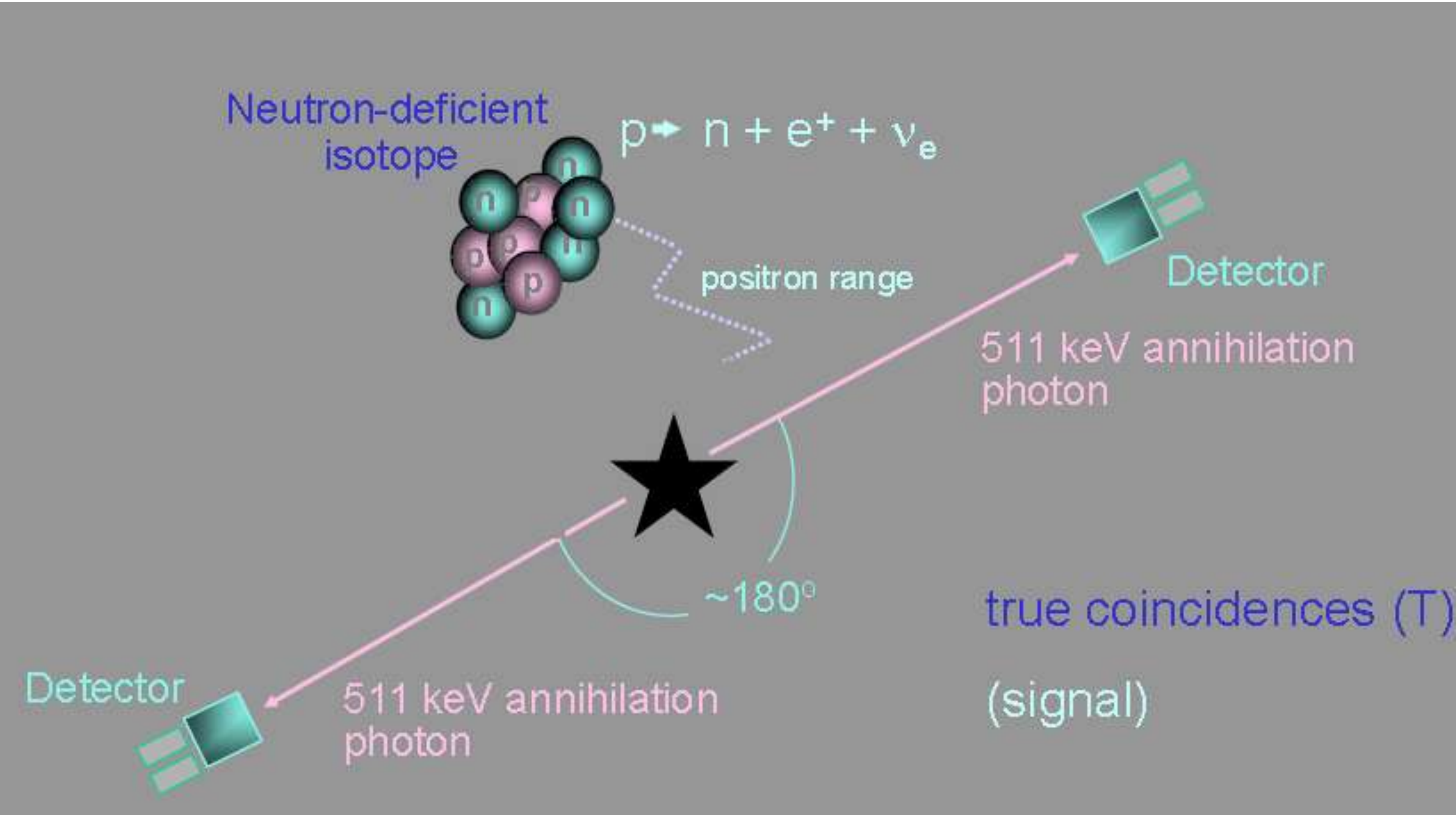


Answer: ^{124}Xe is a p-nucleus



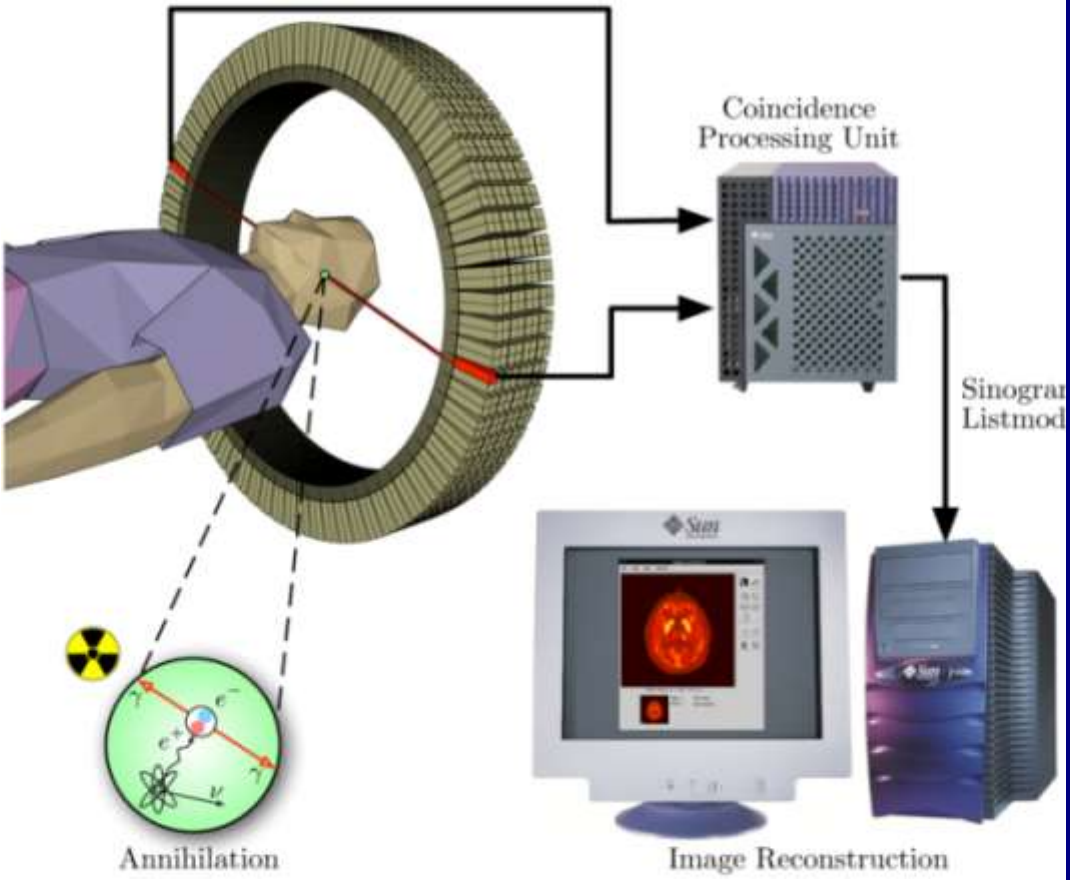
A. Lagoyannis, Russbach 2013.
Artemis Spyrou: Thursday

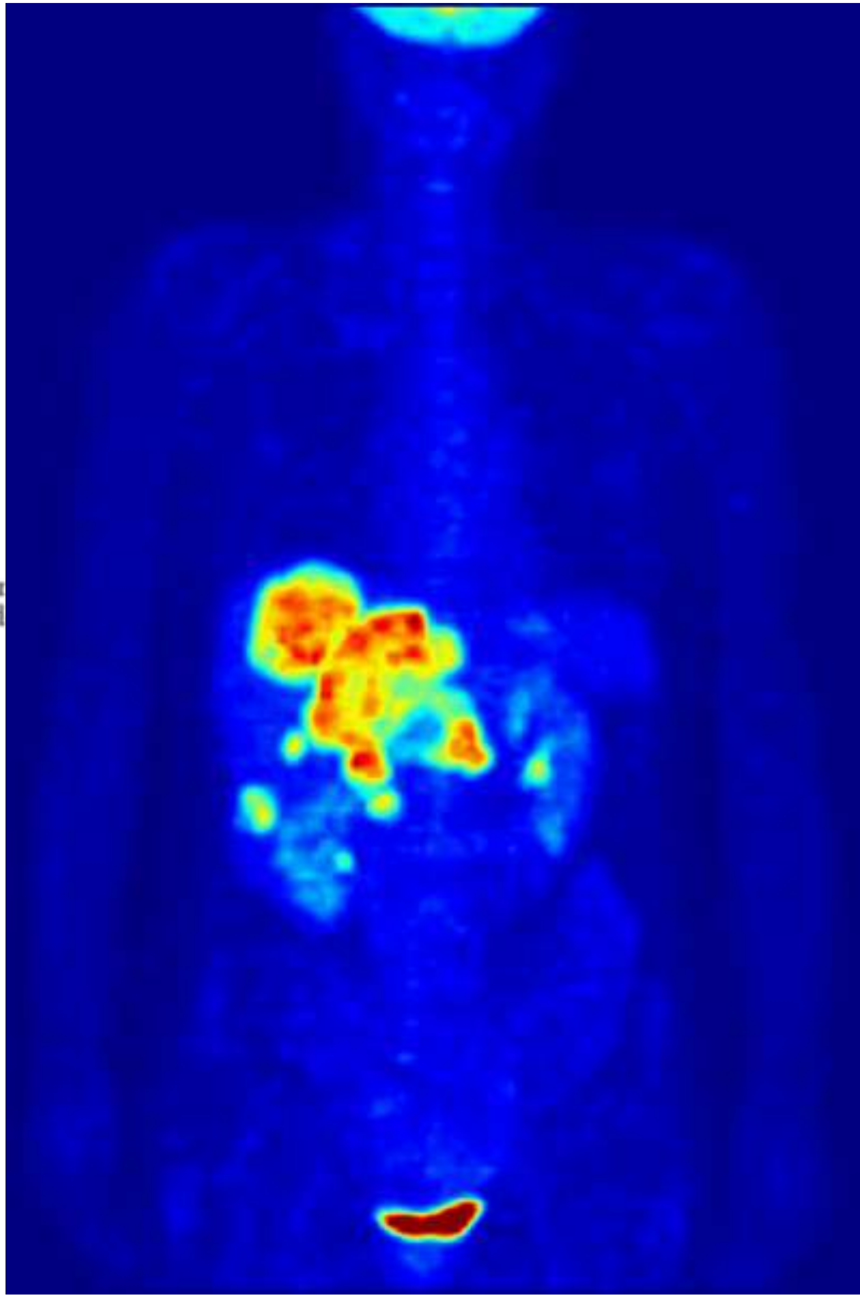
PET: Positron Emission Tomography



Low β^+ energy to minimize range > better spatial resolution.

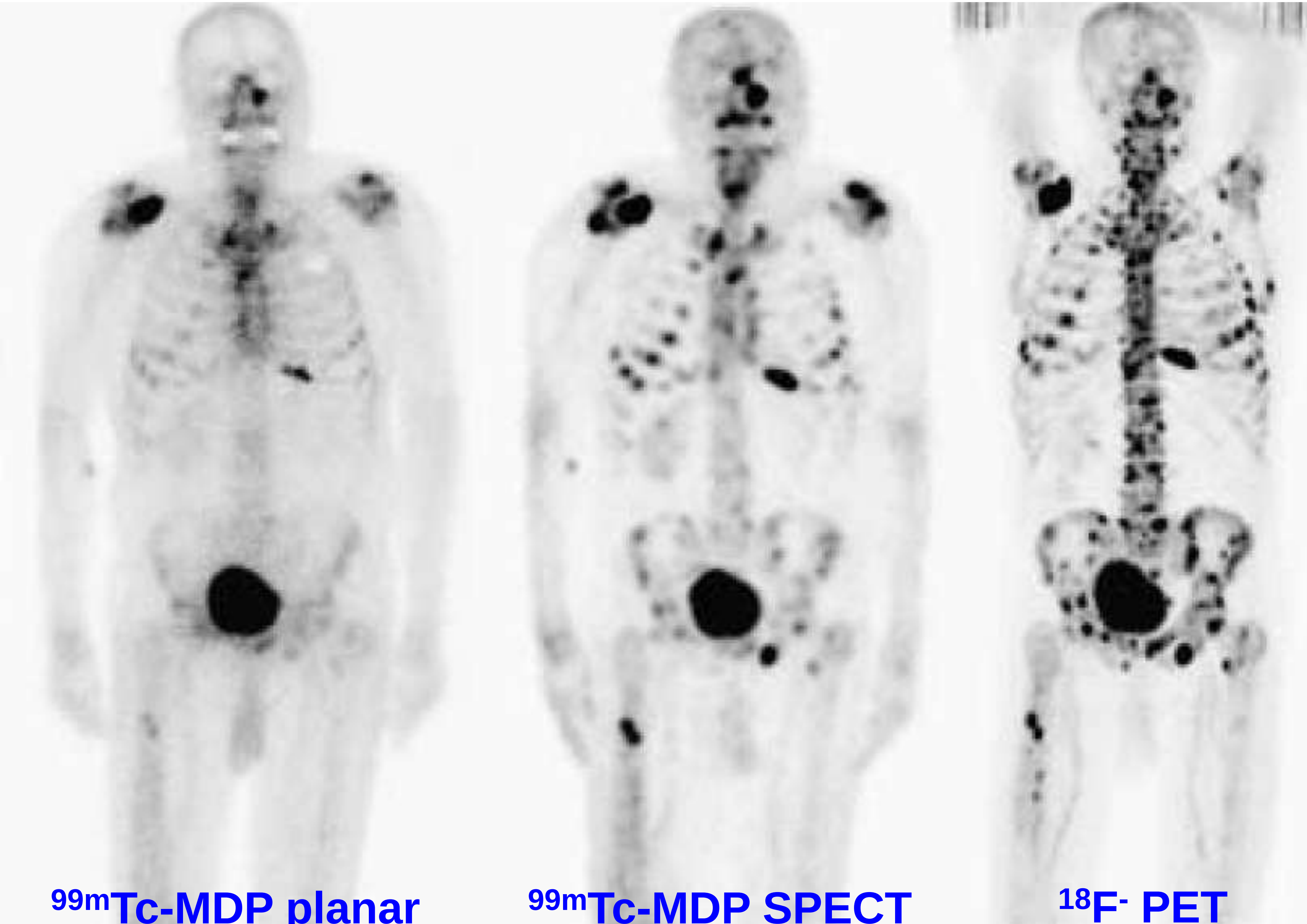
Positron Emission Tomography





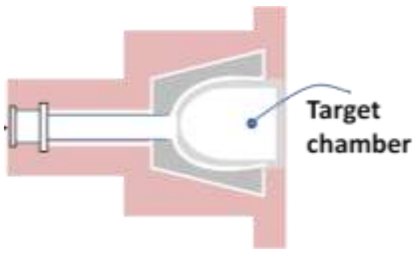
PET isotopes

Radio-nuclide	Half-life (h)	Intensity β^+ (%)	E mean (MeV)	Range (mm)
C-11	0.34	99.8	0.39	1.3
N-13	0.17	99.8	0.49	1.8
O-15	0.03	99.9	0.74	3.2
F-18	1.83	96.7	0.25	0.7
Ga-68	1.13	89.1	0.83	3.8
Rb-82	0.02	95.4	3.38	20

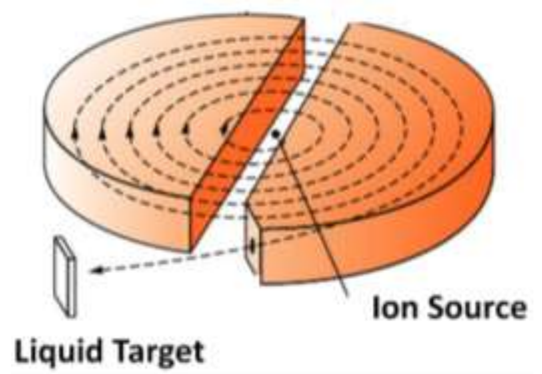


Even-Sapir E *et al., J Nucl Med 2006; 47:287.*

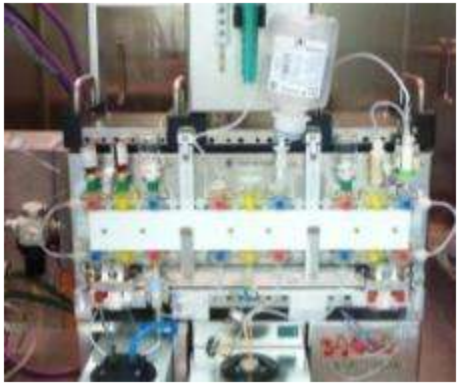
^{18}F production by $^{18}O(p,n)$



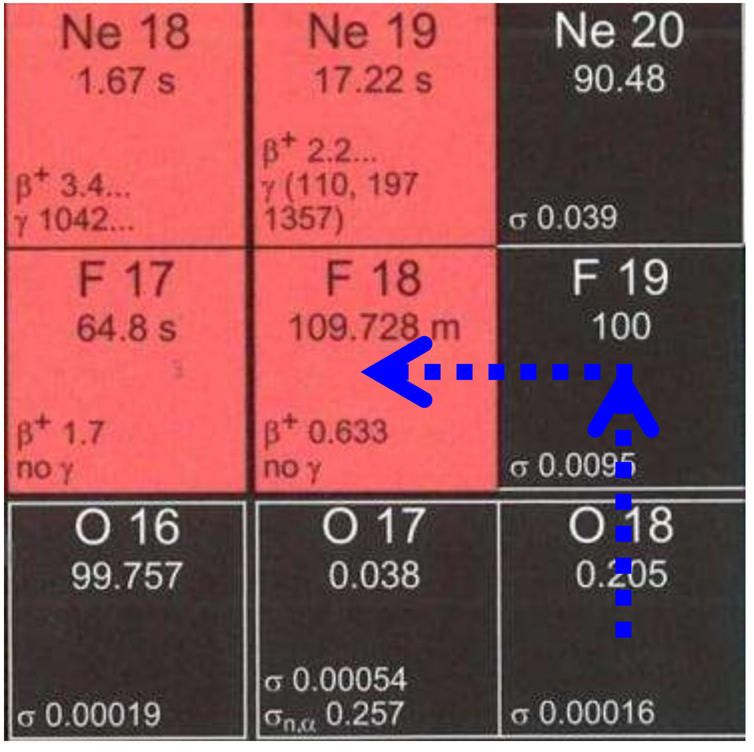
$H_2{}^{18}O$ water

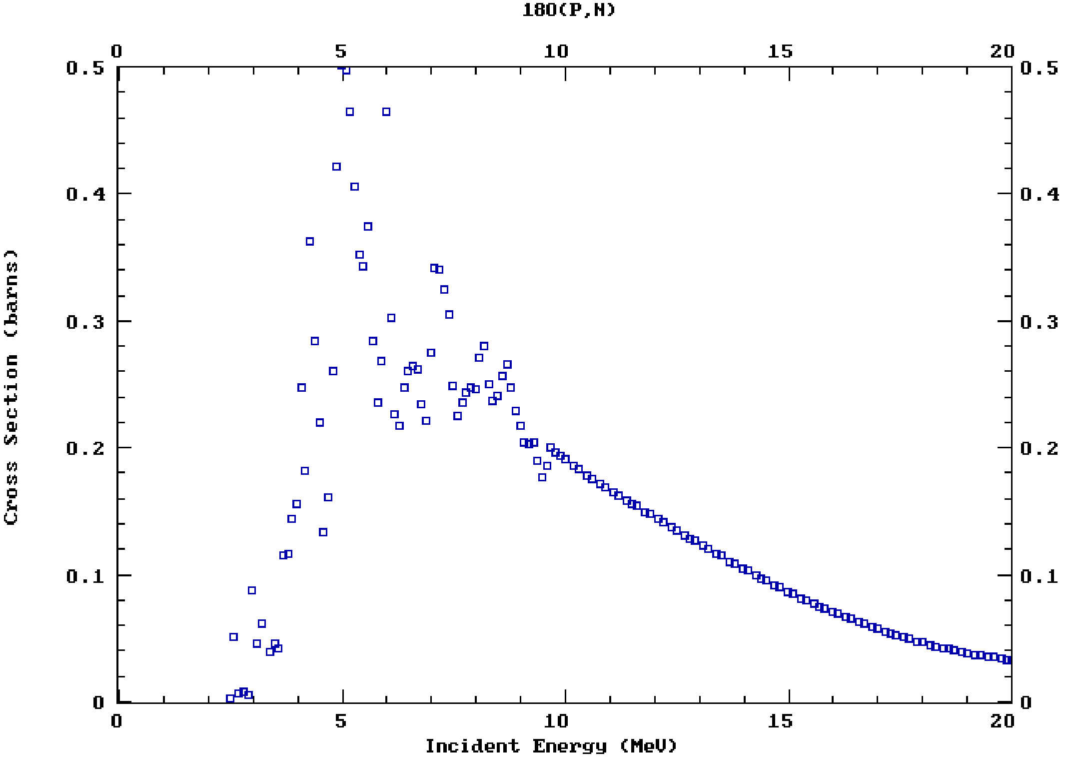


Cyclotron irradiation



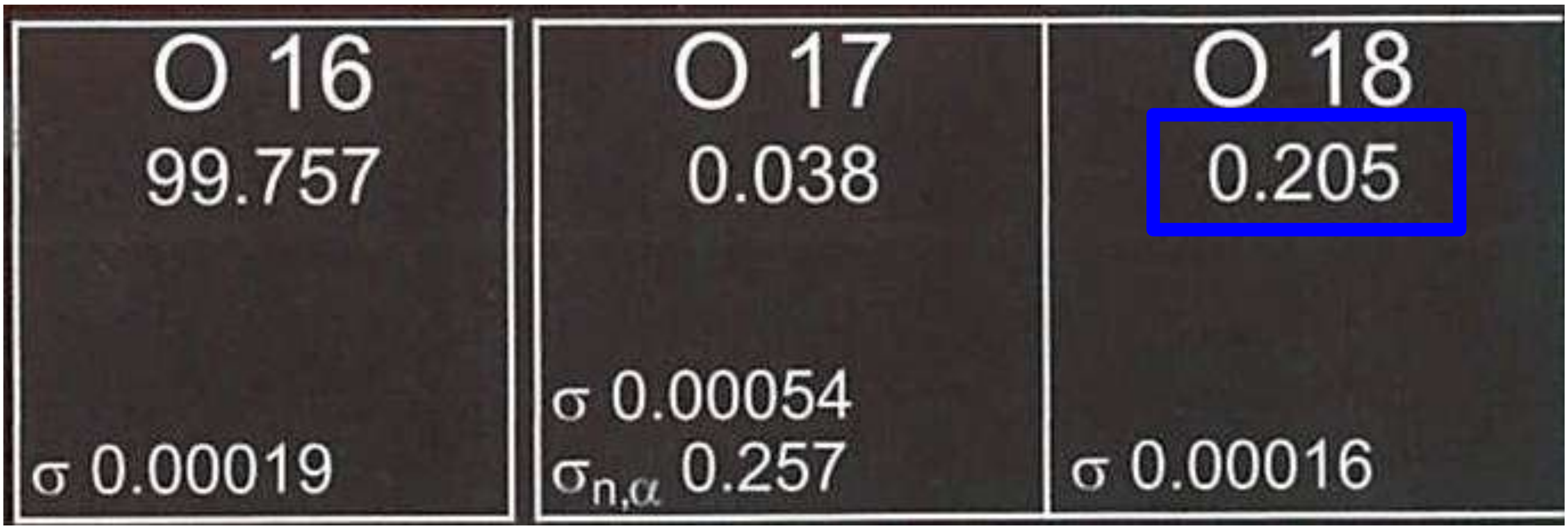
Transformation into FDG



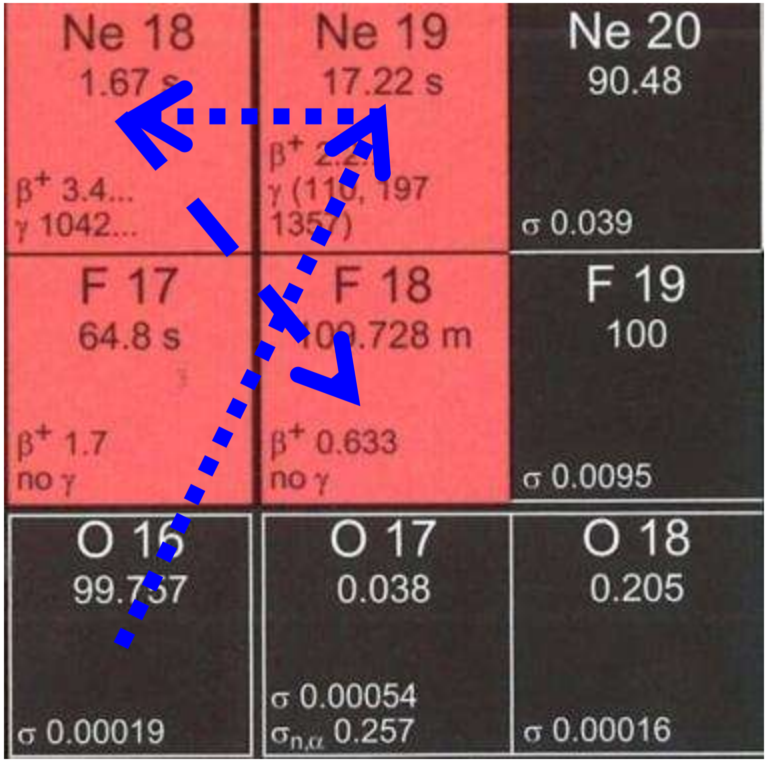


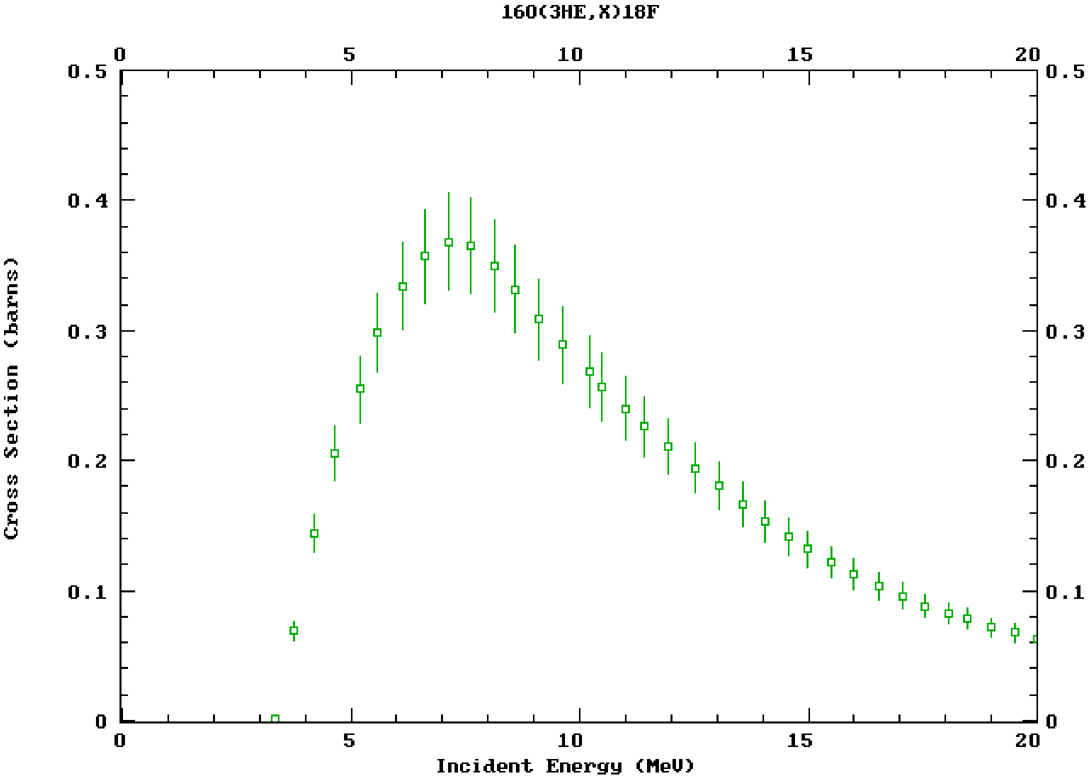
Question

Why is ^{18}O so rare? $^{18}O/^{16}O$ = 2E-3



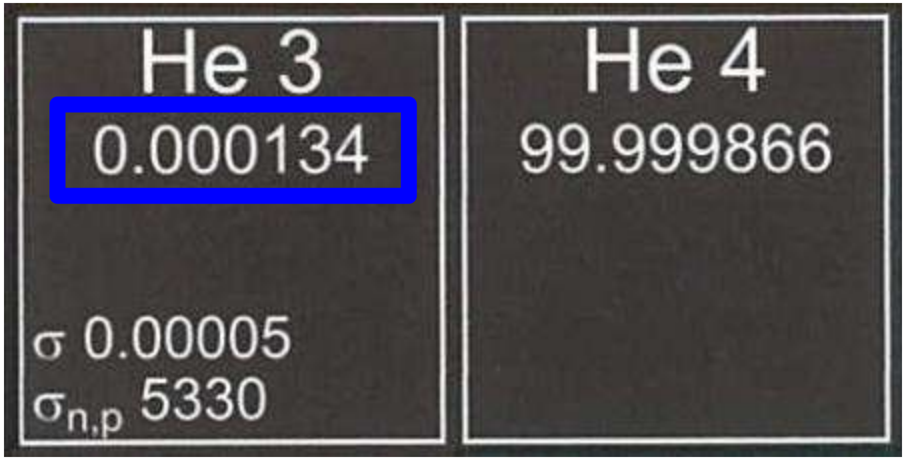
^{18}F production by $^{16}O(^{3}He,n)^{18}Ne(\beta^{+})$

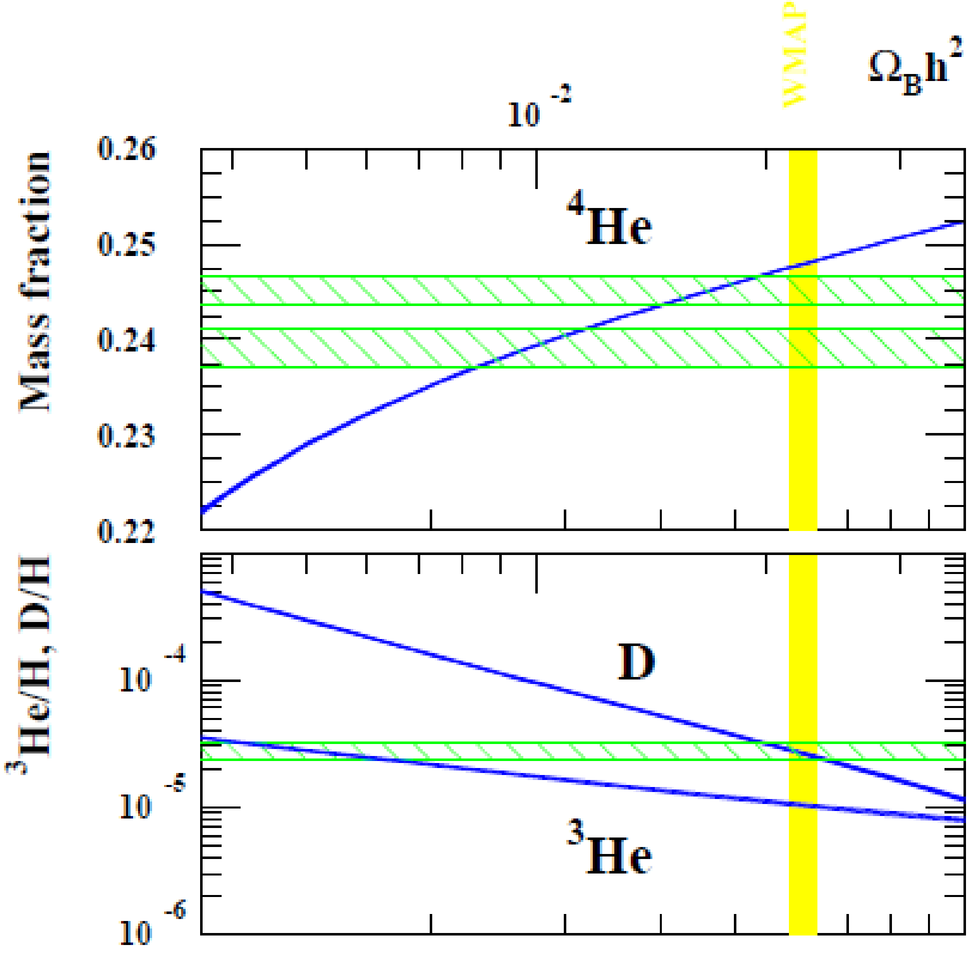




Question

Why is $^3He/^4He$ lower on Earth compared to BBN ?
1.3E-6 versus 4E-5 ⇒ factor 30 depletion !

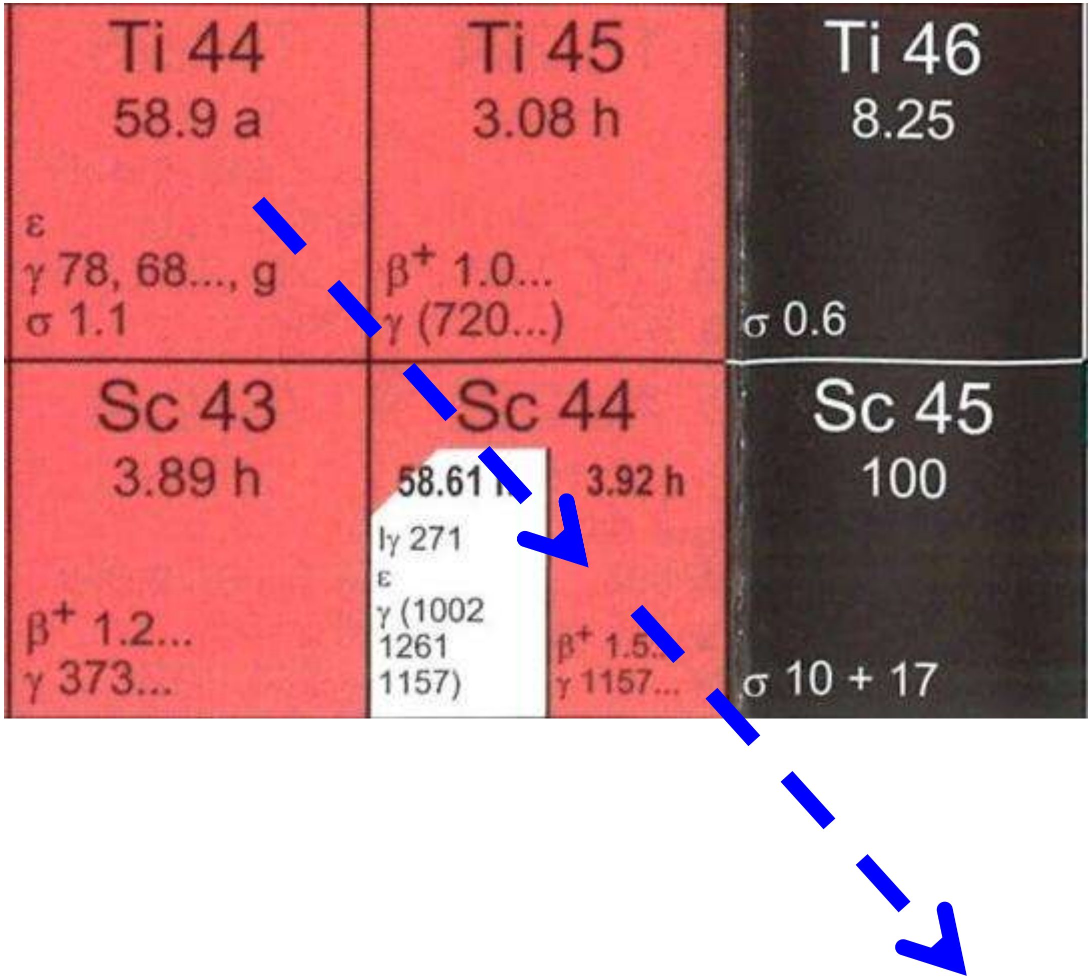


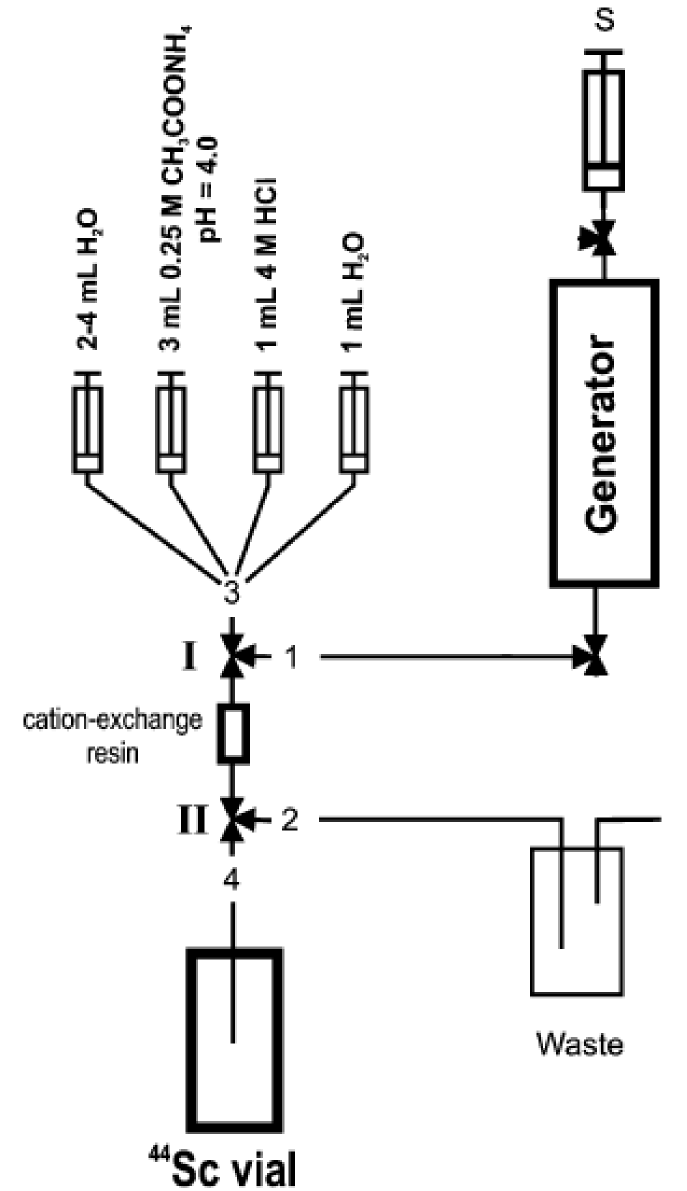


Longer-lived PET isotopes

Radio-nuclide	Half-life (h)	Intensity β^+ (%)	E mean (MeV)	Range (mm)
Sc-44	3.97	94.3	0.63	2.5
Cu-64	12.7	17.6	0.28	0.8
Br-76	16.2	55	1.18	6
Y-86	14.7	31.9	0.66	2.6
Zr-89	78.4	22.7	0.40	1.4
I-124	100	22.8	0.82	3.8

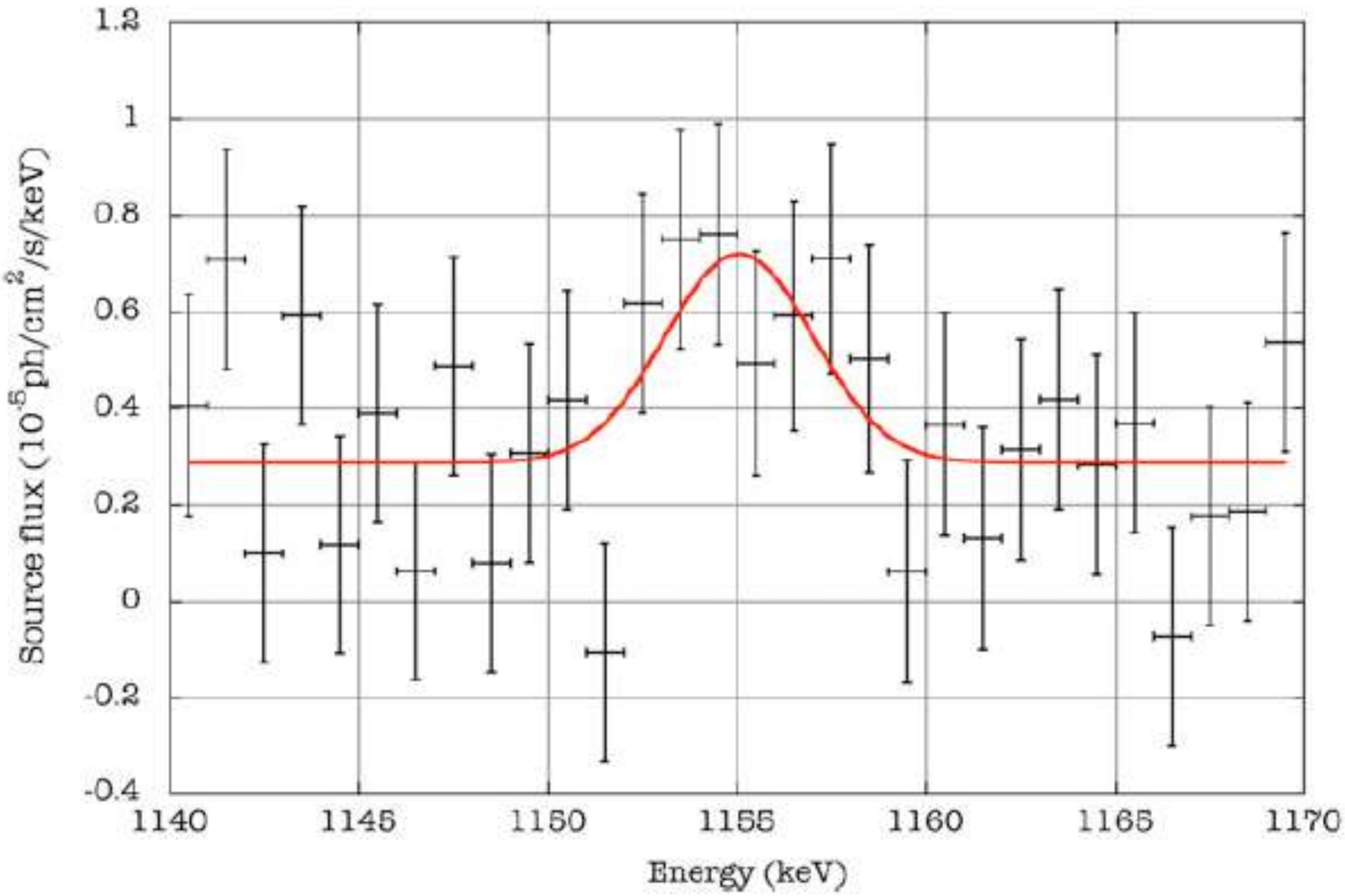
^{44}Sc from ^{44}Ti generator





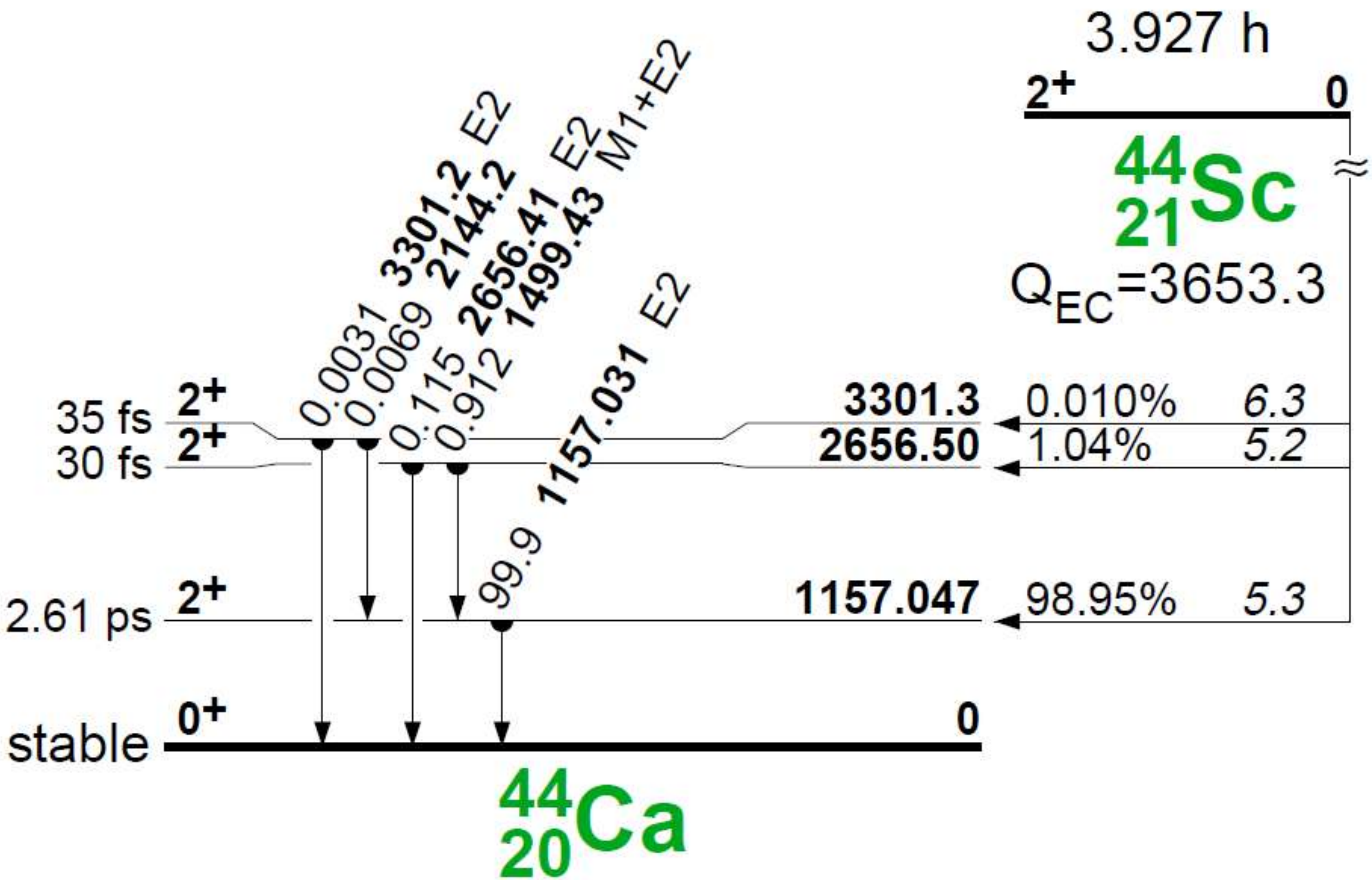
M. Pruszynski et al., Appl Radiat Isot 2010;68:1636.

^{44}Sc in the universe



M. Leising, R. Diehl, PoS 2009.

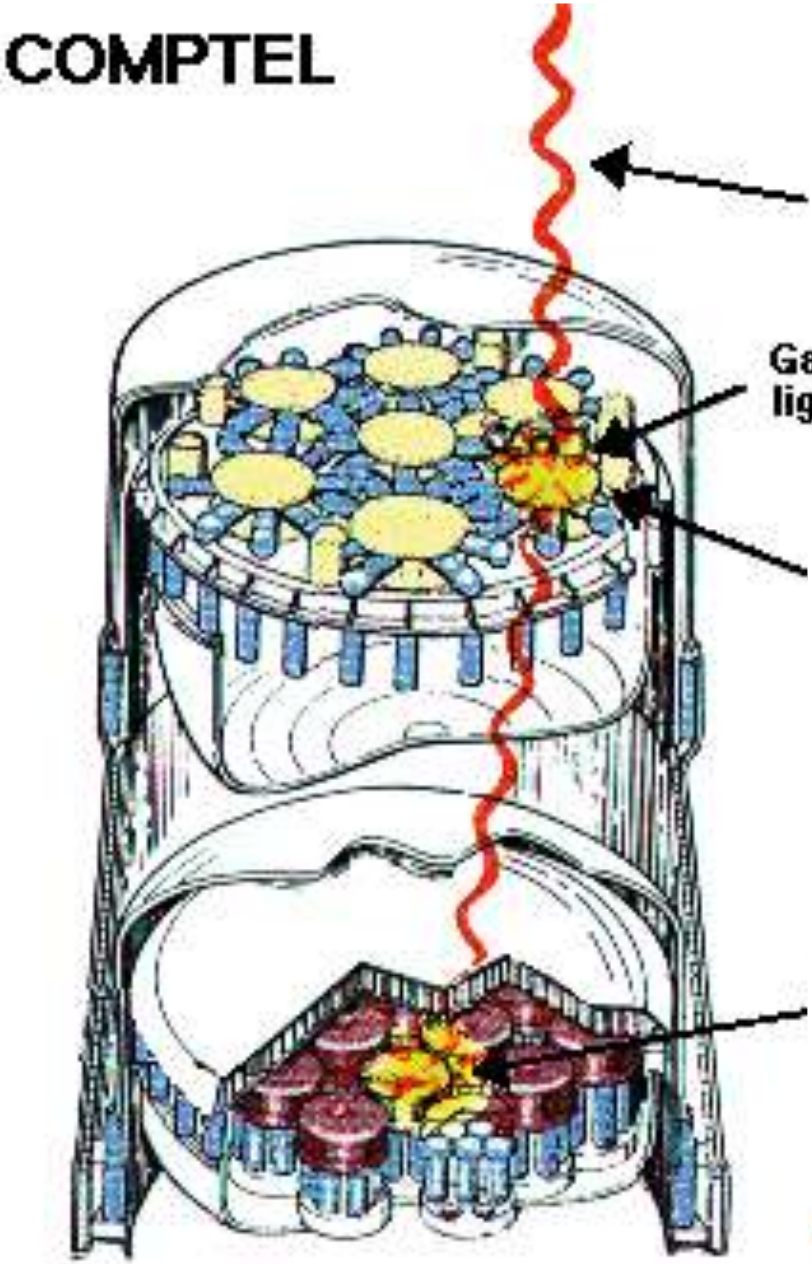
^{44}Sc in the universe

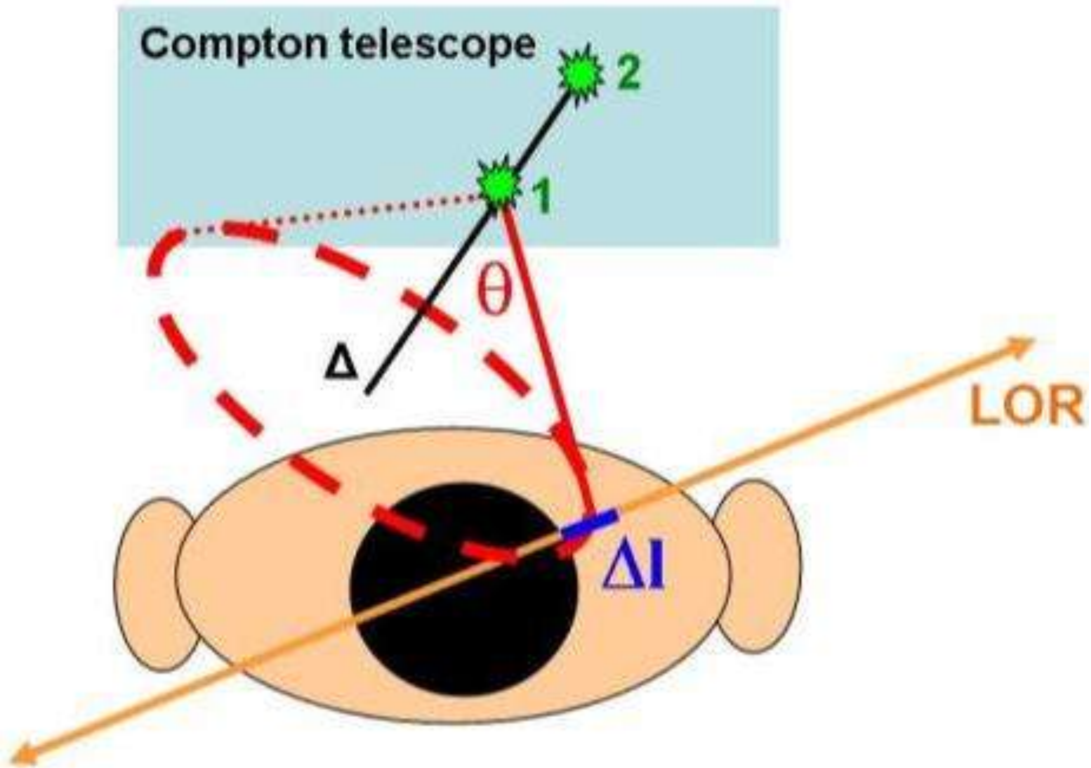


Longer-lived PET isotopes

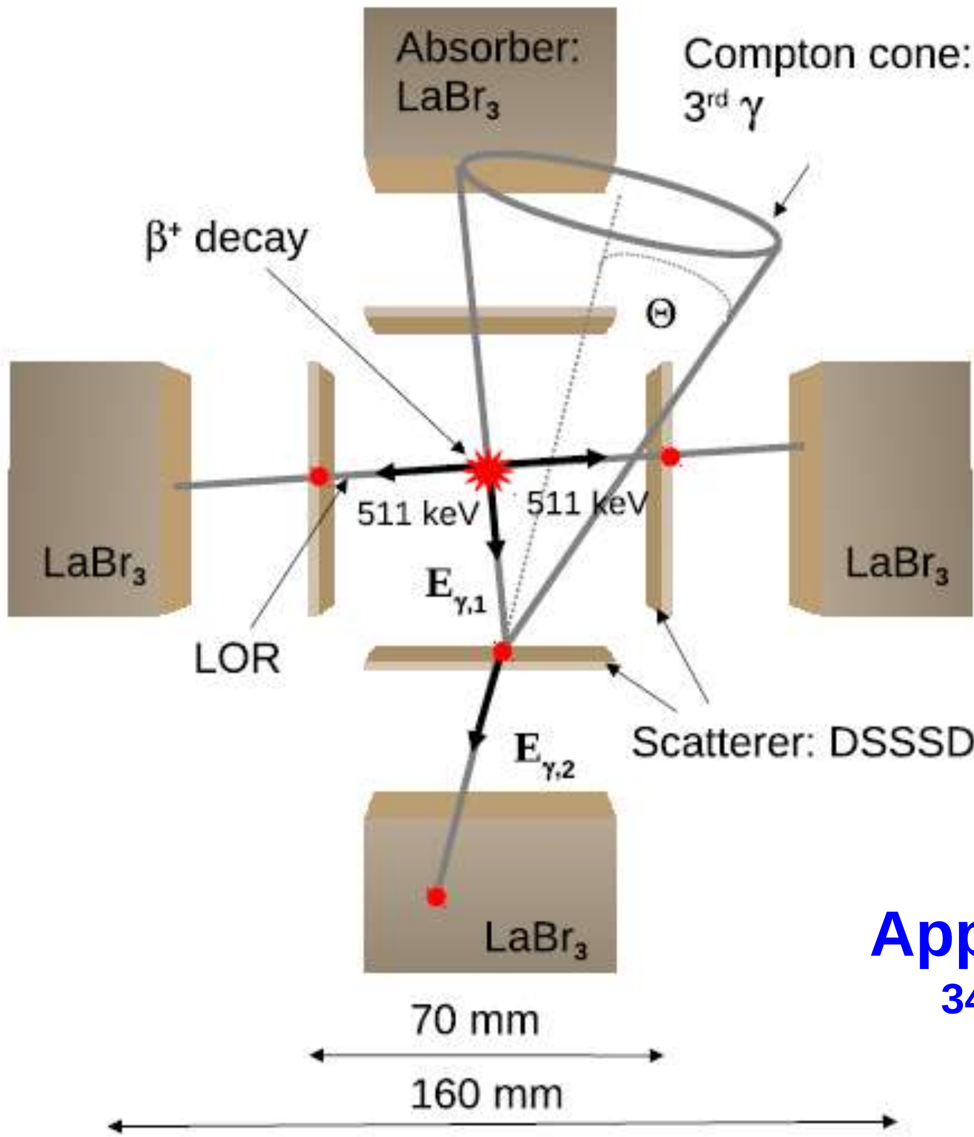
Radio-nuclide	Half-life (h)	Branching ratio β^+ (%)	Branching ratio γ (%)	h_{10} (mSv/h/GBq)
Sc-44	3.97	94.3	101	0.324
Cu-64	**12.7**	**17.6**	**0.5**	**0.03**
Y-86	14.7	31.9	320	0.515
Zr-89	**78.4**	**22.7**	**100**	**0.182**
I-124	**100.2**	**22.8**	**99**	**0.17**
Tb-152	17.5	17	142	

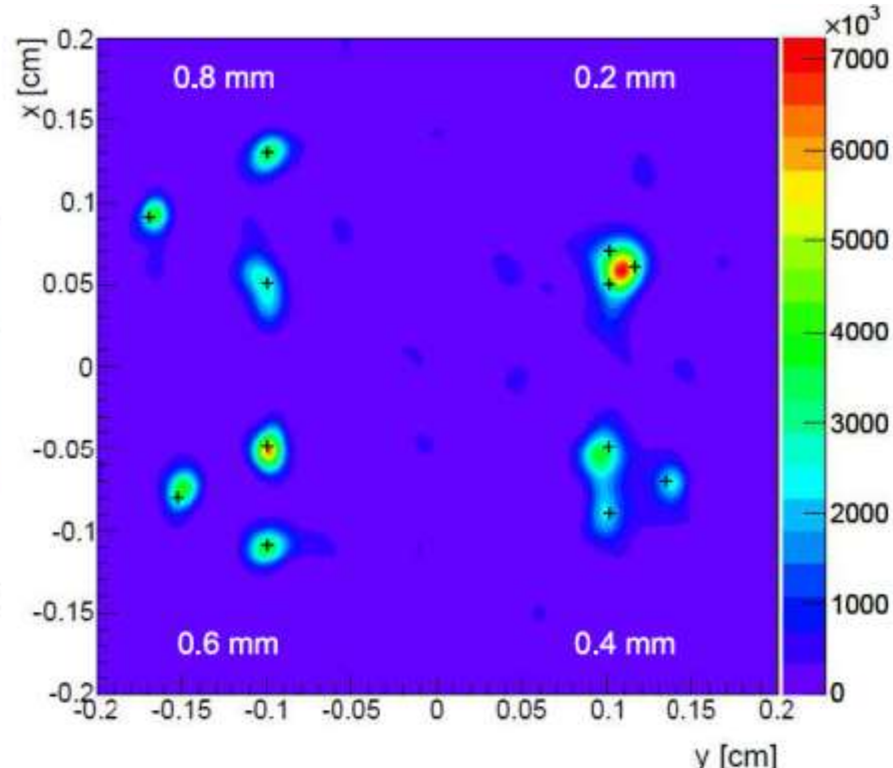
Compton telescope





3-photon-camera: PET-SPECT





Applications:

^{34m}Cl, ^{44}Sc, ^{44m}Sc, ^{52}Mn, ^{52m}Mn, ^{86}Y, ^{94g}Tc, ^{94m}Tc, ^{124}I

C. Lang et al. JINST 2014;9:P01080.

Cancer and efficiency of treatments

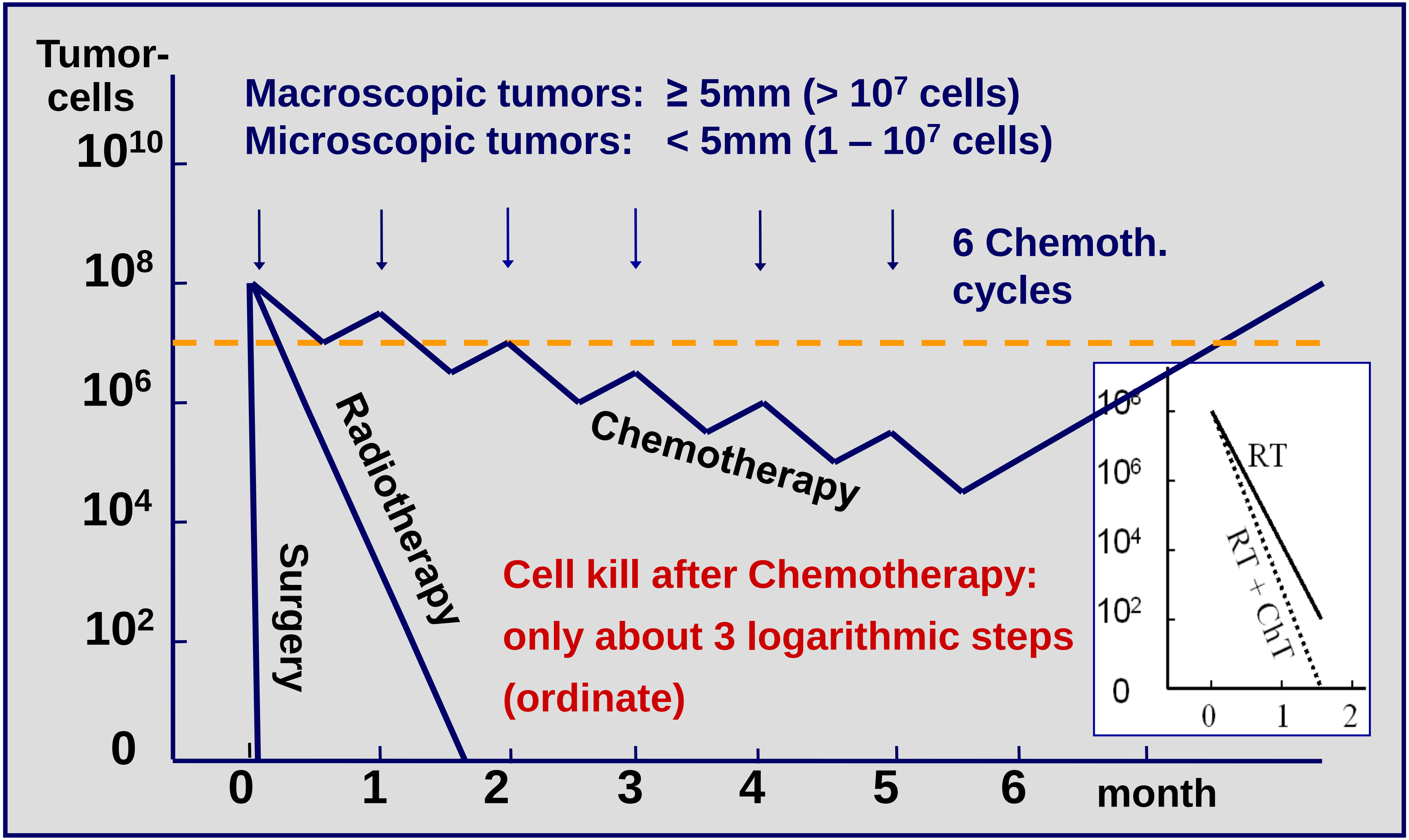
At time of diagnosis	Primary tumor	With metastases	Total
Diagnosed	**58%**	**42%**	**100%**
Cured by:			
Surgery	**22%**		
Radiation therapy	**12%**		
Surgery+radiation therapy	**6%**		
All other treatments and combinations incl. chemotherapy		**5%**	
Fraction cured	**69%**	**12%**	**45%**

Over one million deaths per year from cancer in EU.

⇒ improve early diagnosis

⇒ improve systemic treatments

Comparison of Therapies

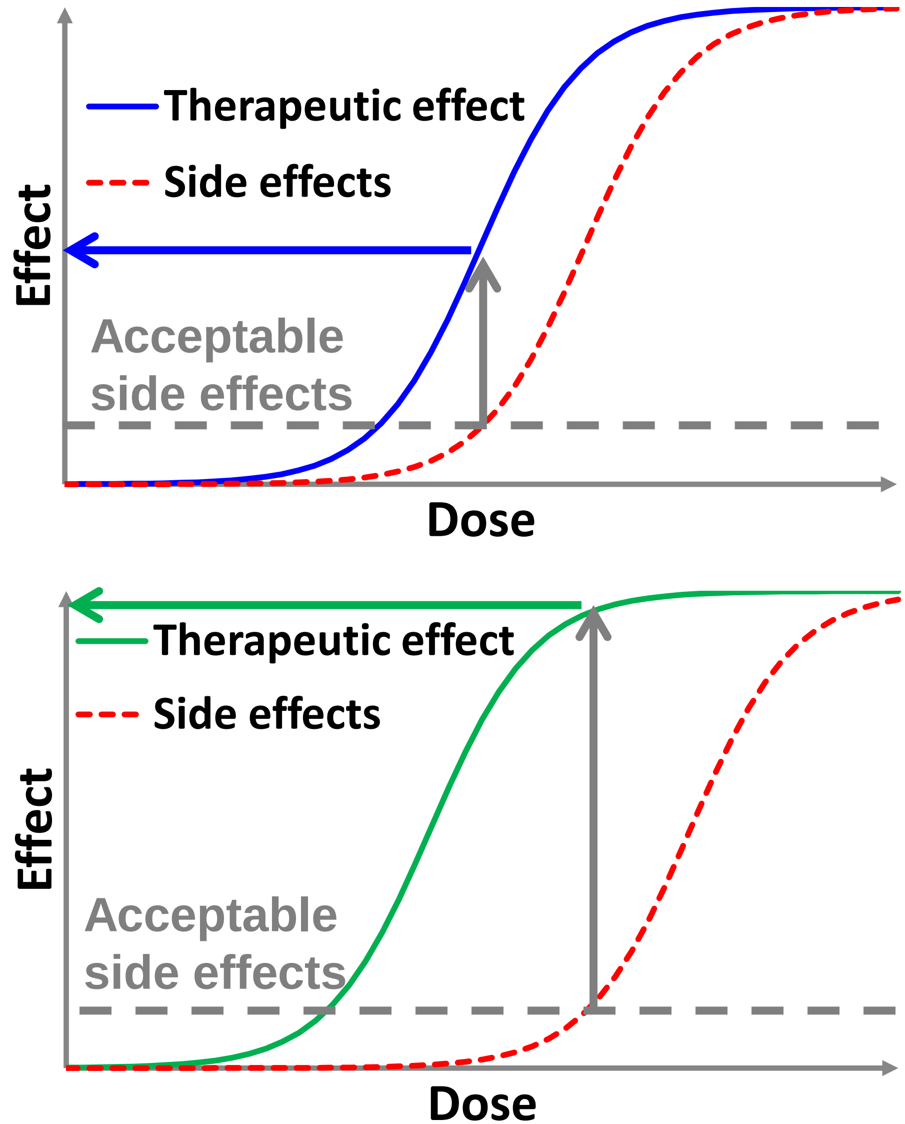


(Molls, TU München; according to Tannock: Lancet 1998, Nature 2006)

Targeted therapies

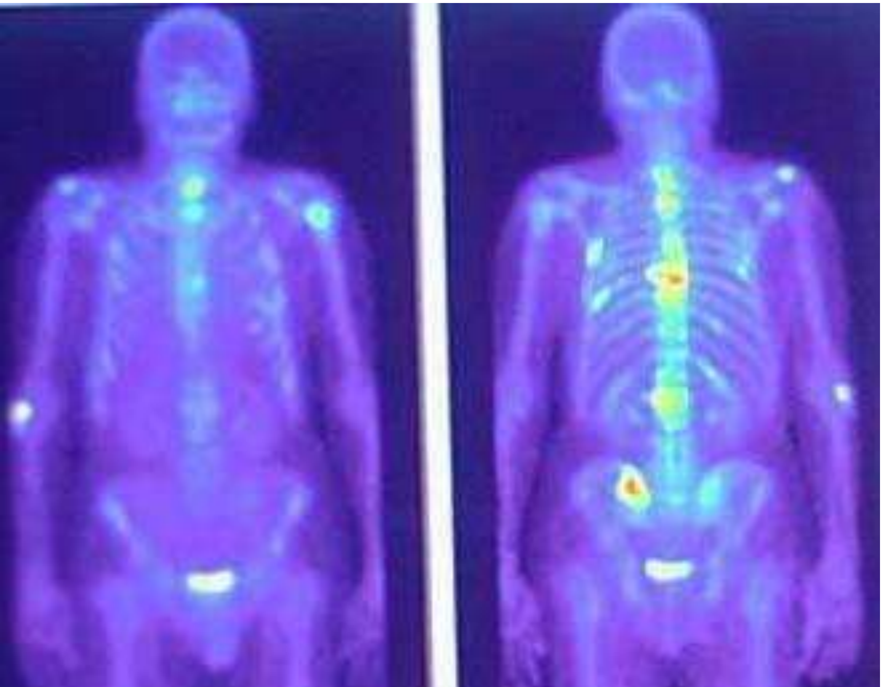
Paracelsus (1493-1541)

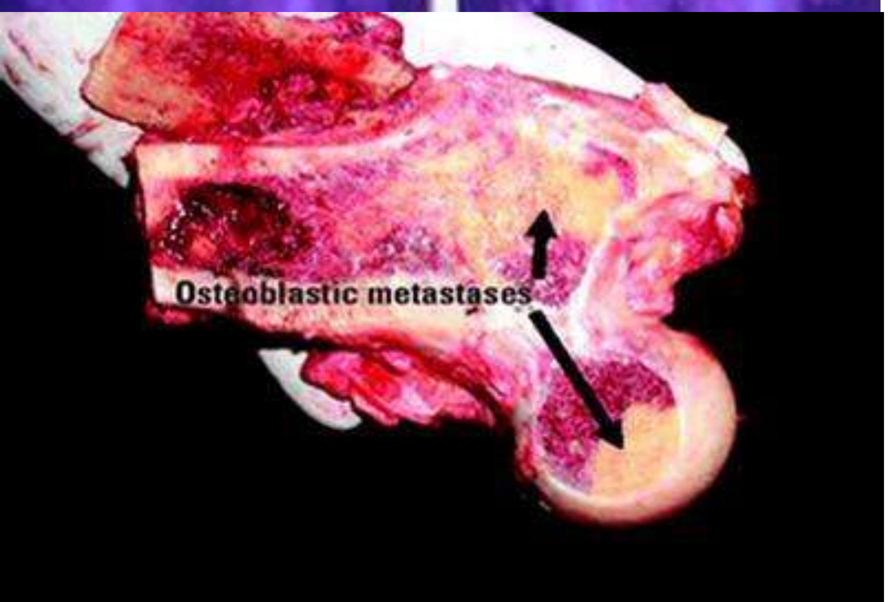
"All things are poison, and nothing is without poison; only the dose permits something not to be poisonous."



Selectivite targeting is essential to widen the therapeutic window!

Metabolic targeting





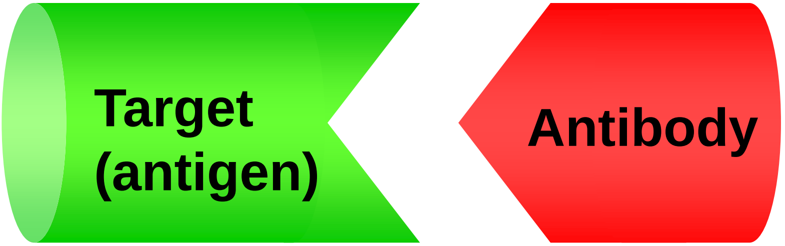
Thyroid cancer
$^{123}I^-$ for imaging
$^{131}I^-$ for therapy

Bone metastases
1.5 million patients world-wide

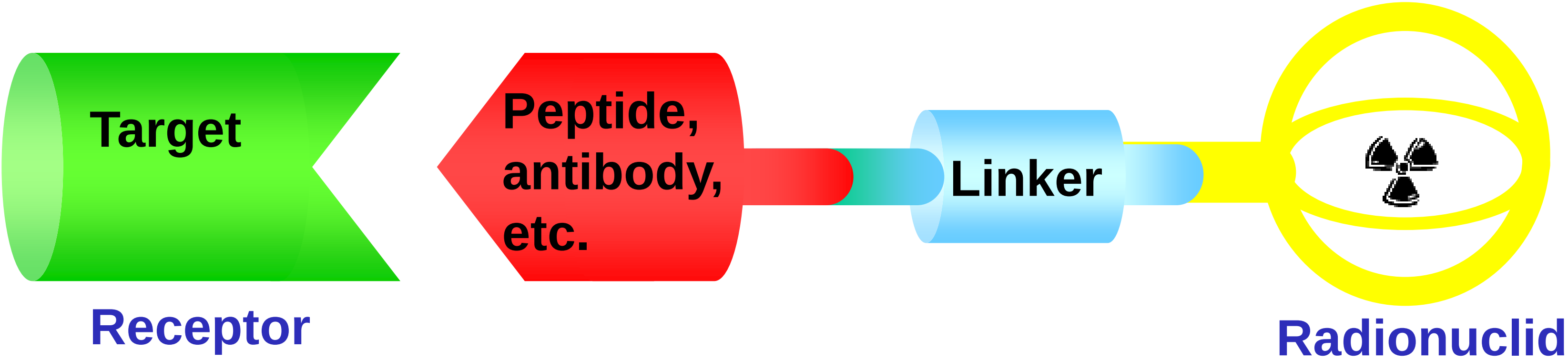
^{99m}Tc-MDP for SPECT imaging
$^{18}F^-$ for PET imaging

Therapy
^{153}Sm-EDTMP (Quadramet)
$^{89}Sr^{2+}$ (Metastron)
$^{223}Ra^{2+}$ (Xofigo/Alpharadin)

Immunology approach



Multidisciplinary collaboration to fight cancer



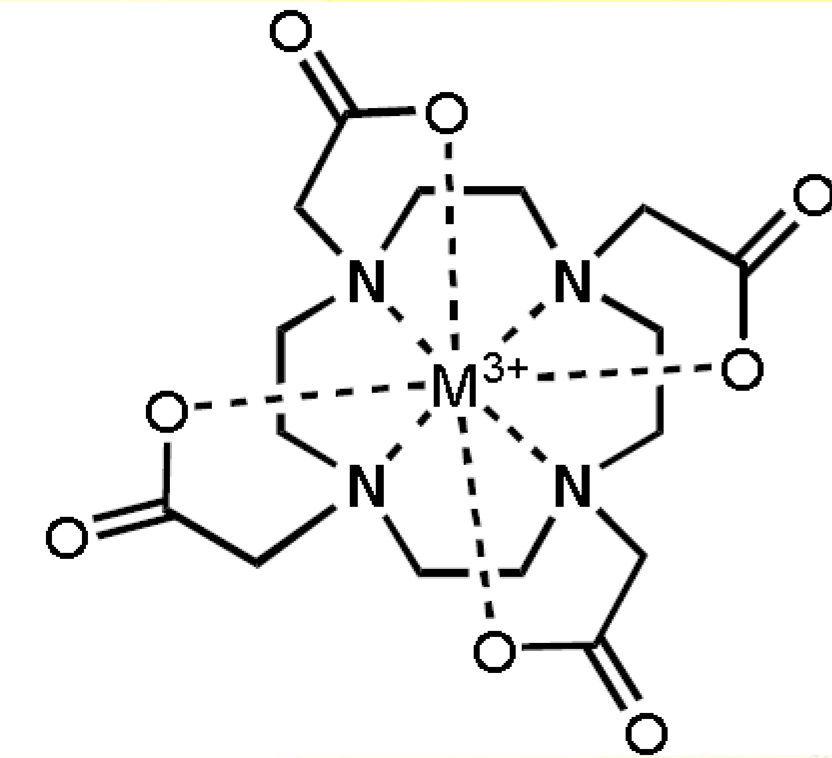
Immunology
Structural biology

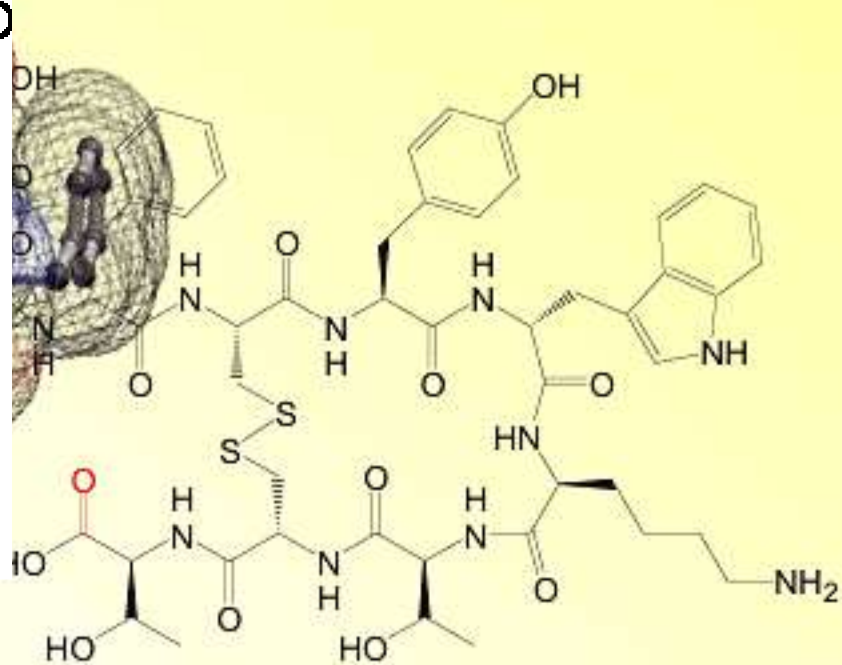
Coordination chemistry

Nuclear physics and radiochemistry

Nuclear medicine and medical physics

Structural Formula of DOTA-TOC/TATE





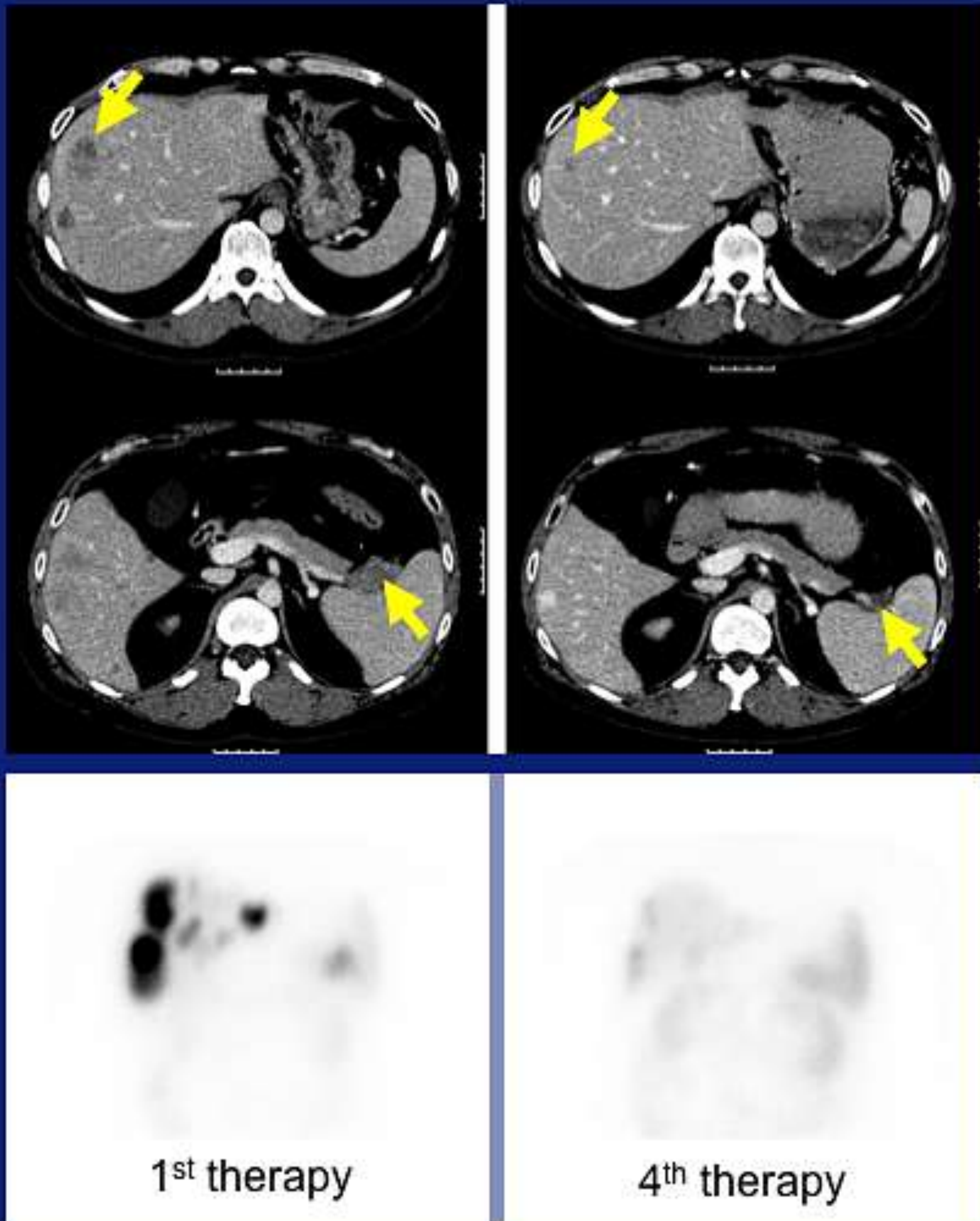
DOTA-TATE

1,4,7,10-tetraazacyclododecantetraacetate

^{111}In	^{90}Y
^{67}Ga	^{177}Lu
^{68}Ga	^{213}Bi

IC_{50} (Y^{III}) = 1.6 ± 0.4 nM

Helmut Maecke, EANM-2007.



Male

36 years of age

Small cell pancreatic neuroendocrine tumour

Liver metastases

Ki-67 index 10-15% (liver biopsy)

4 cycles with ^{177}Lu-octreotate and capecitabine

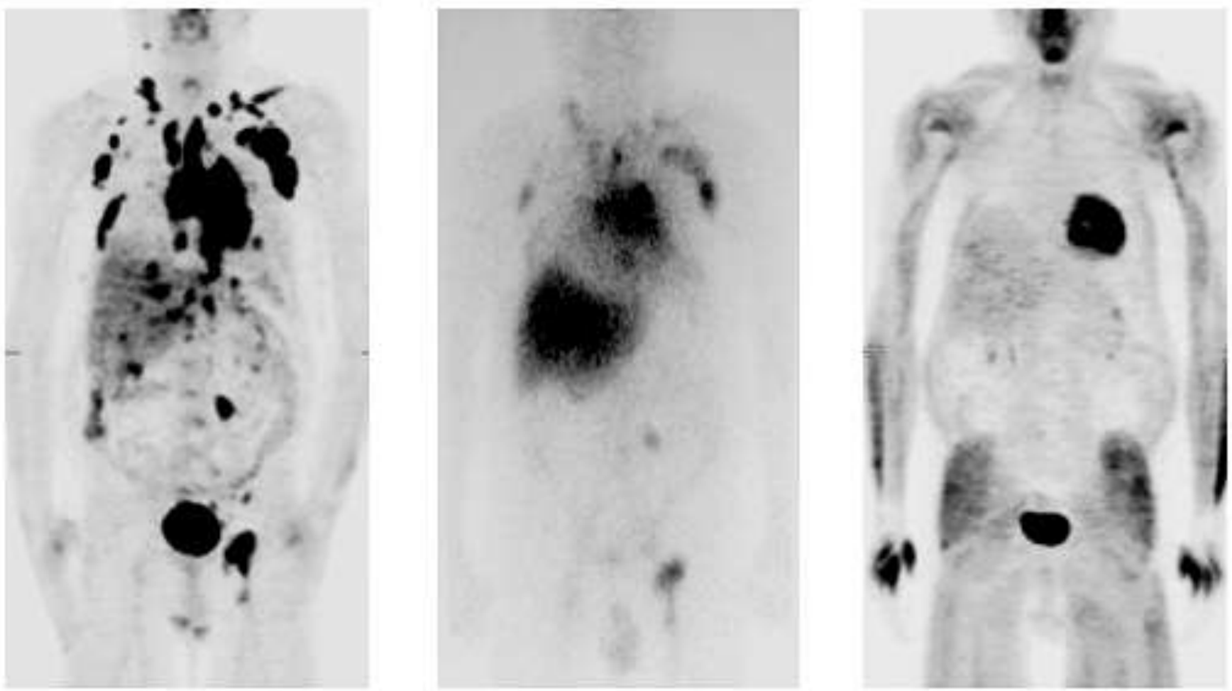
Partial remission

Roelf Valkema, EANM-2008.

Lymphoma therapy: RITUXIMAB+^{177}Lu

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

^{18}FDG PET	^{177}Lu-Scan	^{18}FDG PET	



Still in CR

1.9.2002	13.9.2002	15.11.2002	15.9.2009

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

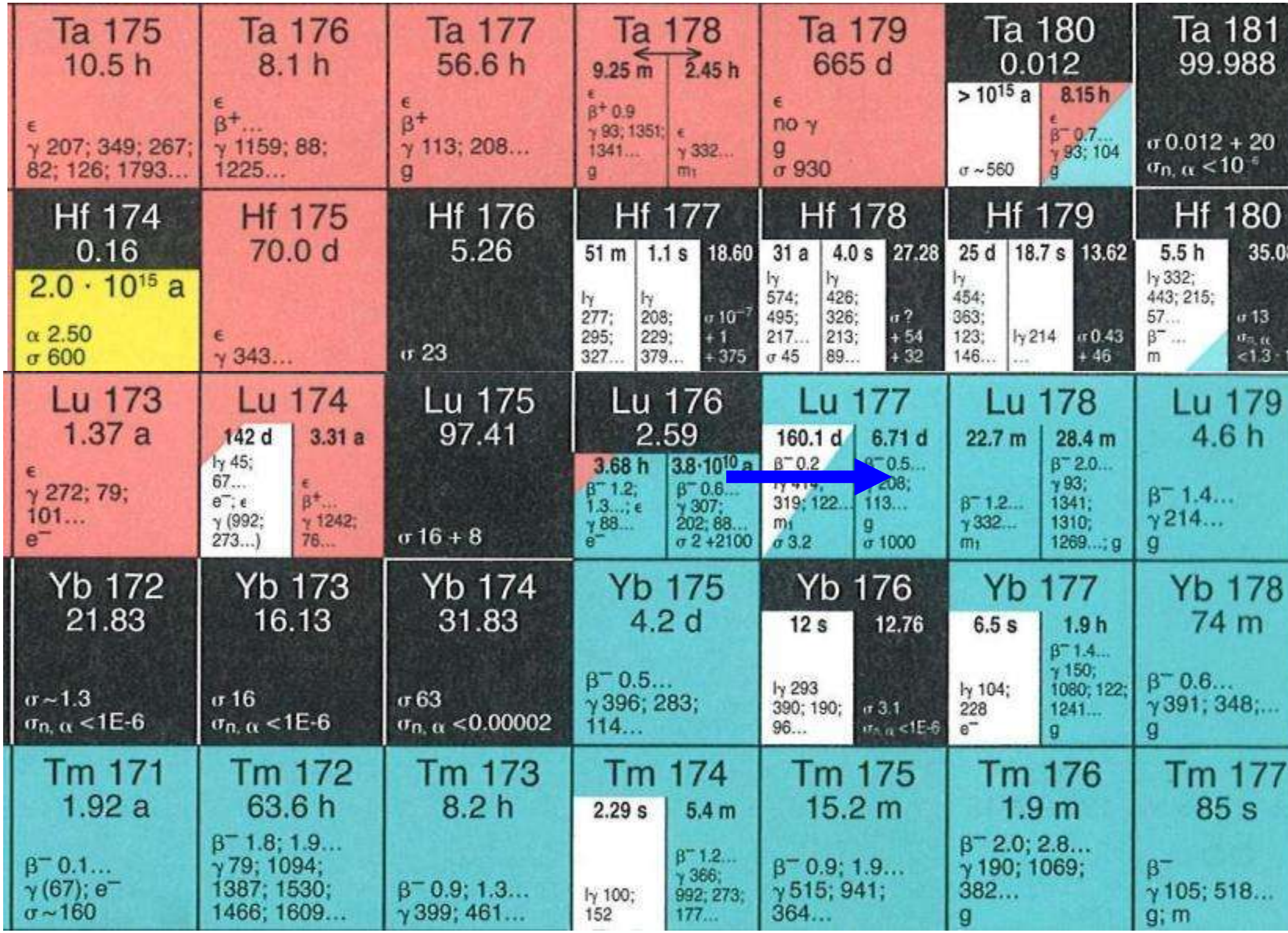
Radionuclides for RIT and PRRT

Radio-nuclide	Half-life (d)	E mean (keV)	Eγ (B.R.) (keV)	Range
Y-90	2.7	934 β	-	**12 mm**
I-131	8.0	182 β	364 (82%)	**3 mm**
Lu-177	6.7	134 β	208 (10%) 113 (6%)	**2 mm**

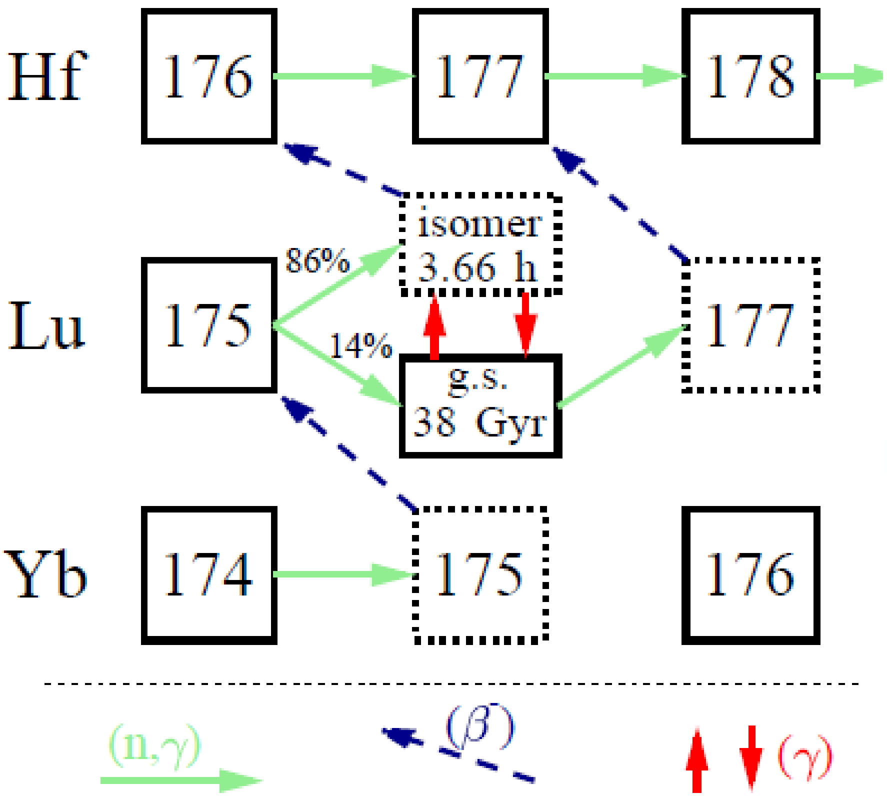
Established isotopes (Y-90, I-131)

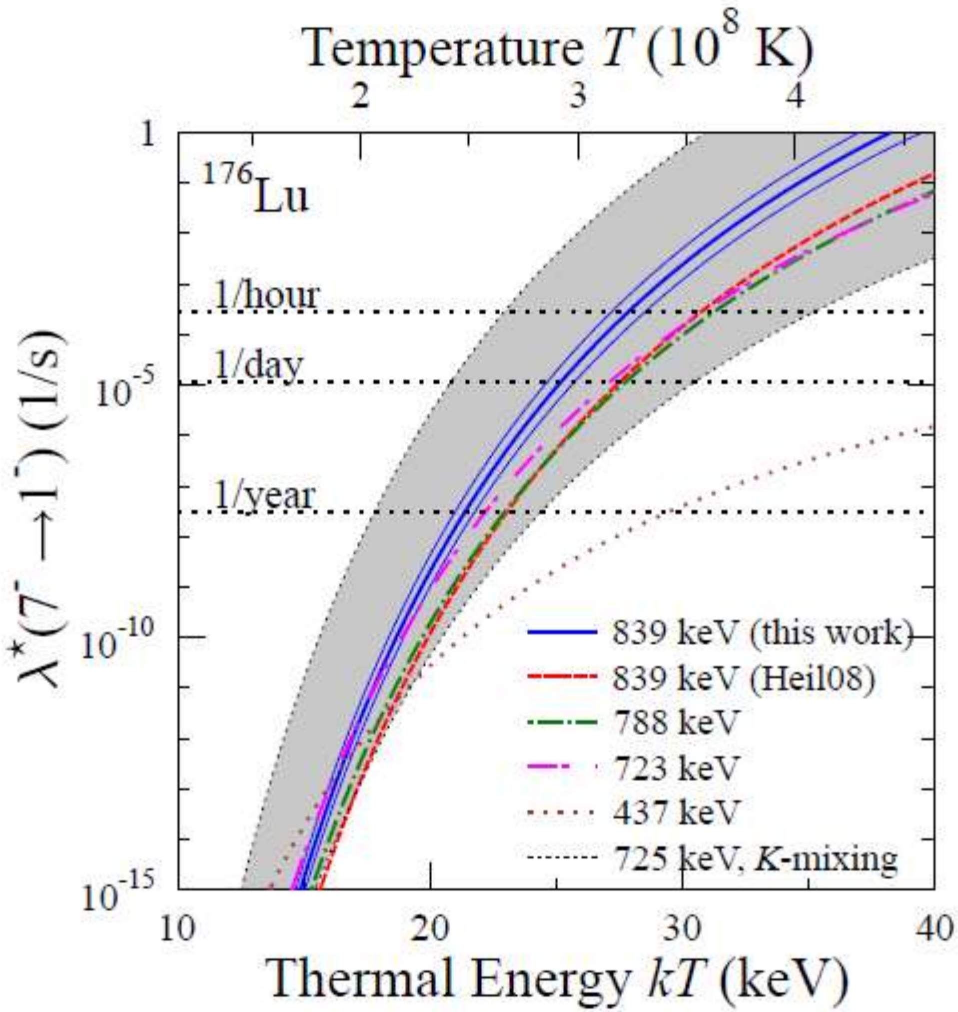
Emerging isotope (Lu-177)

Production of ^{177}Lu



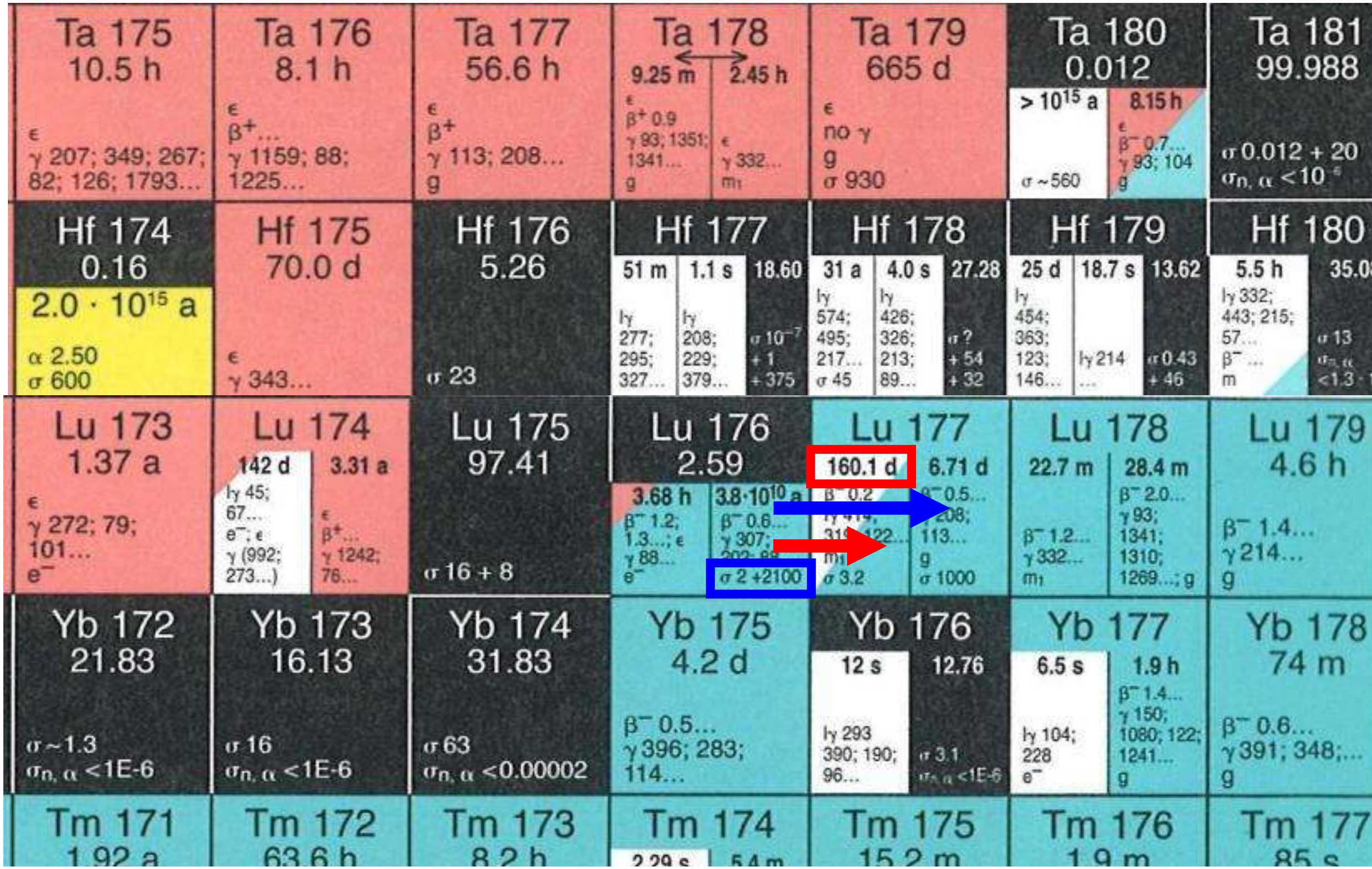
^{176}Lu: cosmochronometer or thermometer?





H. Beer et al., Astrophys. J. Suppl. 1981;46:295.
P. Mohr et al., 2009.
G. Gosselin et al., 2010.

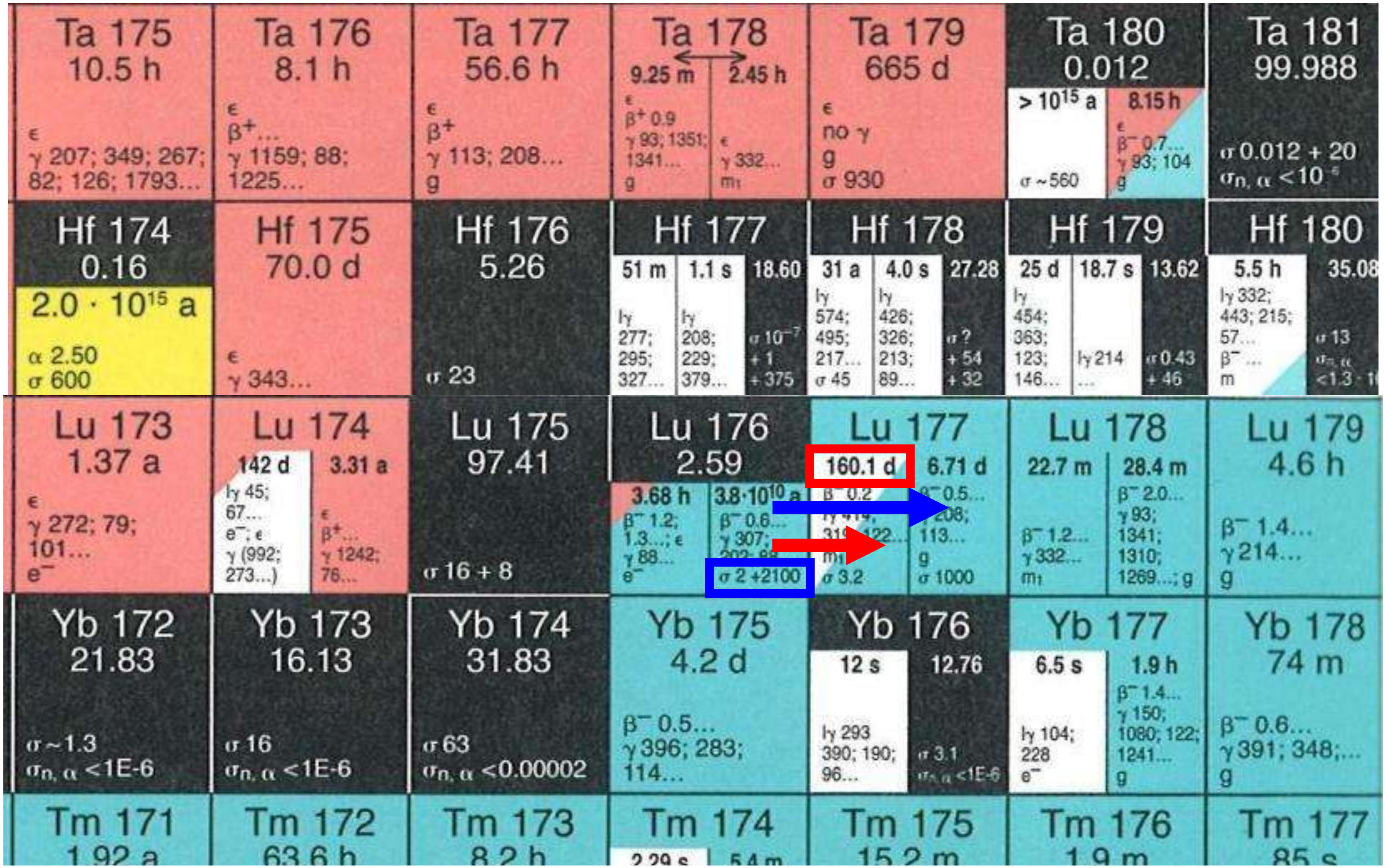
Production of ^{177}Lu



Waste problem for hospitals!

R. Henkelmann et al., Eur. J. Nucl. Med. Mol. Imag. 36 (2009) S260.

Production of ^{177}Lu

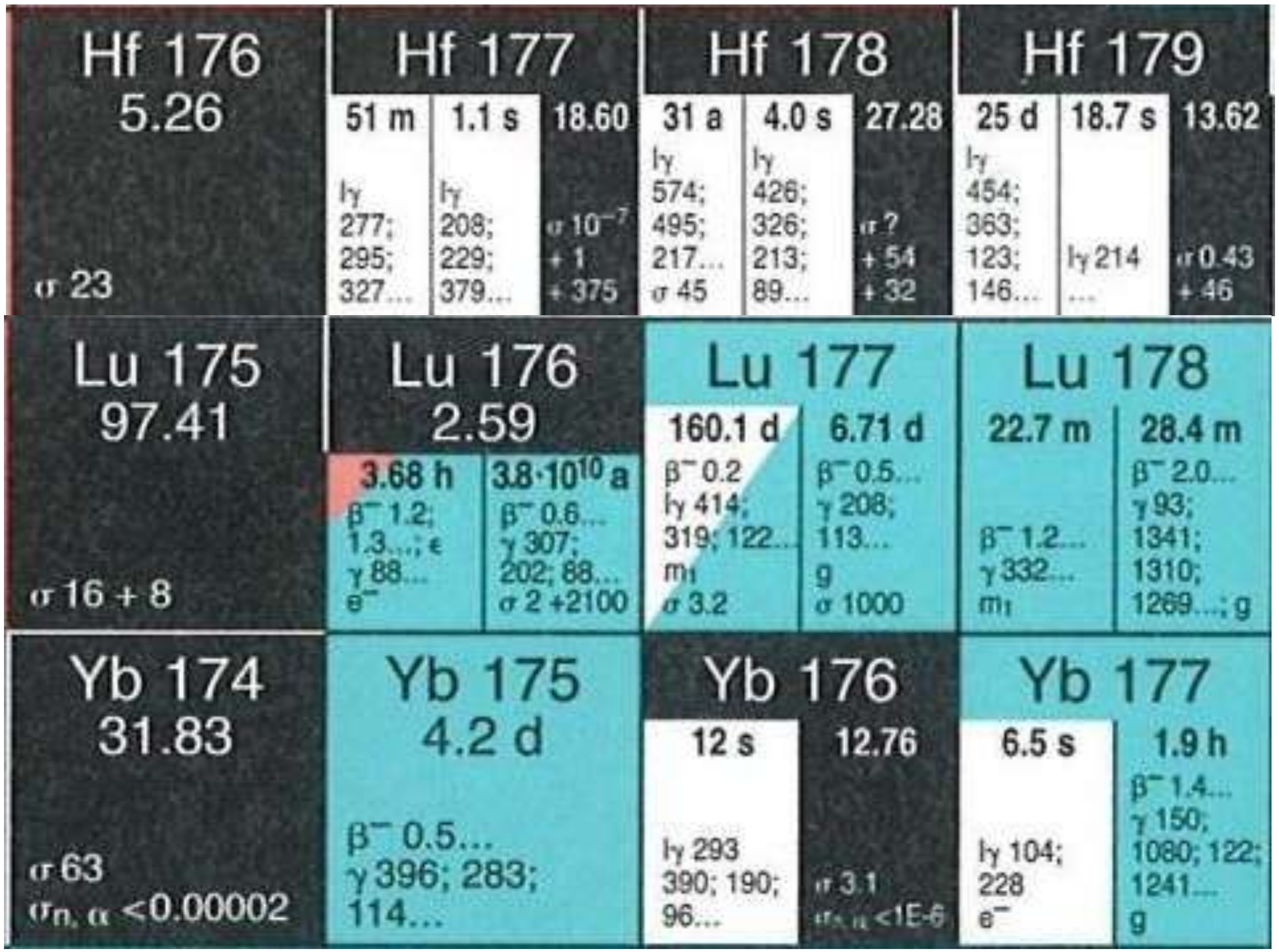


Waste problem for hospitals!

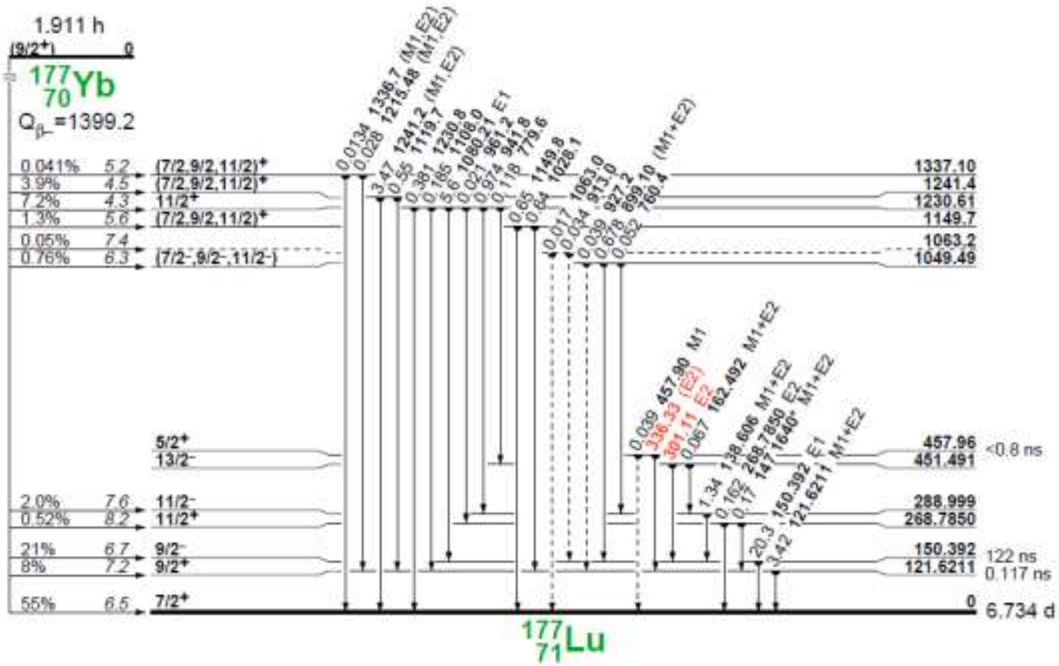
R. Henkelmann et al., Eur. J. Nucl. Med. Mol. Imag. 36 (2009) S260.

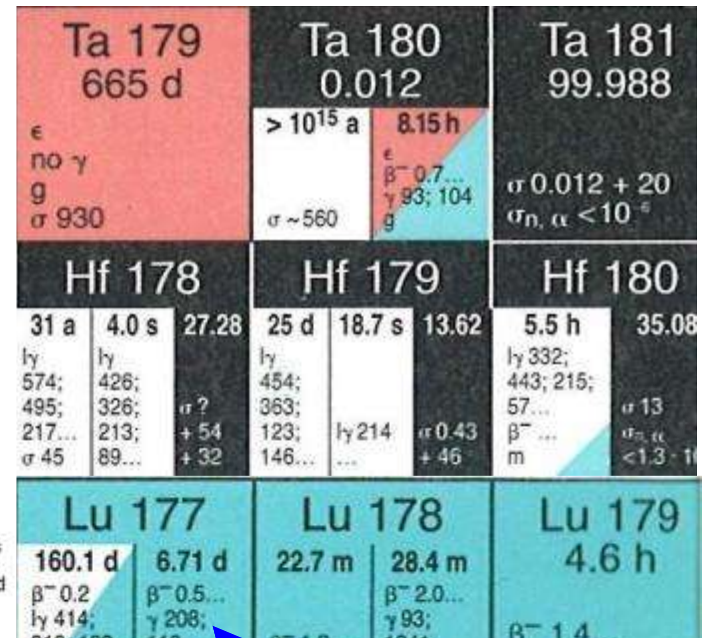
Question

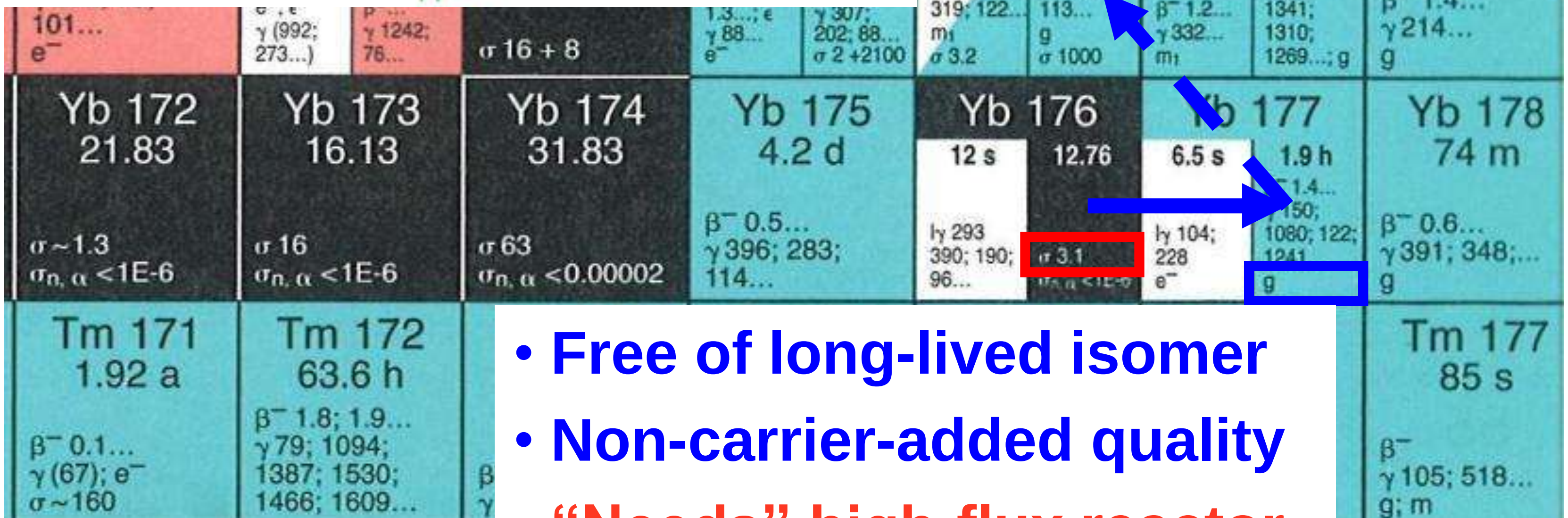
How to get ^{177g}Lu without ^{177m}Lu contamination ?



Alternative production route to ^{177}Lu







- **Free of long-lived isomer**
- **Non-carrier-added quality**
- **“Needs” high-flux reactor**

Question

How long does it take to separate lutetium from ytterbium?

Answer: The history of lutetium separation

1878 Separation of Yb
by Jean-Charles Galissard de Marignac

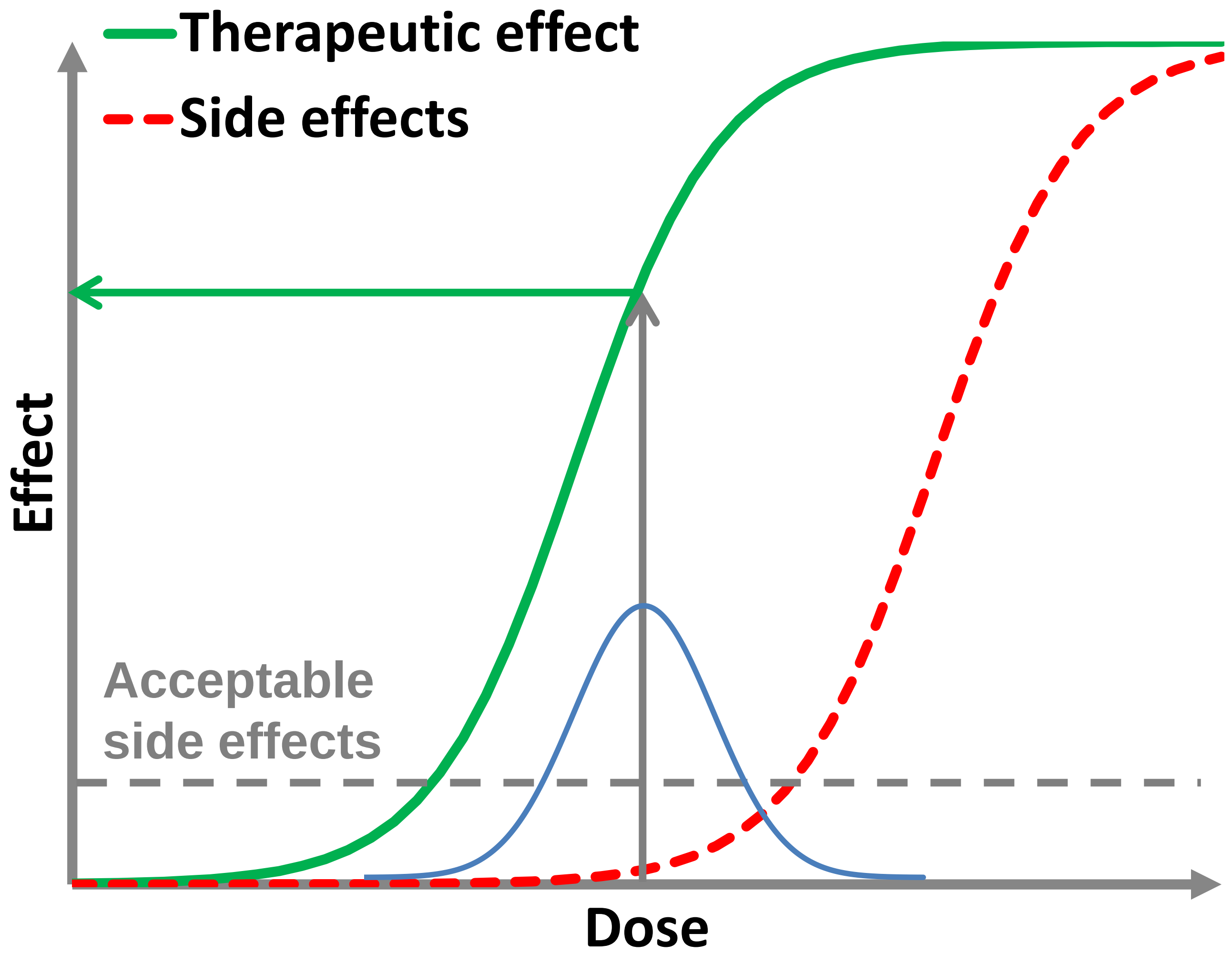
1907 Separation of Lu from Yb
Georges Urbain
Carl Auer von Welsbach
Charles James

1995- Large-scale separation of Lu
for production of LSO and LYSO crystals
by Mark Andreaco (CTI) and
George Schweitzer (Univ. Tennessee)

2007 Rapid large-scale separation
of n.c.a. ^{177}Lu from irradiated Yb
by ITG Garching

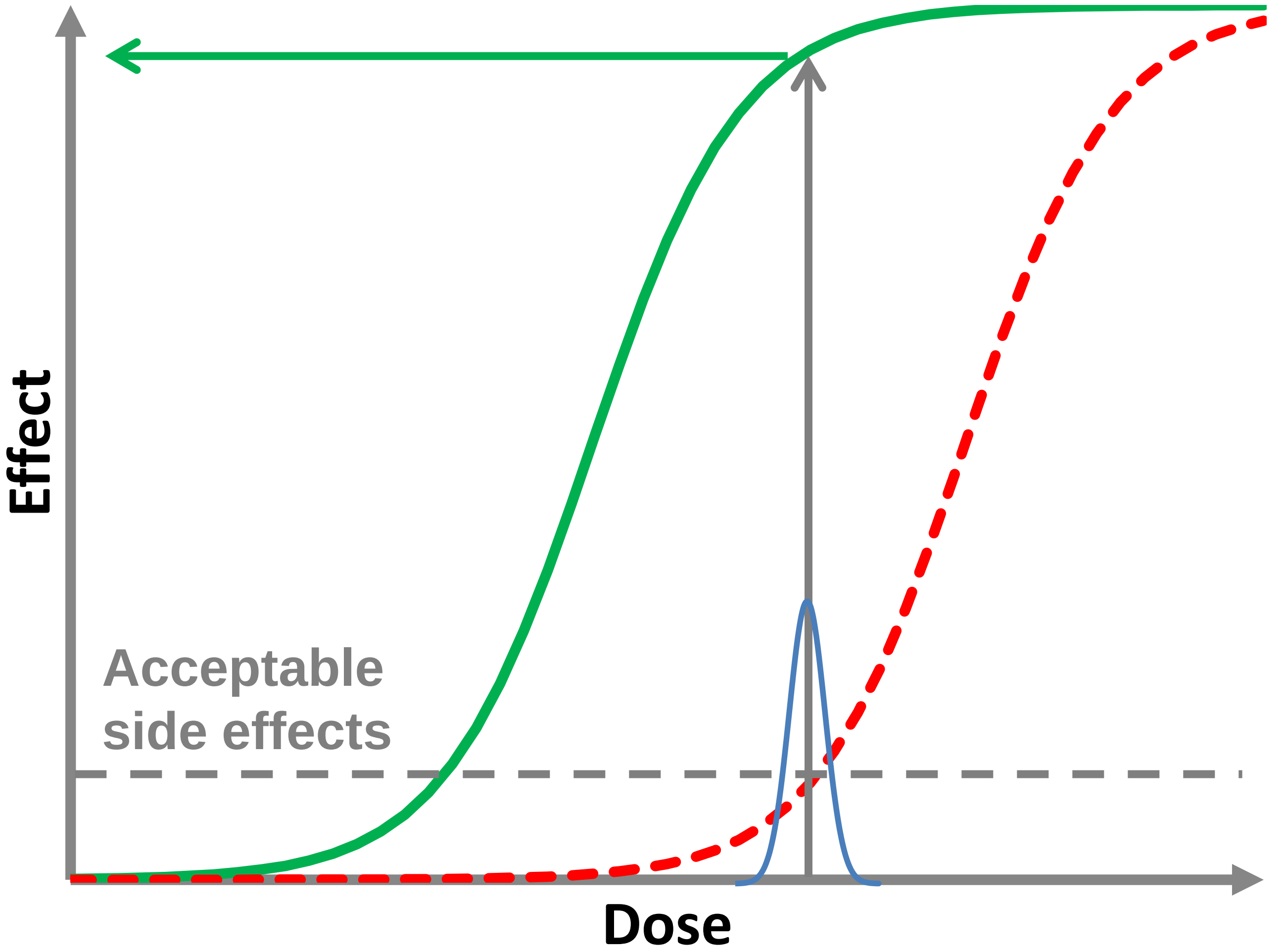
The rising star for therapy

Theranostics



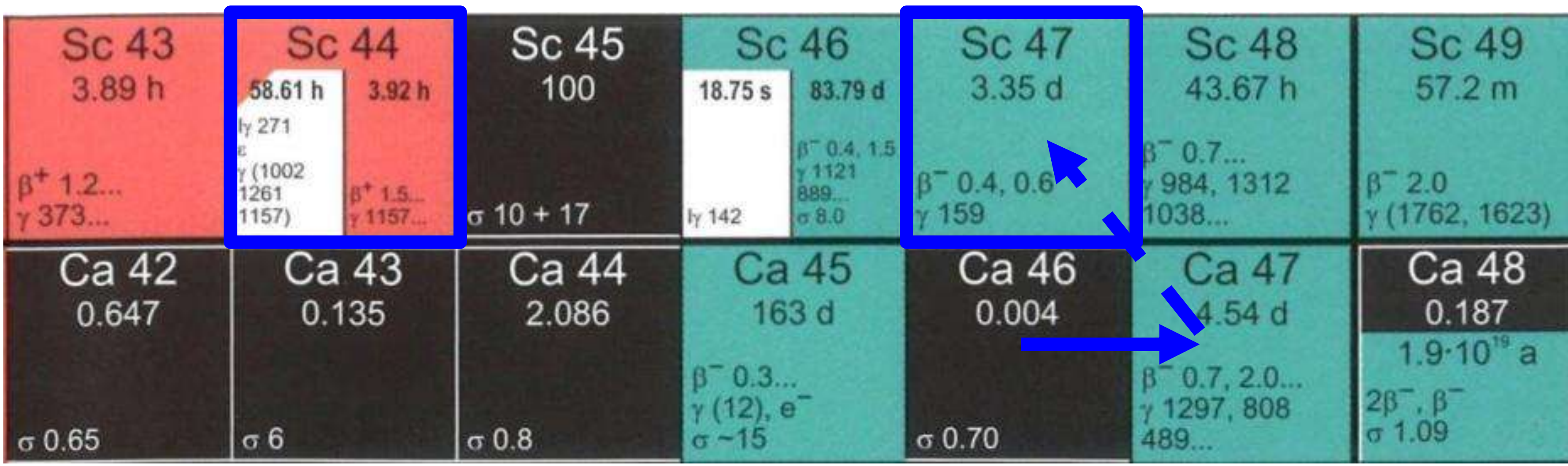
Accurate dosimetry is essential for optimum use of the therapeutic window.

Theranostics



Accurate dosimetry is essential for optimum use of the therapeutic window.

Matched pairs for theranostics

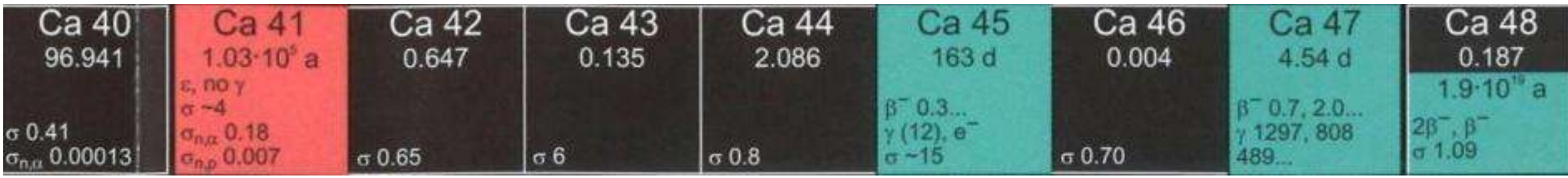


^{44}Sc for diagnostics ^{47}Sc for therapy

Question

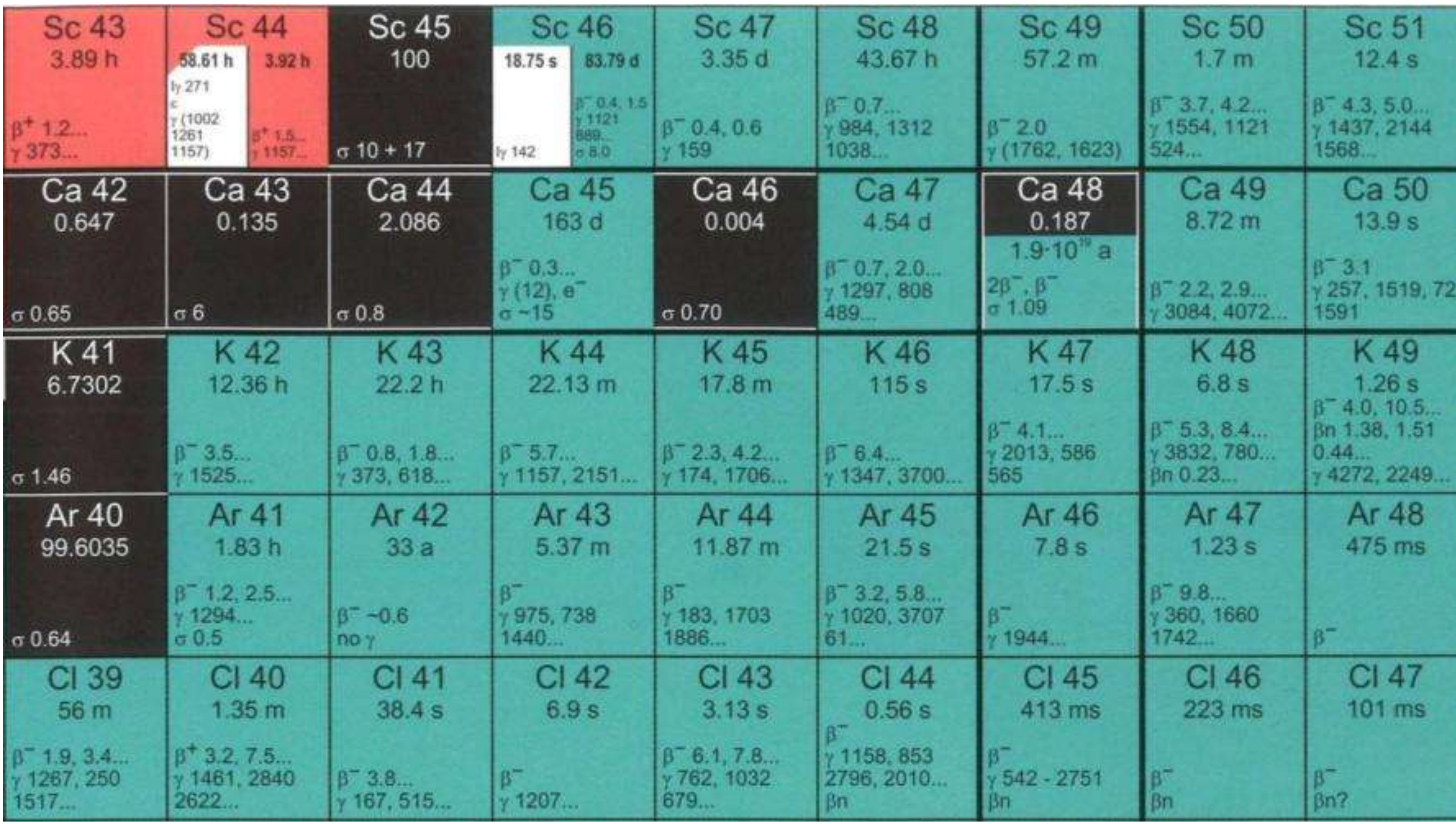
Why is ^{46}Ca so rare ?

$^{46}Ca/Ca = 4E\text{-}5$

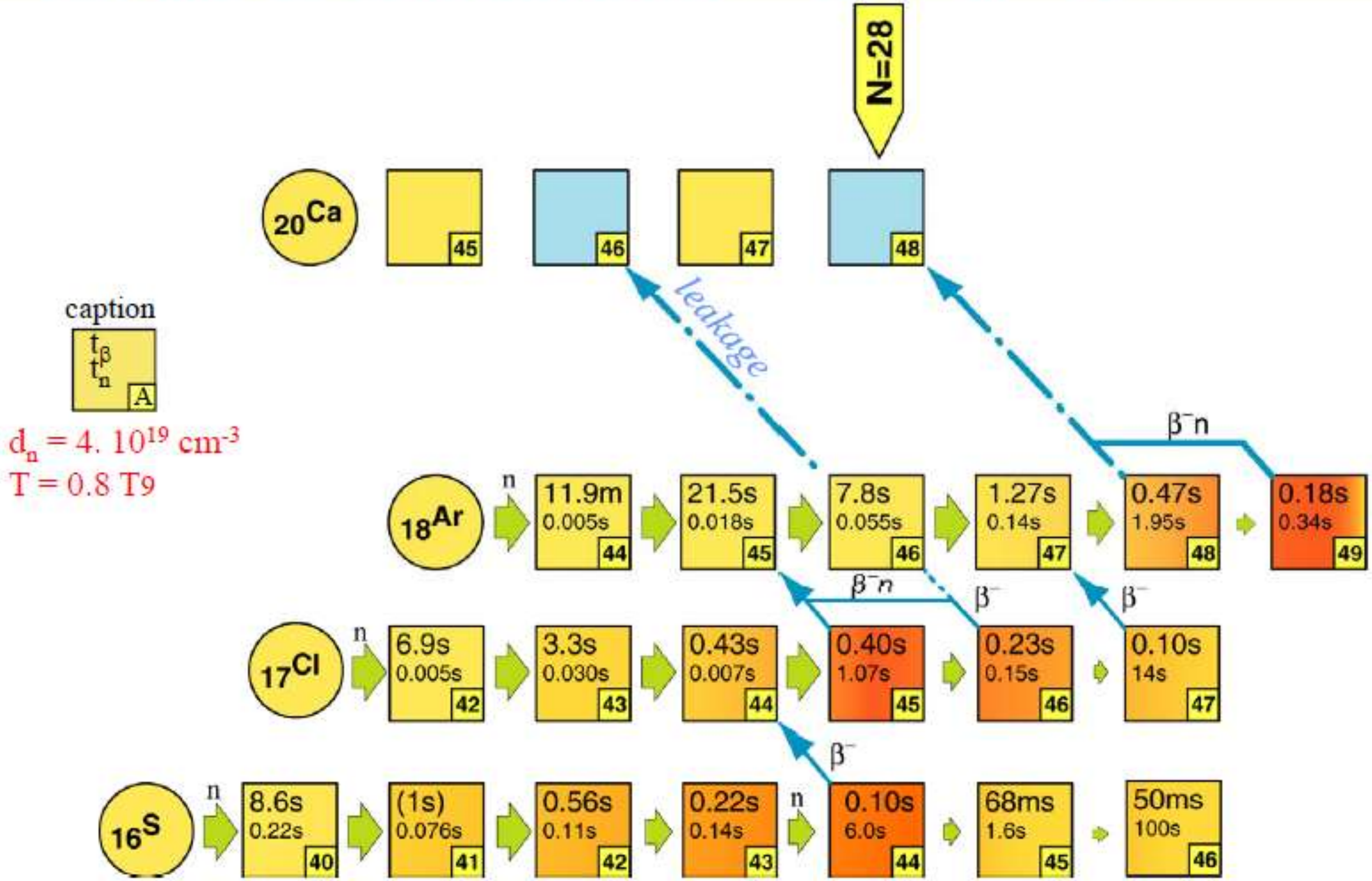


Answer by B²FH and Olivier

this region. Only for S^{36}, Ca^{46}, and Ca^{48} in this region is there no other method of production than the *r* process.



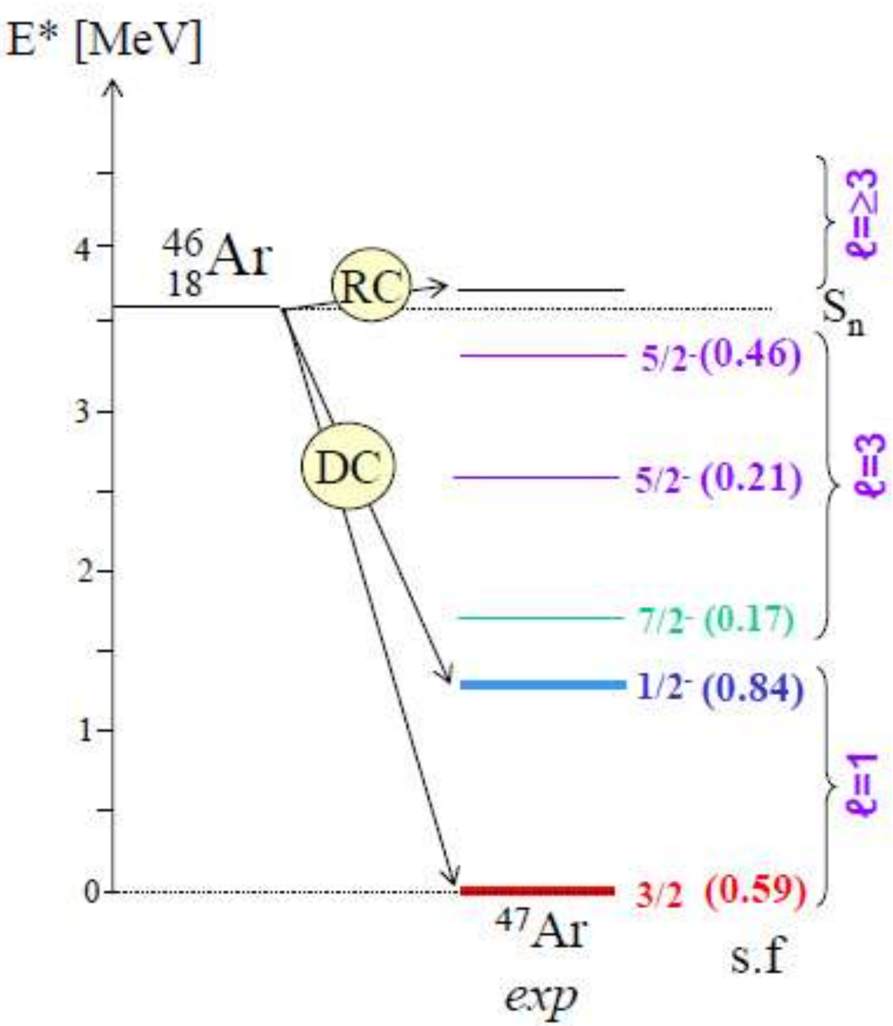
Explain the abundance ratio $^{48}Ca/^{46}Ca = 250$

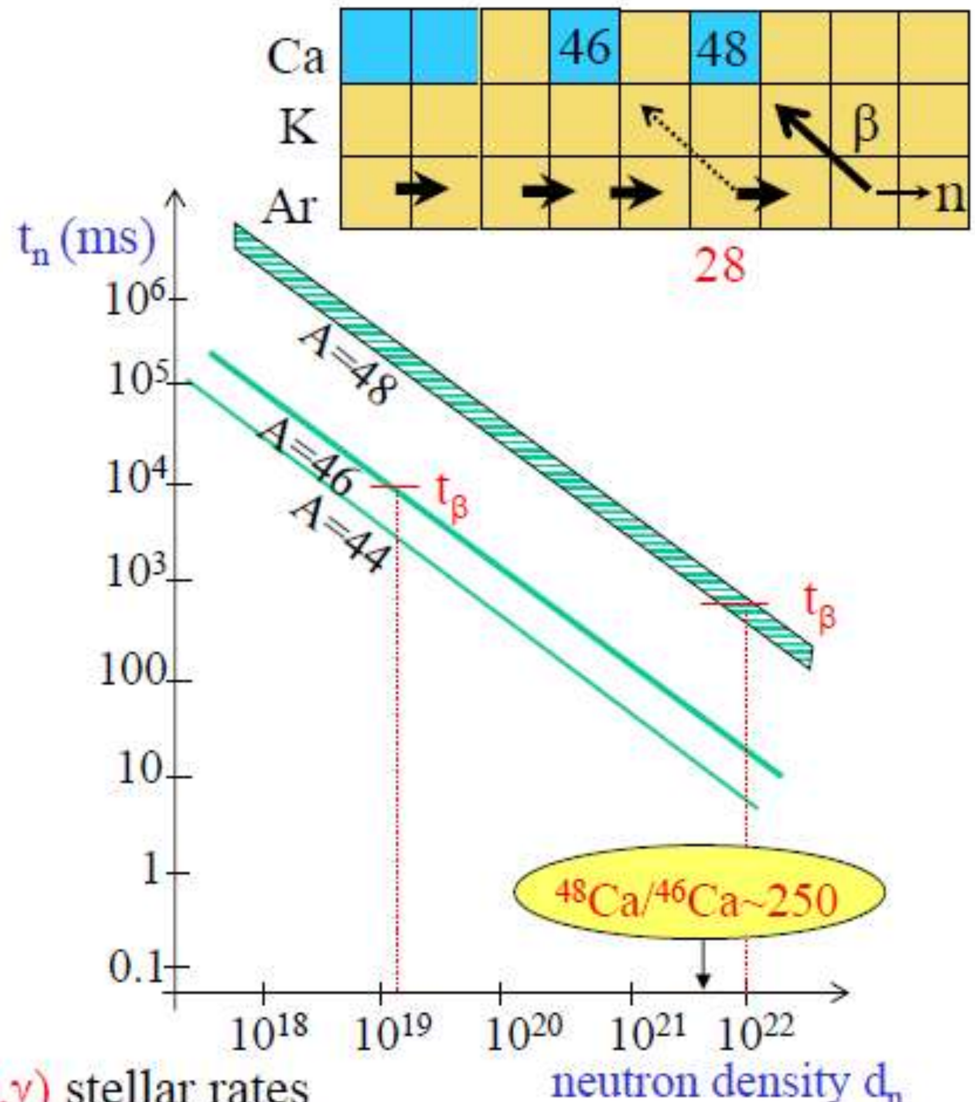


➡ Determine experimental (n,γ) rates on unstable Ar nuclei.

Olivier Sorlin, Russbach 2008.

Neutron capture rates on $^{44,46,48}Ar$





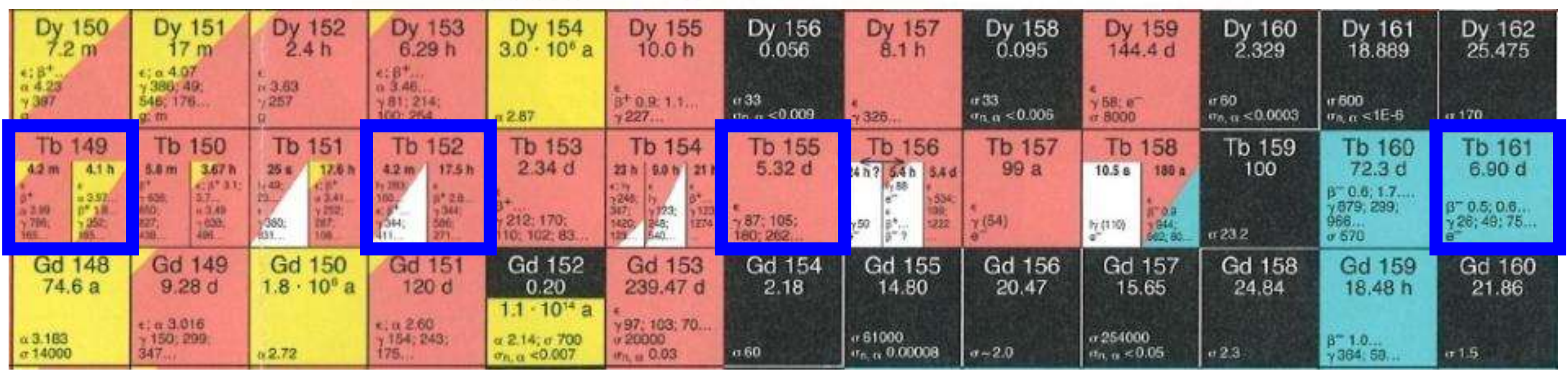
(d,p) access to E*, s.f., spins → derive (n,γ) stellar rates

Direct capture (E1) with $\ell_n = 0$ on *p* states dominates

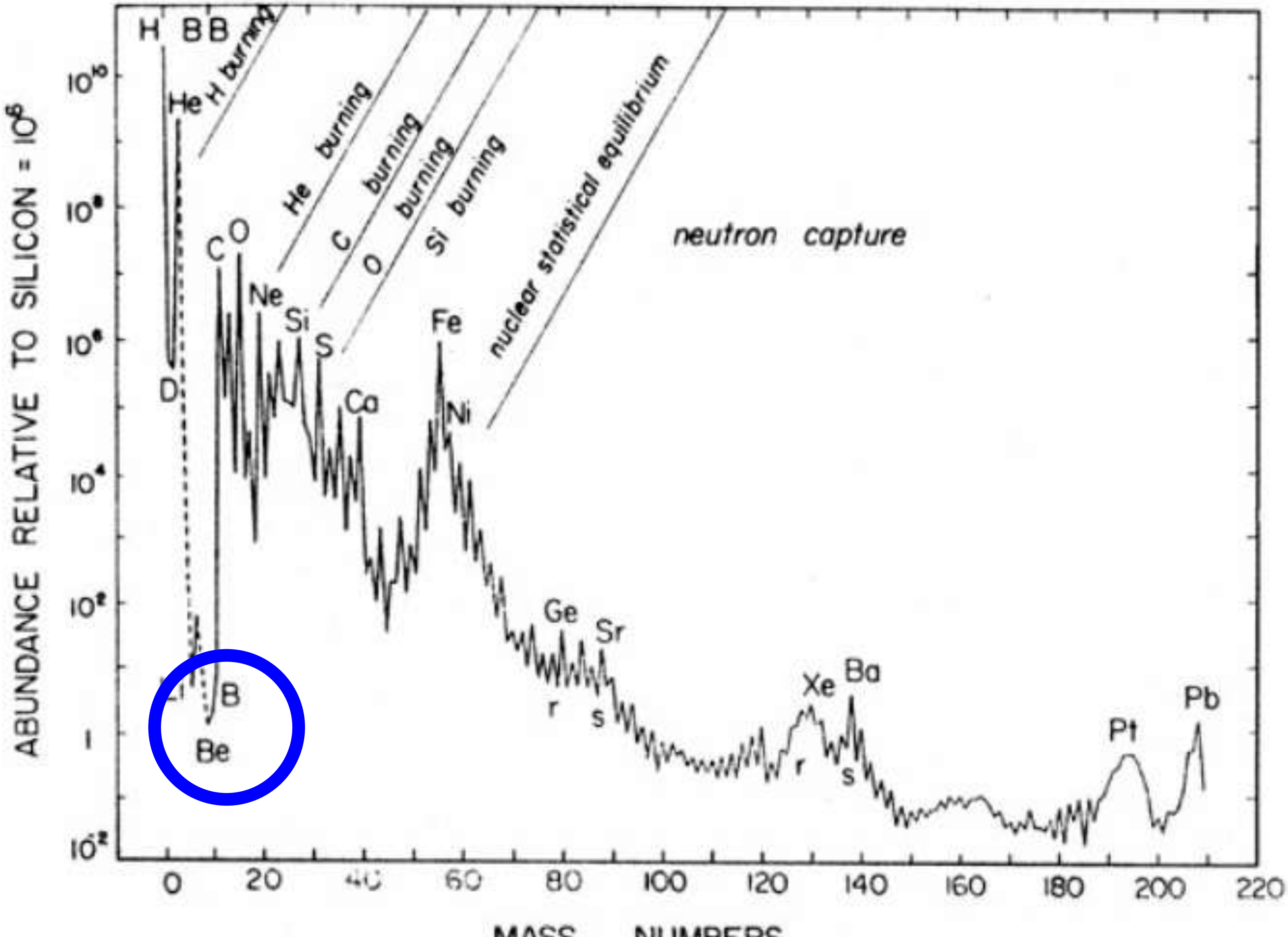
Speed up neutron-captures at the N=28 closed shell

collab. with T.Rauscher

Terbium: a unique element for nuclear medicine

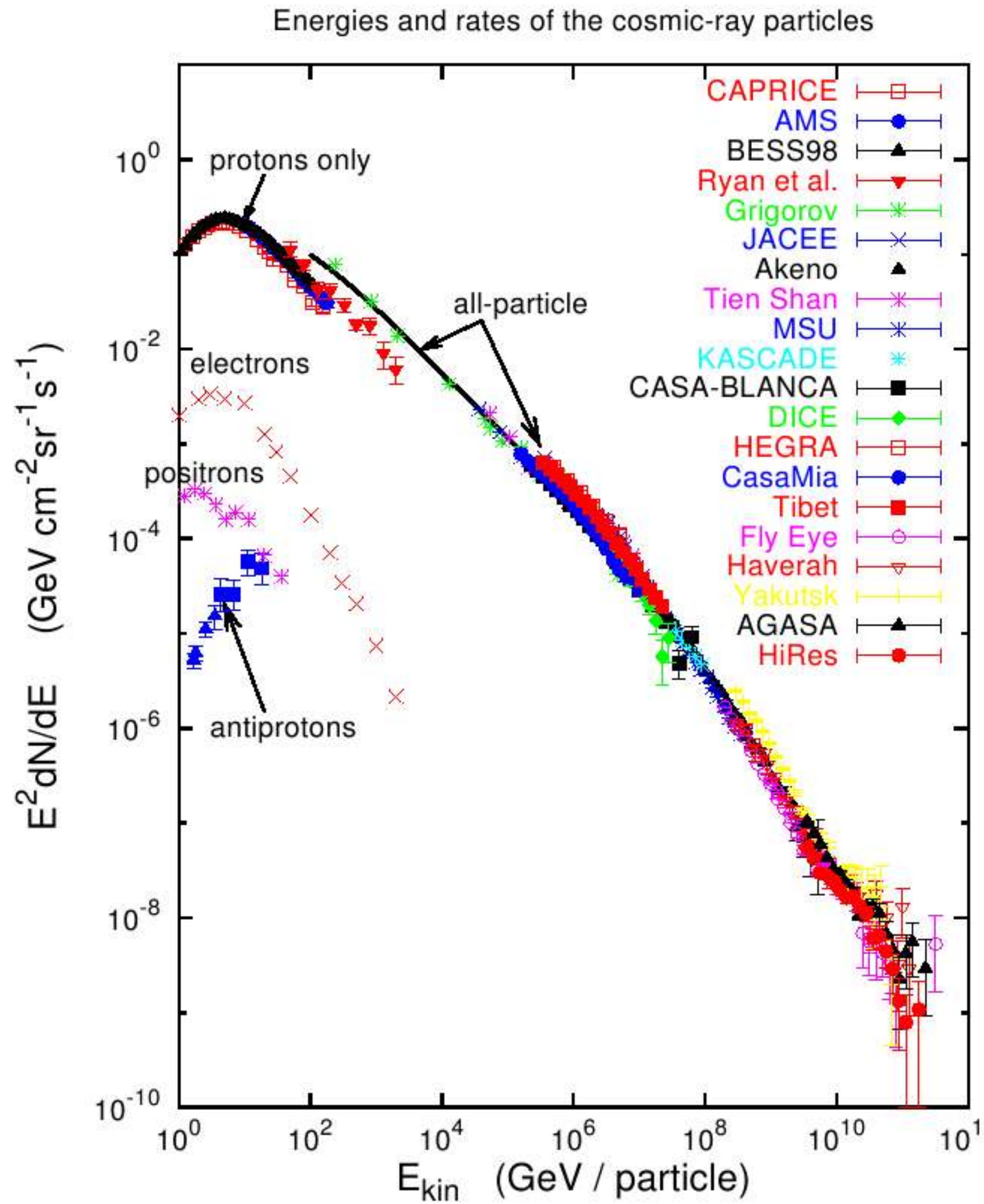


Question: How is Be and B produced ?

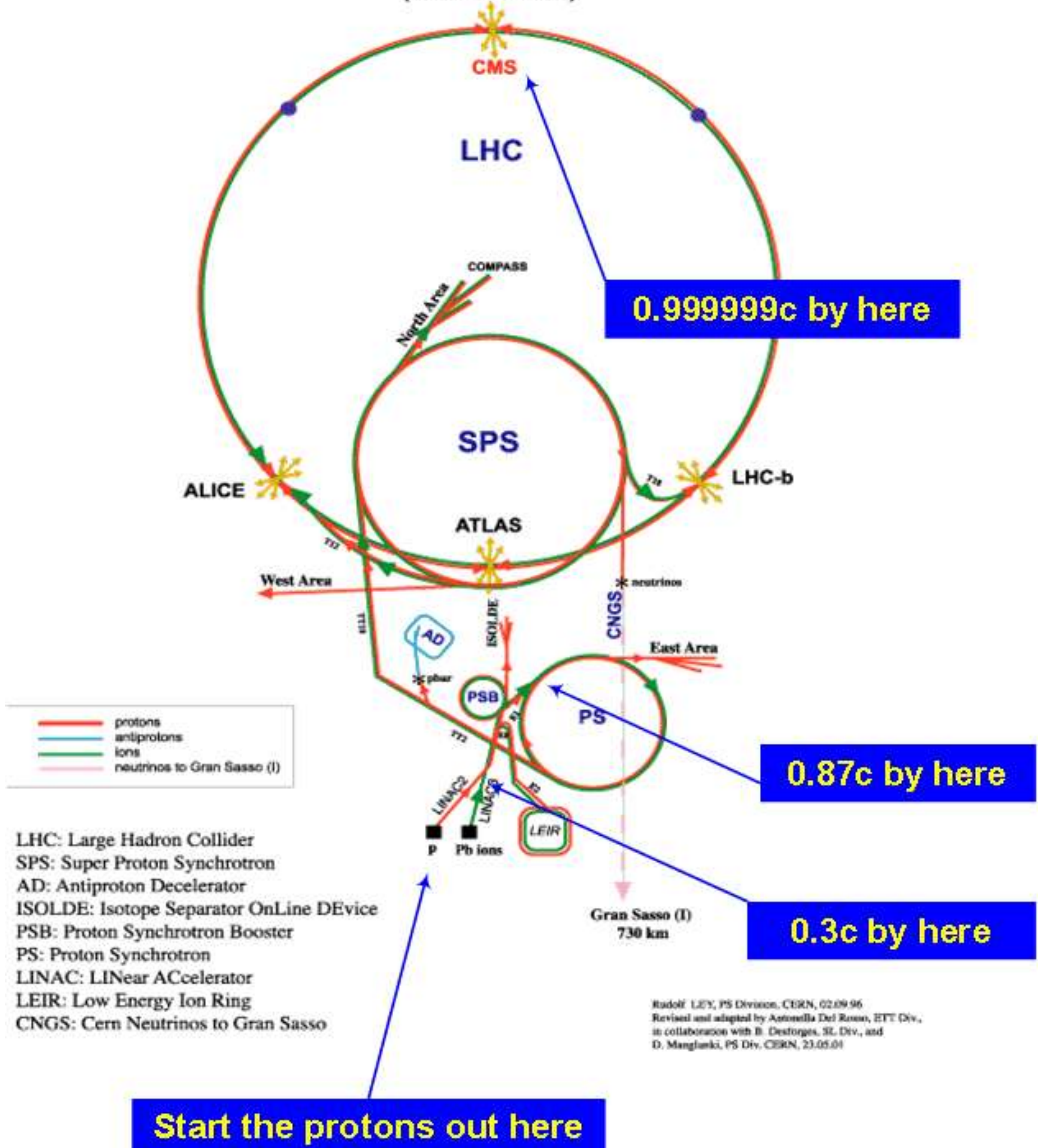


Answer: spallation production

$^{12}C(p,X)$
$^{16}O(p,X)$
etc.



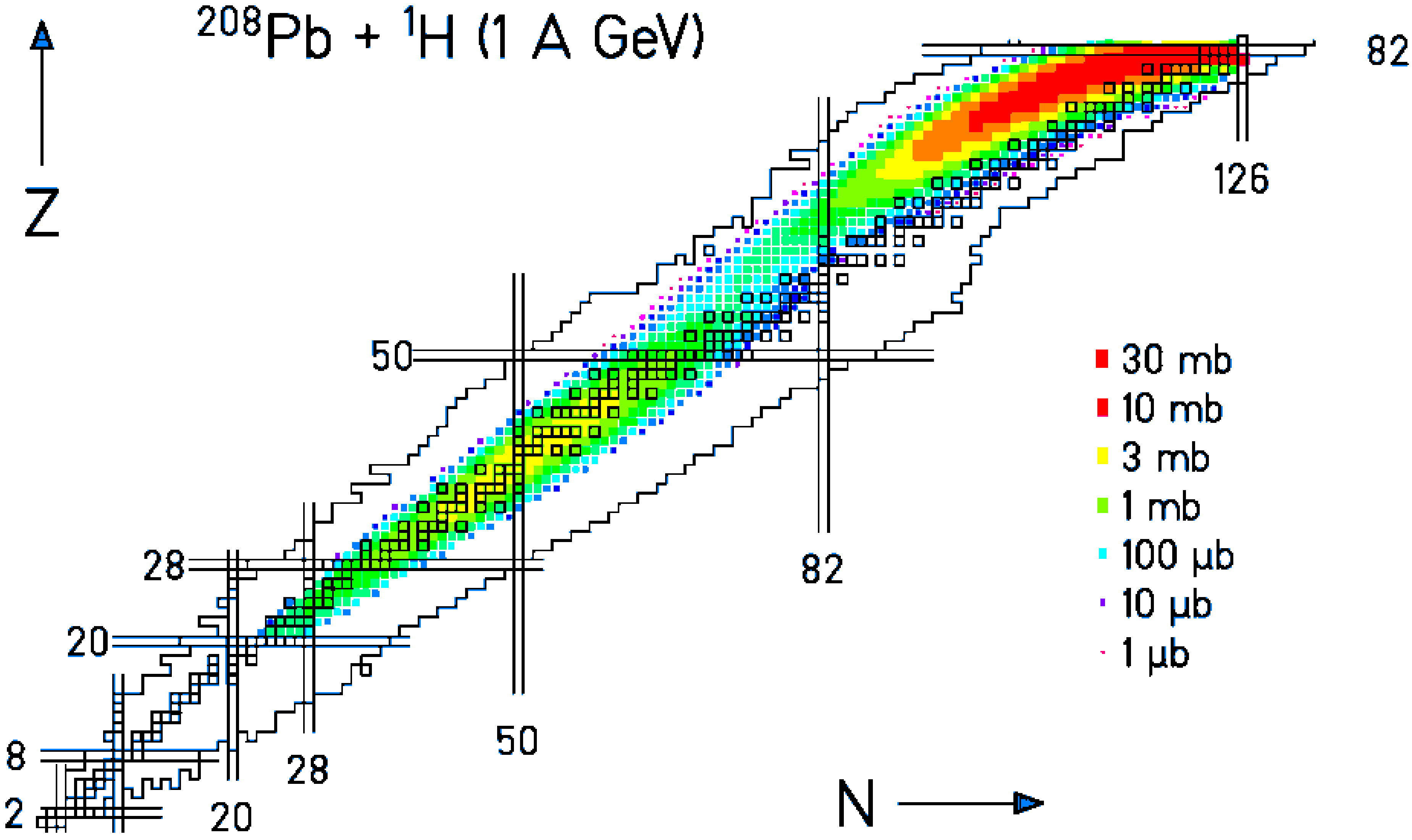
CERN Accelerators
(not to scale)



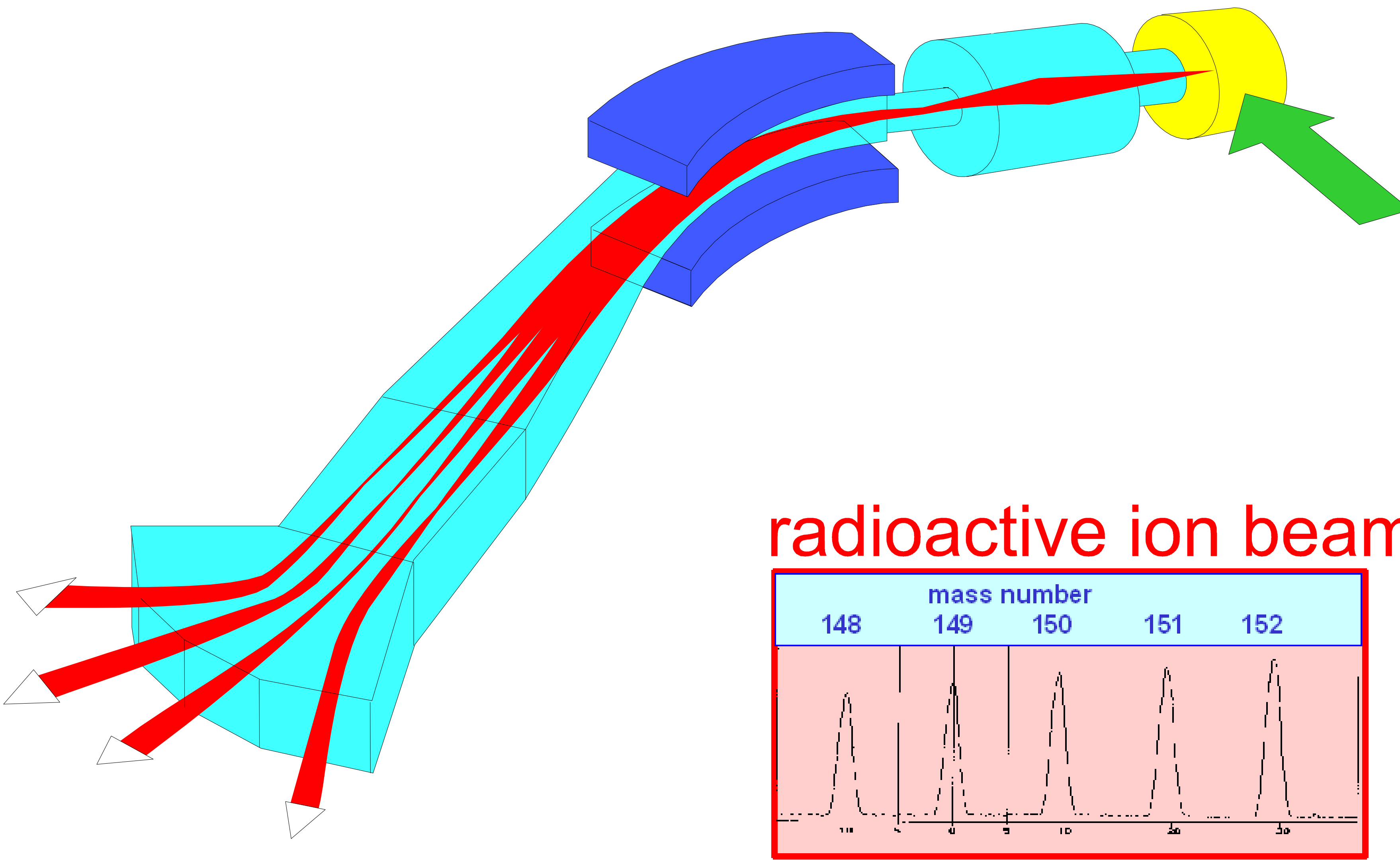
LHC: Large Hadron Collider
SPS: Super Proton Synchrotron
AD: Antiproton Decelerator
ISOLDE: Isotope Separator OnLine DEvice
PSB: Proton Synchrotron Booster
PS: Proton Synchrotron
LINAC: LINear ACcelerator
LEIR: Low Energy Ion Ring
CNGS: Cern Neutrinos to Gran Sasso

Rudolf LEY, PS Division, CERN, 02.09.96
Revised and adapted by Antonella Del Rosso, ETT Div.,
in collaboration with B. Desforges, SL Div., and
D. Manglunki, PS Div. CERN, 23.05.01

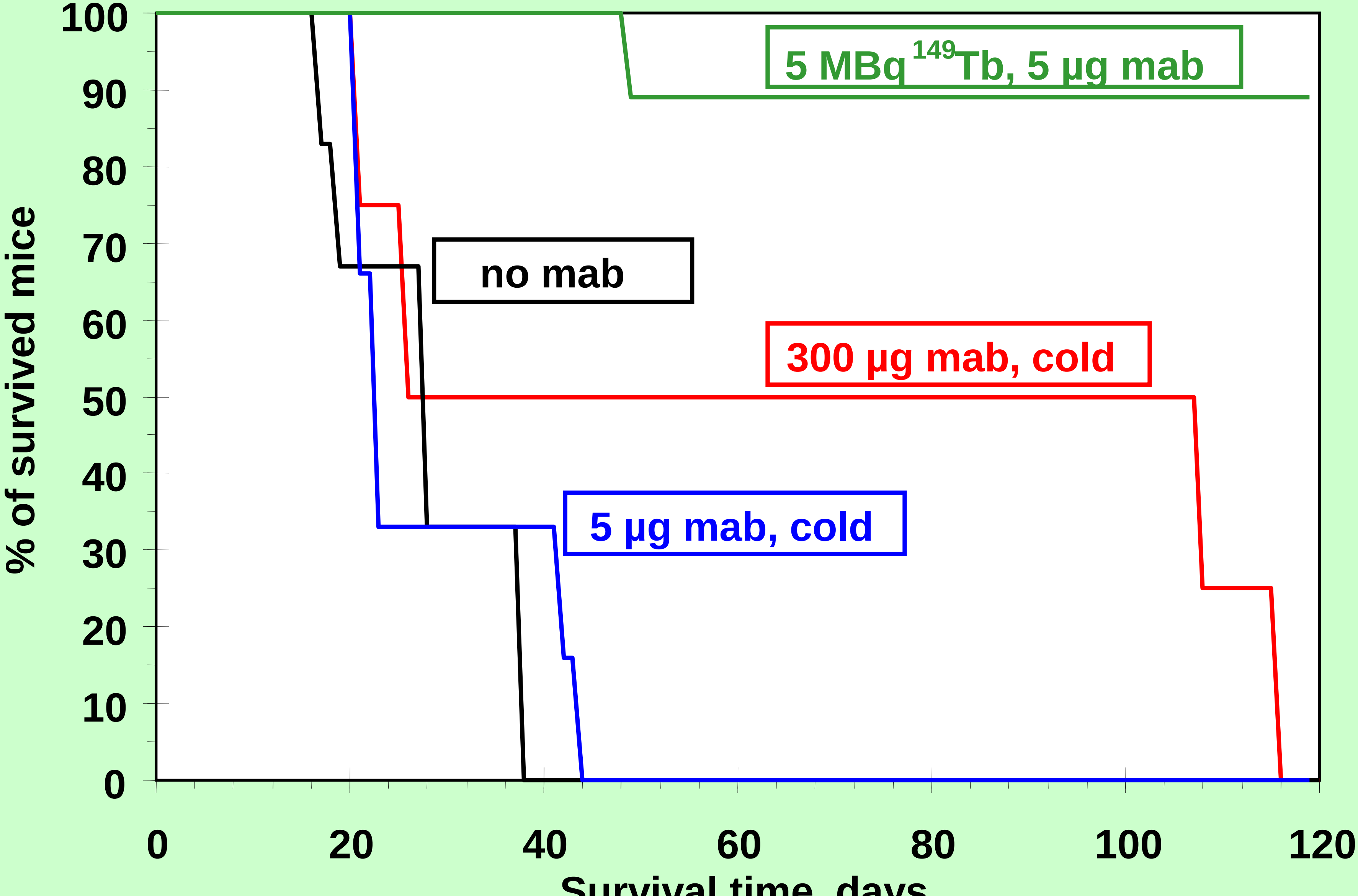
High energy proton induced reactions



Production of ^{149}Tb, ^{152}Tb and ^{155}Tb at ISOLDE



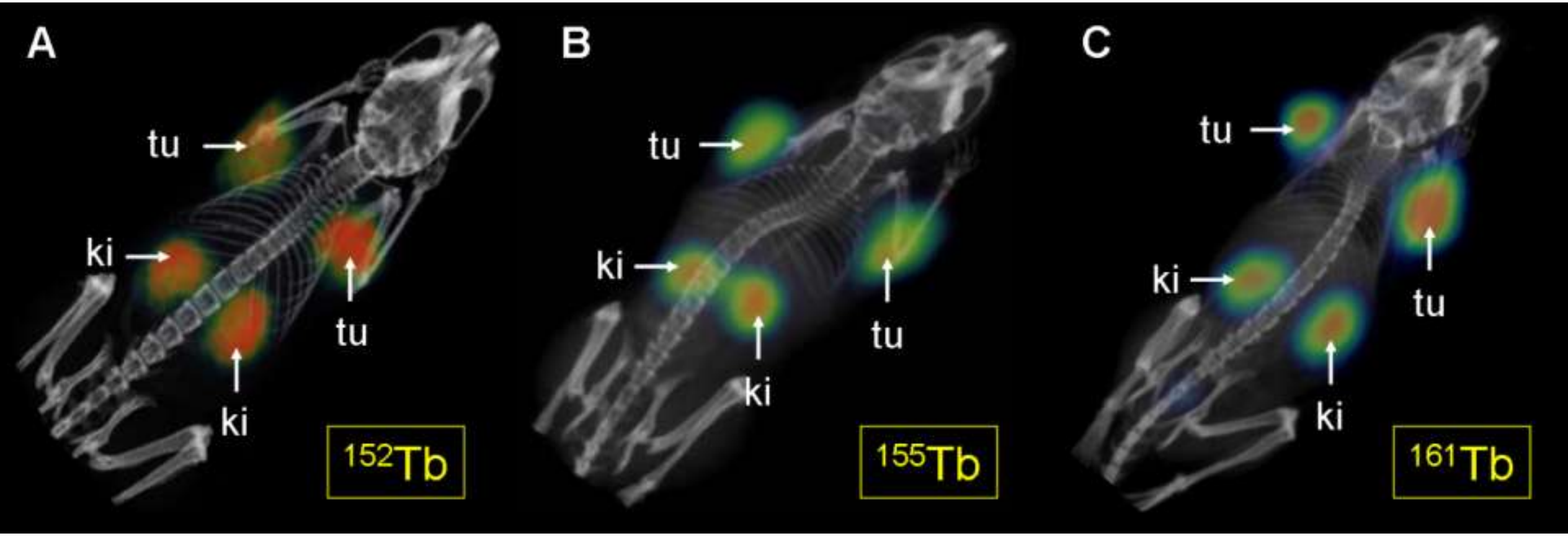
Preclinical study with lymphoma mouse model



G.J. Beyer et al., Eur J Nucl Med Molec Imaging 2004:31;547.

Theranostics with terbium isotopes

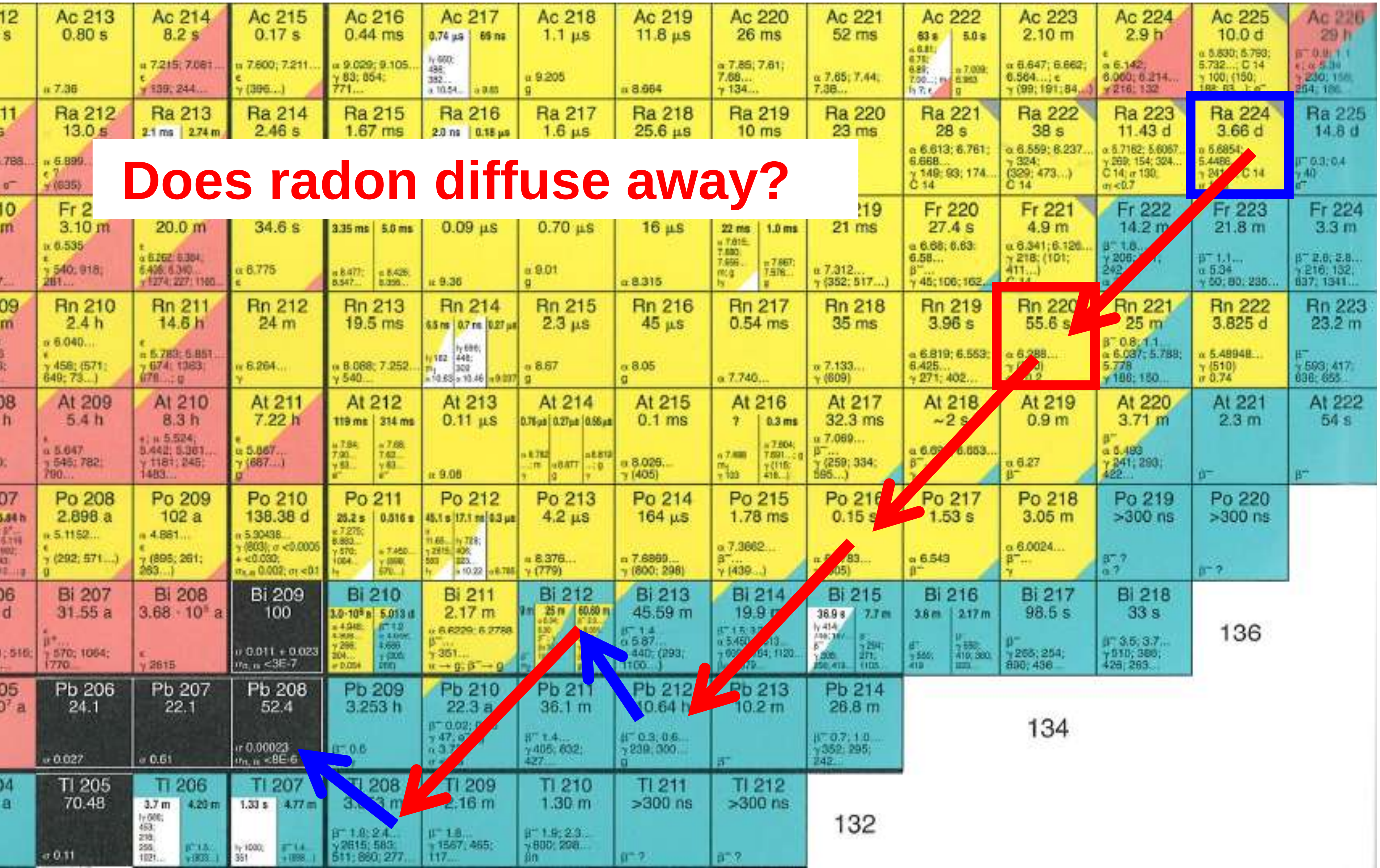
PET *SPECT* *SPECT*



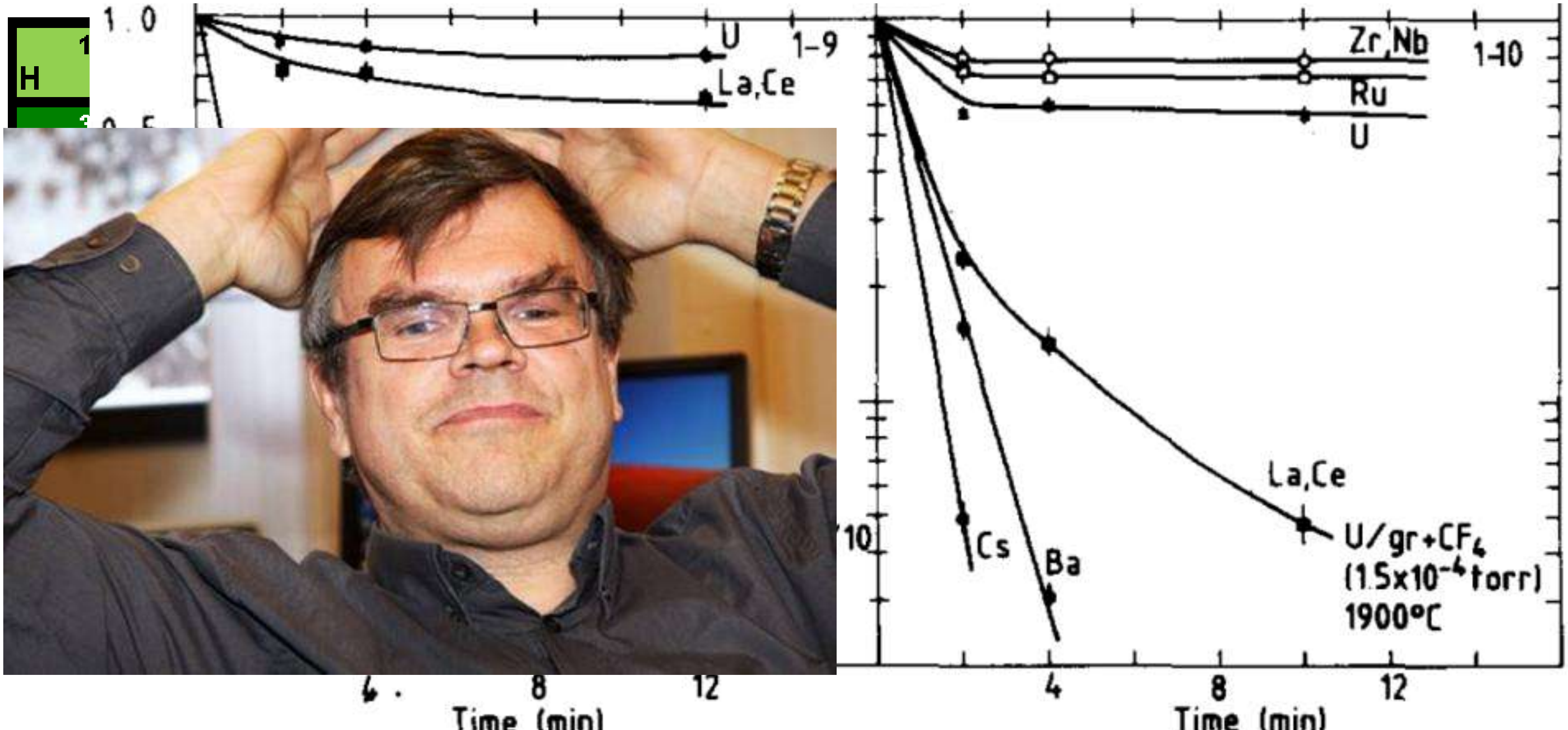
IS528 Collaboration: C. Müller et al., J. Nucl. Med. 2012;53:1951.

Radio-nuclide	Half-life	Daugh-ters	Half-life	Cumulative α/decay	E_{α} mean (MeV)	Range (μm)
Tb-149	4.1 h			0.17	3.97	25
Pb-212	*10.6 h*	Bi-212 Po-212	1.01 h 0.3 μs	1	7.74	65
Bi-212	1.01 h	Po-212	0.3 μs	1	7.74	65
Bi-213	*0.76 h*	Po-213	4 μs	1	8.34	75
At-211	7.2 h	Po-211	0.5 s	1	6.78	55
Ra-223	11.4 d	Rn-219 Po-215 *Pb-211* Bi-211	4 s 1.8 ms *0.6 h* 130 s	4	6.59	>50
Ra-224	3.66 d	Rn-220 Po-216 *Pb-212* Bi-212	56 s 0.15 s *10.6 h* 1.01 h	4	6.62	>50
Ac-225	10.0 d	Fr-221 At-217 *Bi-213* Po-213	294 s 32 ms *0.76 h* 4 μs	4	6.88	>50

Isotopes for targeted alpha therapy



Radioisotopes available at ISOLDE-CERN



90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr

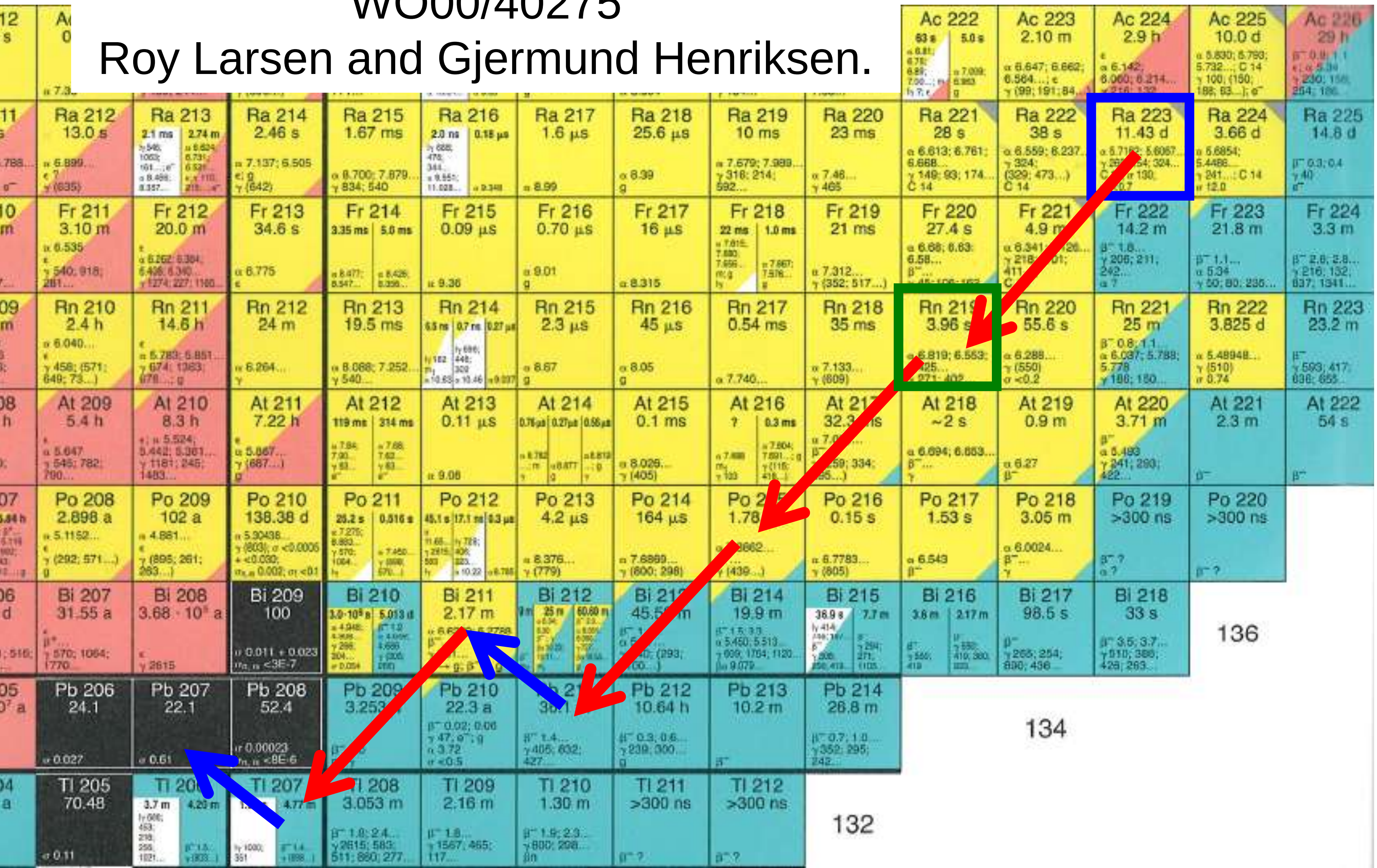
Diffusion and release measurements to develop new beams

e.g. *P. Hoff et al., NIM 221 (1984) 313.*

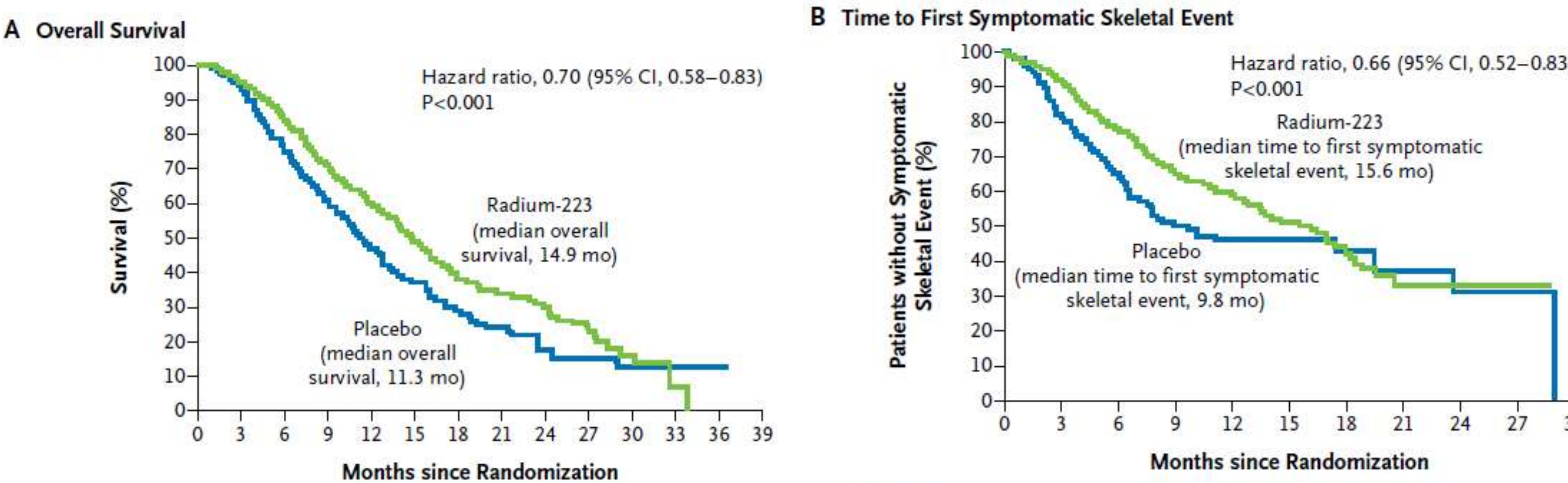
Isotopes for targeted alpha therapy

WO00/40275

Roy Larsen and Gjermund Henriksen.



^{223}Ra: Alpharadin/Xofigo



No. at Risk

Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

No. at Risk

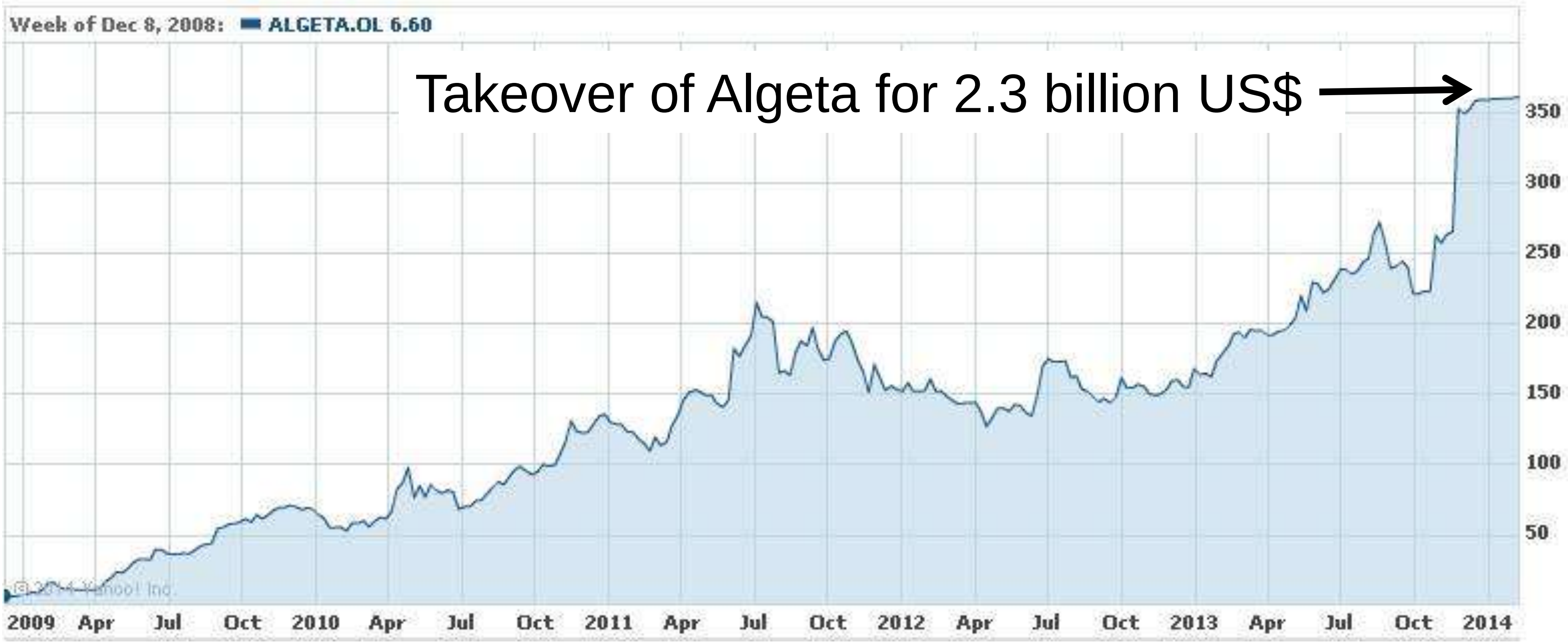
Radium-223	614	496	342	199	129	63	31	8	8	1	0
Placebo	307	211	117	56	36	20	9	7	4	1	0

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Prospects of targeted alpha therapies ?



Bayer HealthCare

SANOFI

AREVA Med

^{212}Pb for Powerful Targeted Therapies

Roche

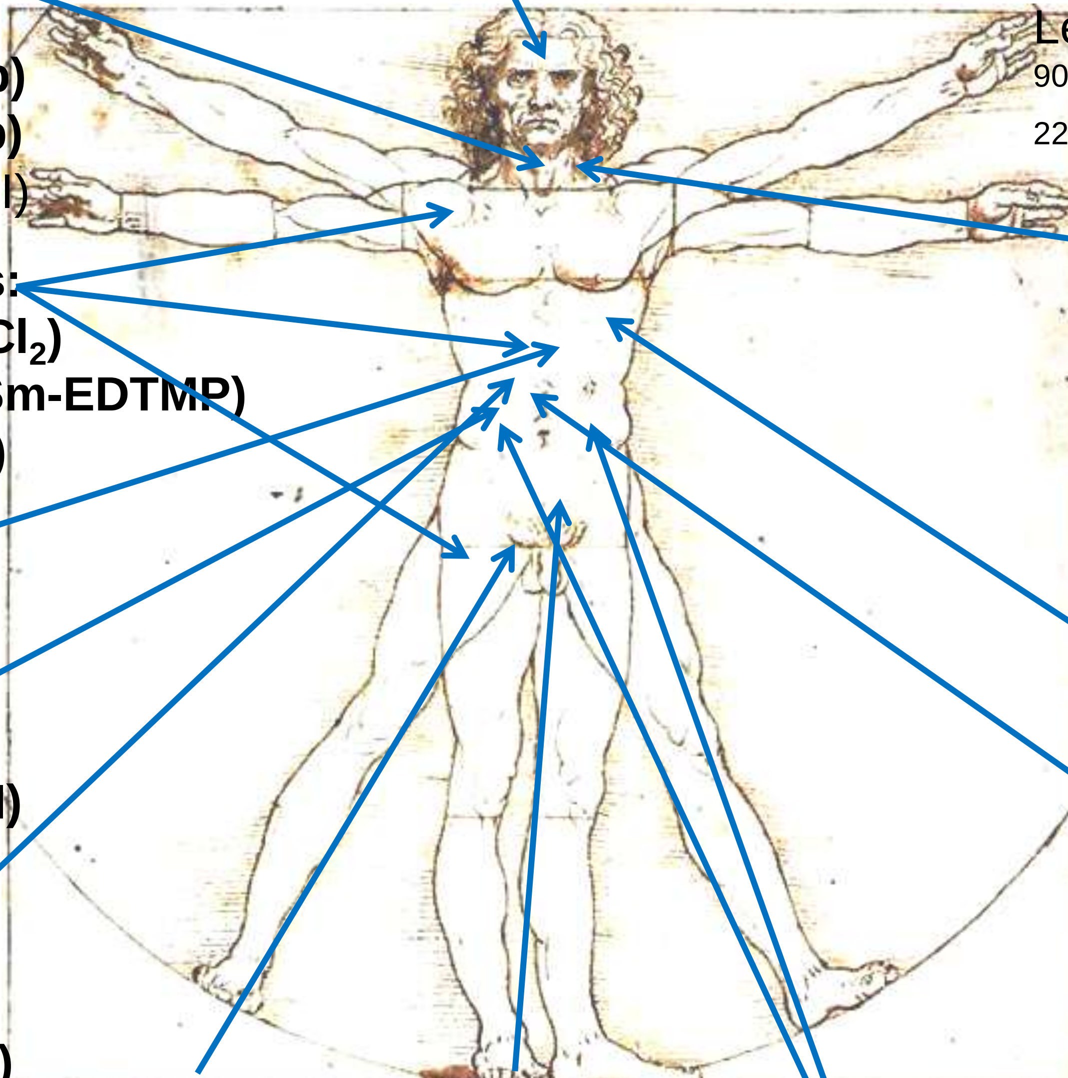
Targeted radionuclide therapies in the clinic

Thyroid: $^{131}I^-$

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

Lymphoma:
Zevalin® (^{90}Y-mab)
Bexxar® (^{131}I-mab)
^{131}I/^{177}Lu-mabs (I/II)

Leukemia, myeloma:
^{90}Y-mab, ^{213}Bi-mab (II)
^{225}Ac-mab



Bone metastases:
Metastron® ($^{90}SrCl_2$)
Quadramet® (^{153}Sm-EDTMP)
Zofigo® ($^{223}RaCl_2$)

Medullary Thyroid:
^{131}I-mab (II)
^{90}Y-pept.

Neuroblastoma:
^{131}I-MIBG

Breast:
^{90}Y-mab, ^{90}Y-pept.
^{212}Pb-mab (I)

Neuroendocrine (GEP-NET):
^{177}Lu-peptides (III)
^{90}Y-peptides

Lung (SCLC):
^{177}Lu-mab (II)

Pancreas:
^{90}Y-mab (II)

Liver (HCC):
Theraspheres® &
SIRspheres® (^{90}Y)
^{188}Re-Lipiodol (II)
^{166}Ho-microspheres

Ovary:
^{212}Pb-mab (I)
^{90}Y/^{177}Lu-mab

Colon & rectum:
^{131}I-mab (II)

Prostate:
^{177}Lu-mab (II)

Kidneys (RCC):
^{90}Y/^{177}Lu-mab (I)

Melamoma:
^{213}Bi-mab(I)

Radionuclides for RIT and PRRT

Radio-nuclide	Half-life	E mean (keV)	Eγ (B.R.) (keV)	Range
Y-90	64 h	934 β	-	**12 mm**
I-131	8 days	182 β	364 (82%)	**3 mm**
Lu-177	7 days	134 β	208 (10%) 113 (6%)	**2 mm**
Tb-161	7 days	154 β 5, 17, 40 e^-	75 (10%)	**2 mm** **1-30 μm**
Tb-149	4.1 h	3967 α	165,..	**25 μm**
Ge-71	11 days	8 e^-	-	**1.7 μm**
Er-165	10.3 h	5.3 e^-	-	**0.6 μm**

cross-fire

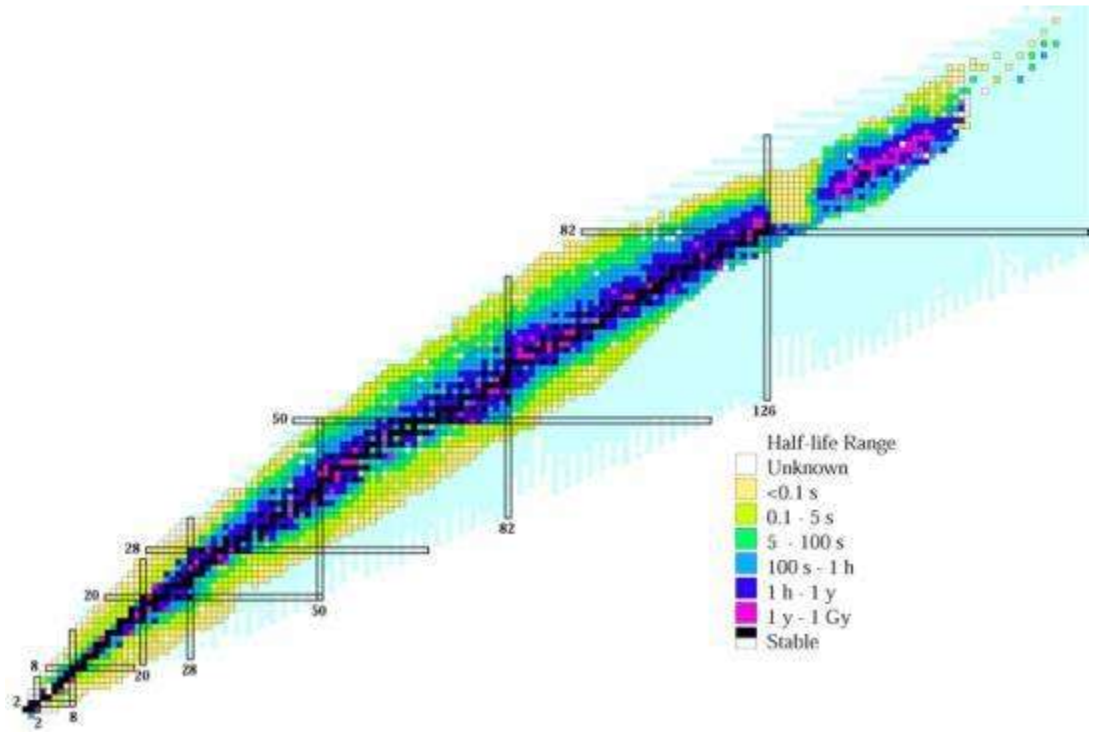
Estab-lished isotopes

Emerging isotopes

R&D isotopes: supply-limited!

localized

Modern, better targeted bioconjugates require shorter-range radiation ⇒ need for adequate (R&D) radioisotope supply.



Paracelsus (1493-1541)

"Many have said of Alchemy, that it is for the making of gold and silver. For me such is not the aim, but to consider only what virtue and power may lie in medicines."

(Edwardes)

500 years later:

"Many have said of nuclear physics, that it is for the making of gold and silver (and other elements') isotopes. For us such is not the only aim, but also to consider what virtue and power may lie in it for medicine."