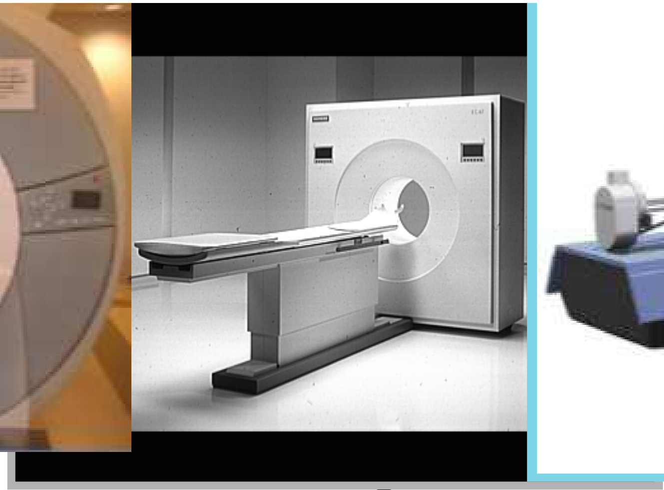
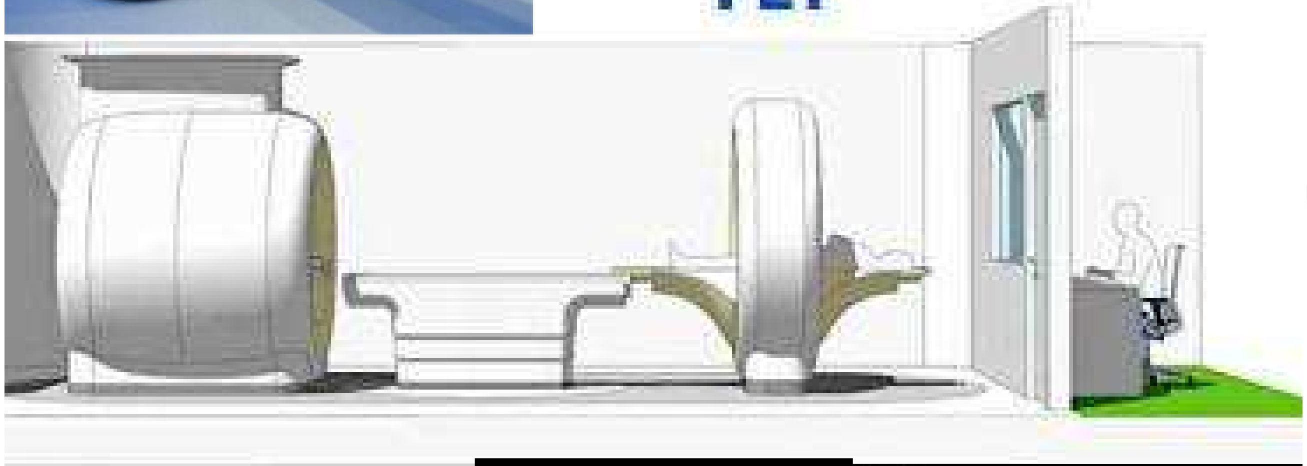
Isotopes for Nuclear Medicine

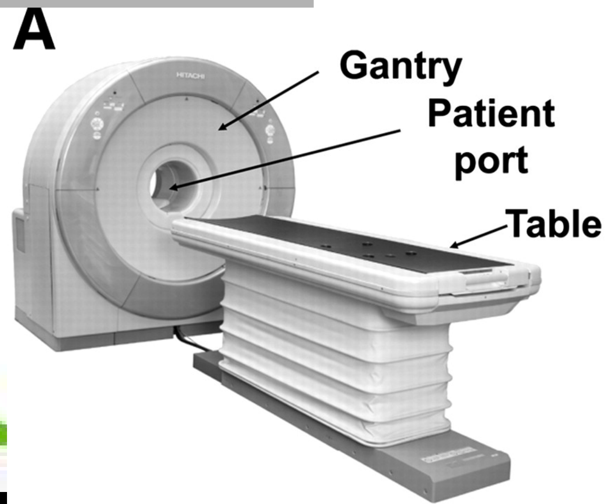
Ulli Köster

Institut Laue Langevin, Grenoble

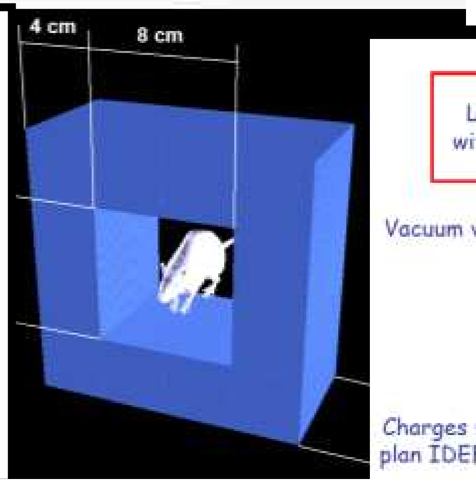
PET

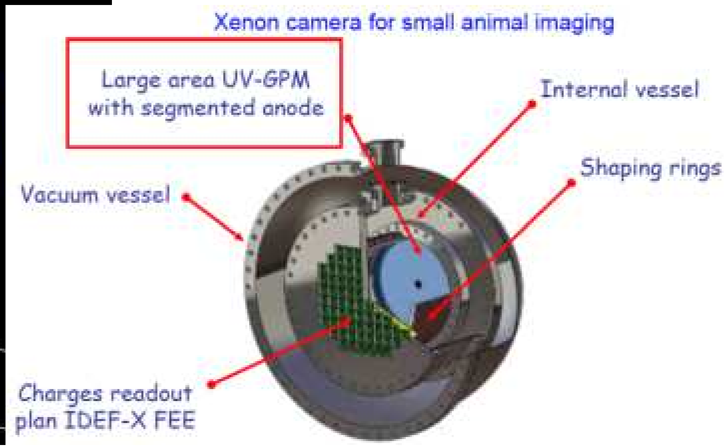





A
Gantry
Patient port
Table


NanoSPECT/CT


4 cm
8 cm


Xenon camera for small animal imaging
Large area UV-GPM with segmented anode
Internal vessel
Shaping rings
Vacuum vessel
Charges readout plan IDEF-X FEE

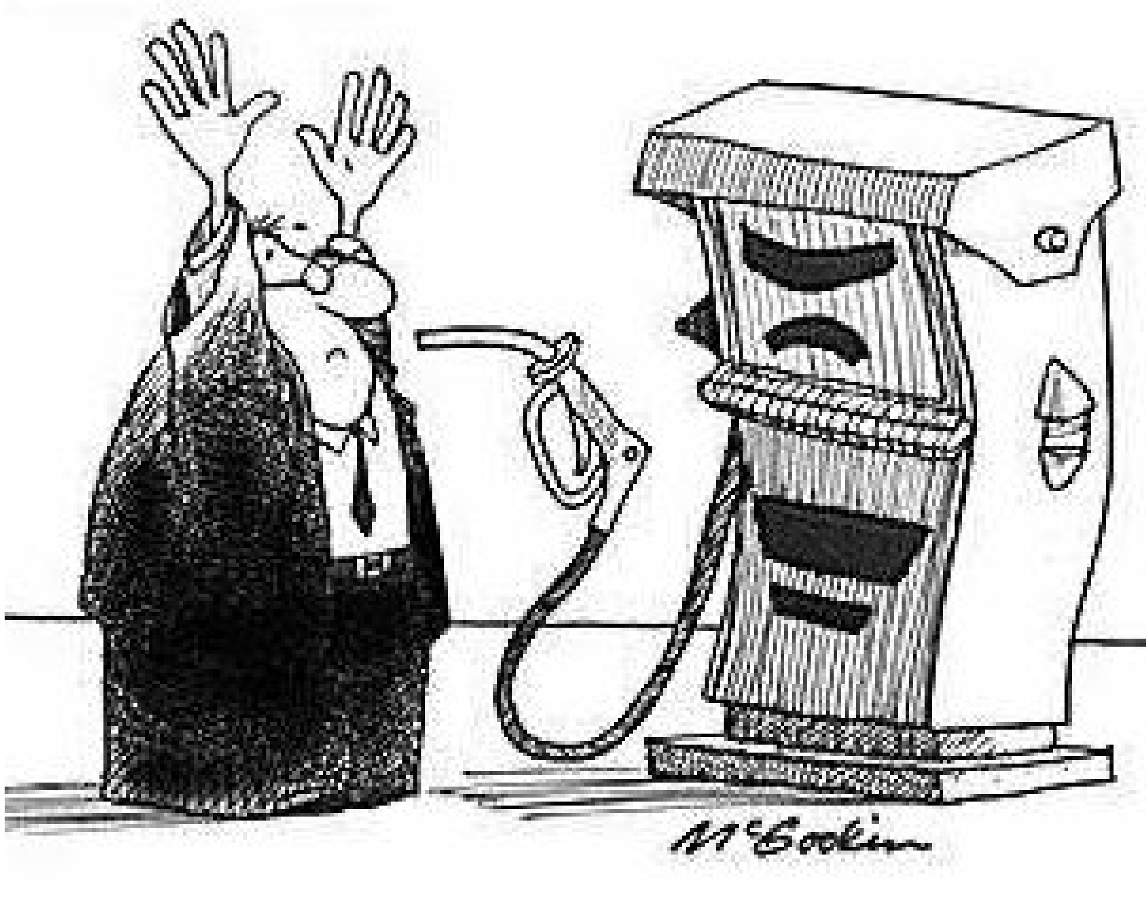

GENEVA
8–18
MARCH
2012
82ND INTERNATIONAL
MOTOR SHOW
AND ACCESSORIES

BENTLEY





Don’t forget the fuel!



Radioisotopes:
the “fuel” for nuclear medicine

1. What is the optimum fuel for an application ?

2. Are we using today the optimum fuel ?

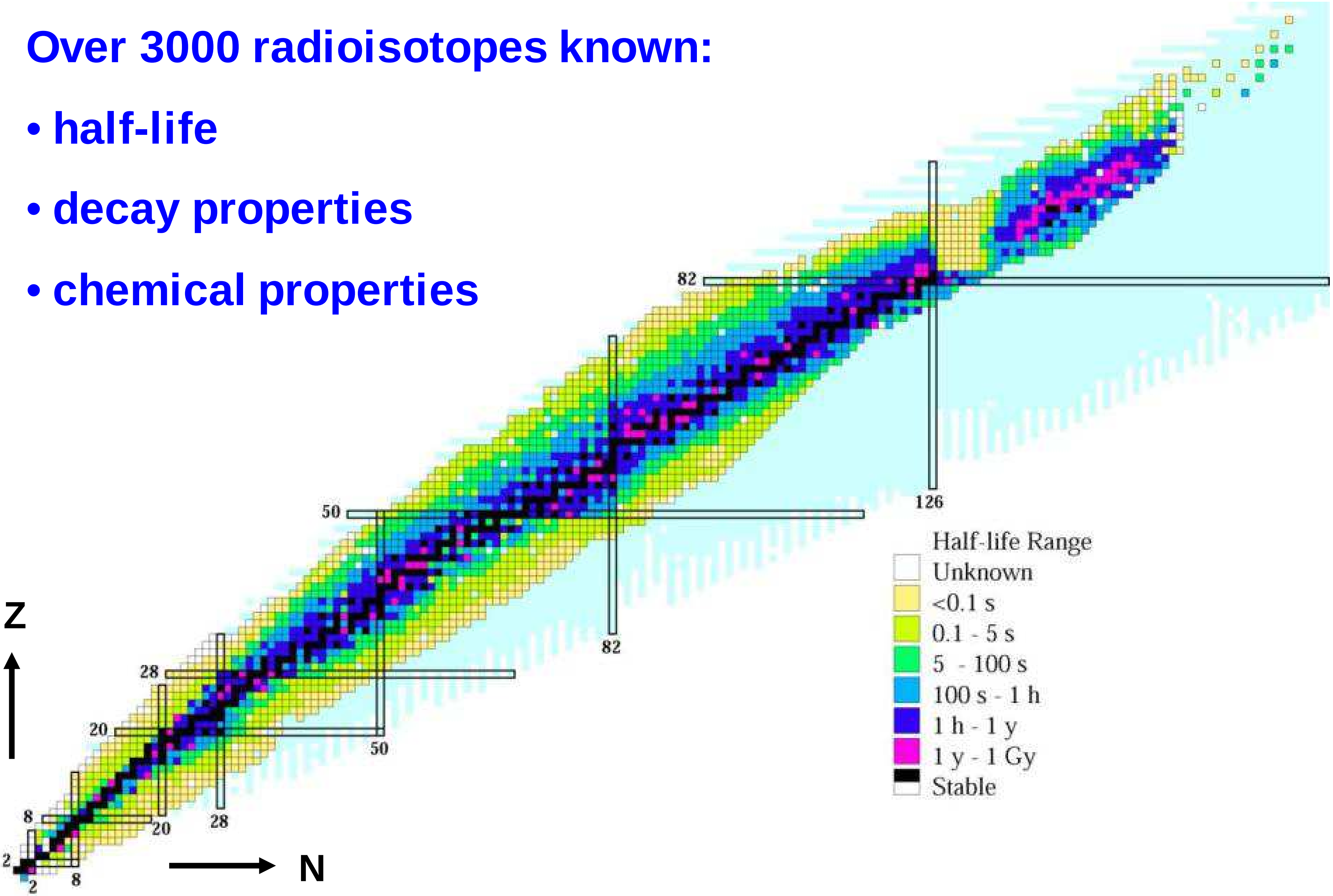
3. Is there sufficient supply of fuel
   at reasonable cost?

4. How reliable is the fuel supply ?

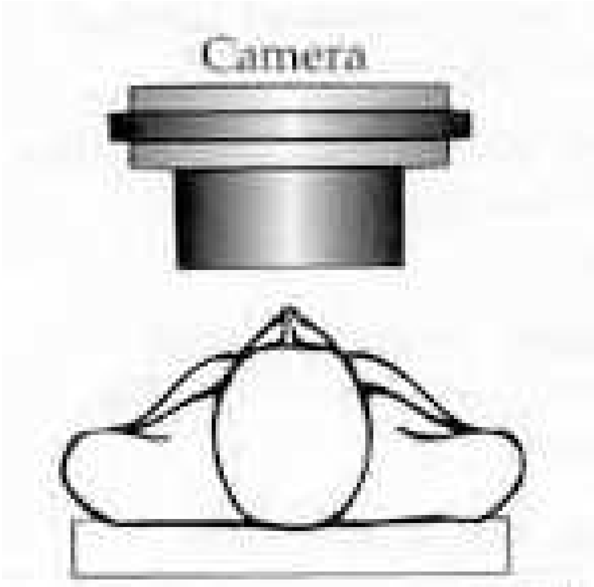
The quest for the optimum isotope

Over 3000 radioisotopes known:

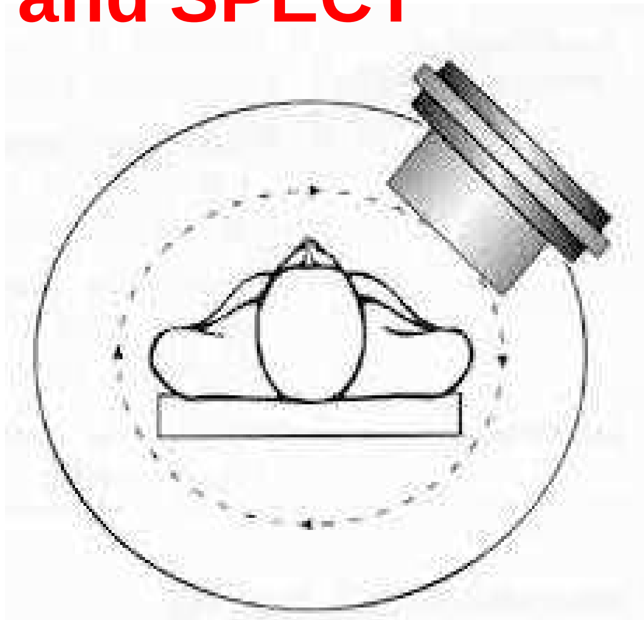
- **half-life**
- **decay properties**
- **chemical properties**



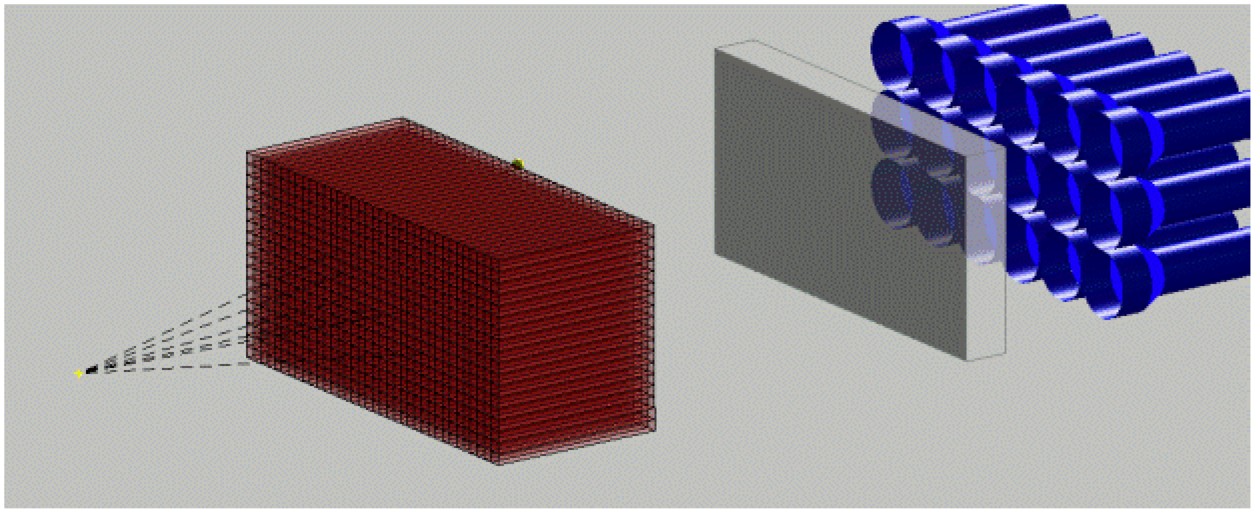
Gamma camera and SPECT



2D: planar scan



3D: SPECT: Single Photon Emission Computer Tomography



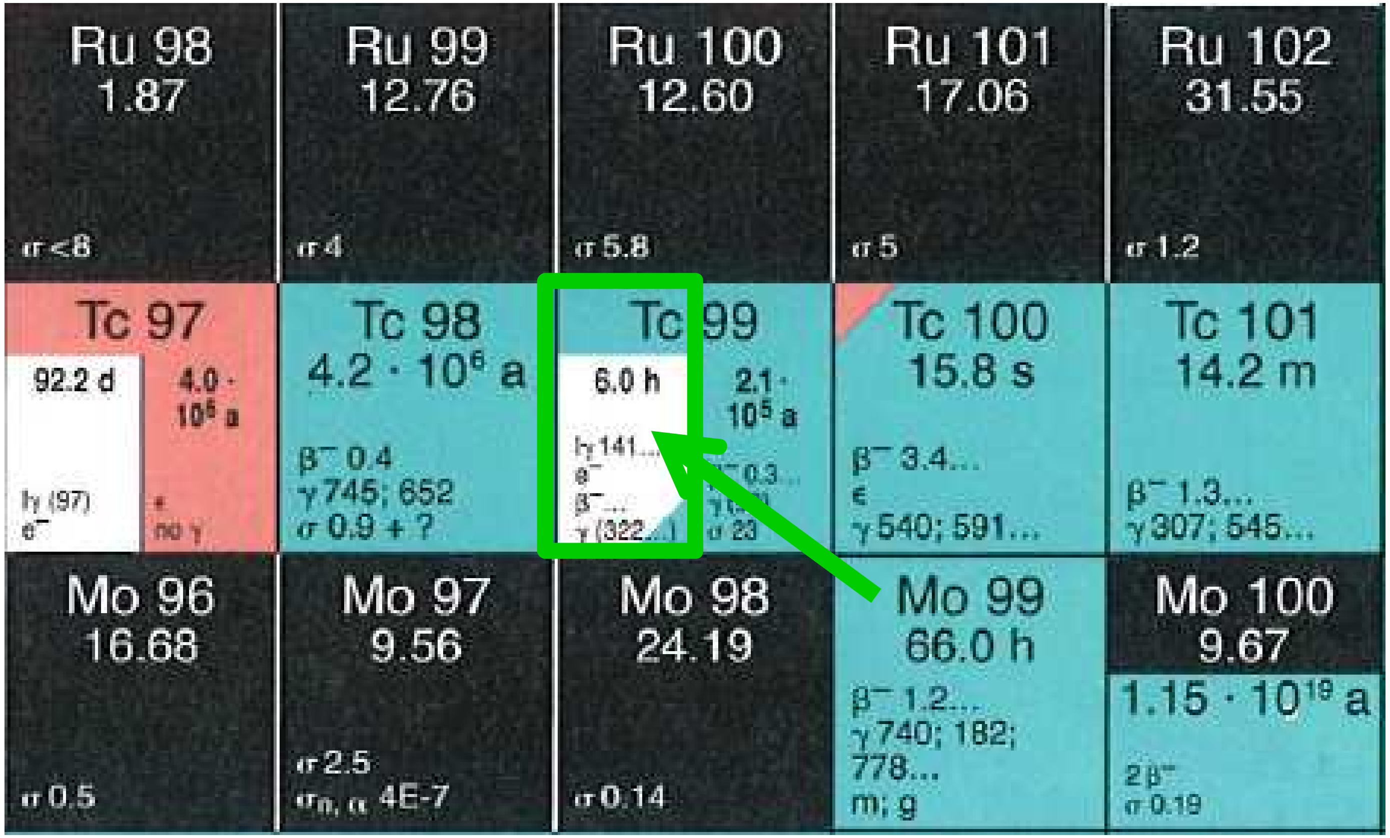
E_γ > 70 keV

absorption in body

E_γ < 300 keV

efficient collimation and detection

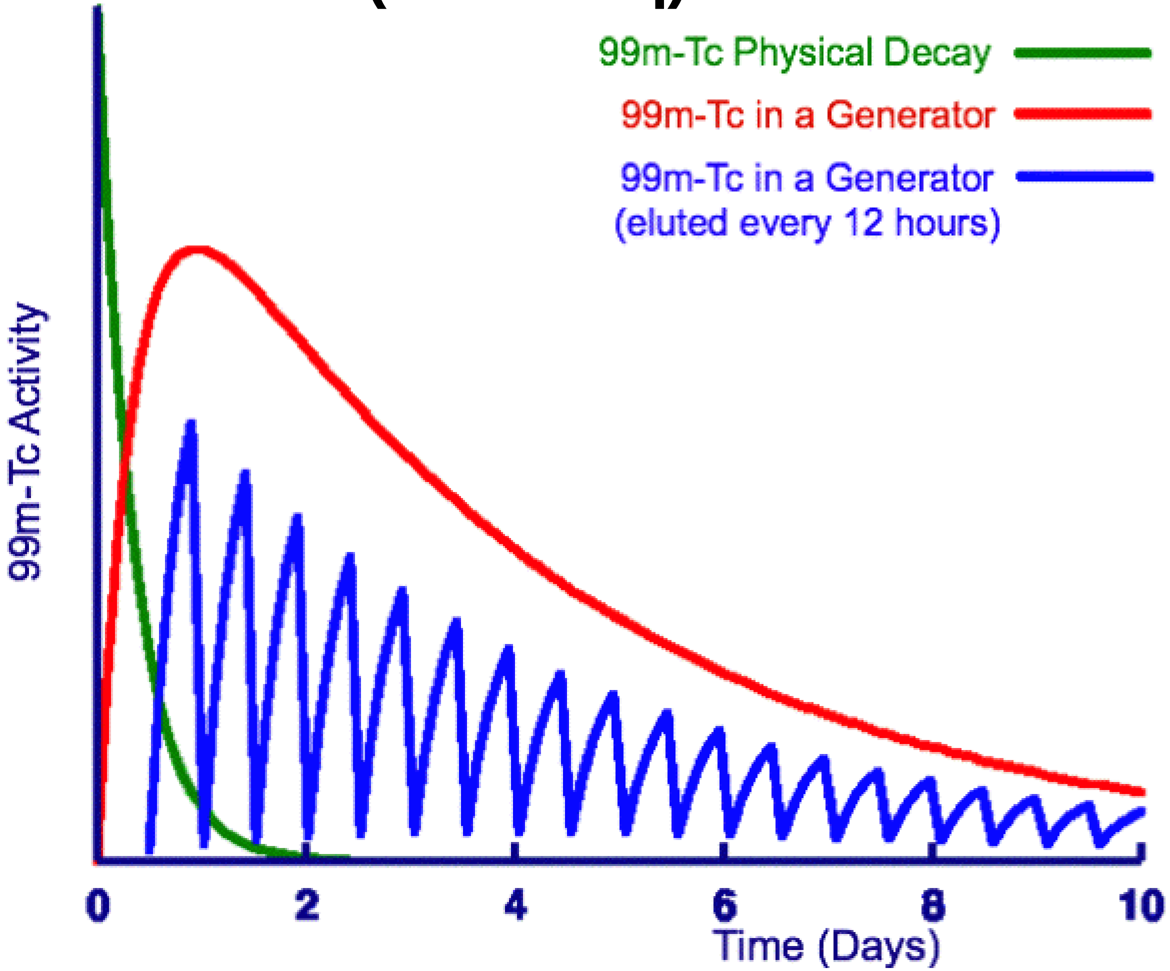
^{99m}Tc: ideal for SPECT and gamma cameras



- **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**

The "technetium cow" ($^{99}Mo/^{99m}Tc$ generator)

- ^{99m}Tc is the most important radionuclide in nuclear medicine (80% of all nuclear medicine applications)
- 30 million applications per year
- 80 000 Ci (3000 TBq) of ^{99}Mo needed per week



BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: December 4, 1958

TO: Addressees Below

FROM: Daniel M. Schaeffer, Head DMS
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."

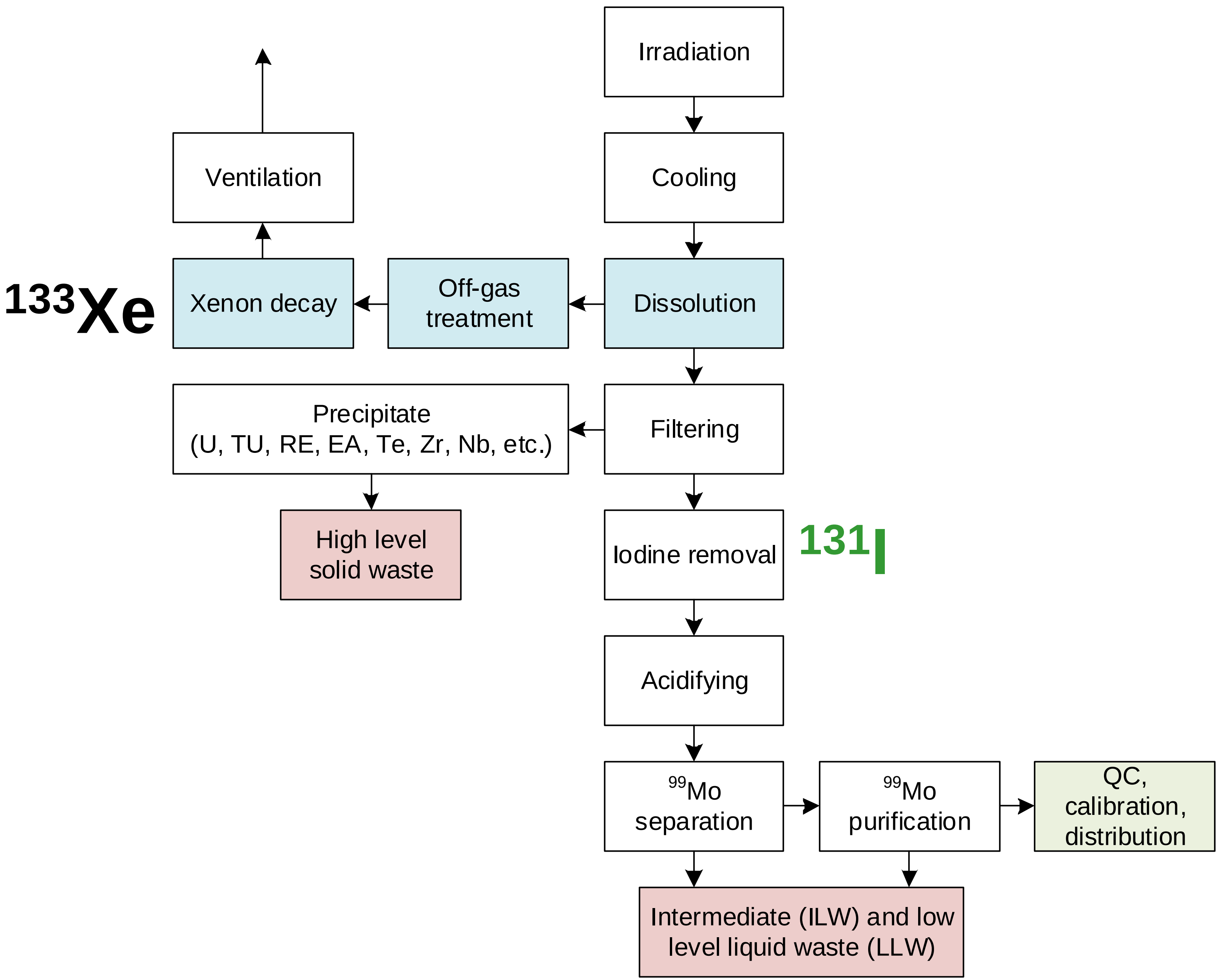
believe that this attitude is significant. We are not aware of a potential market for technetium-99 great enough to encourage one to undertake the risk of patenting in hopes of successful and rewarding licensing. We would recommend against filing on the Tucker, Greene and Murrenhoff separation process."

Fission production

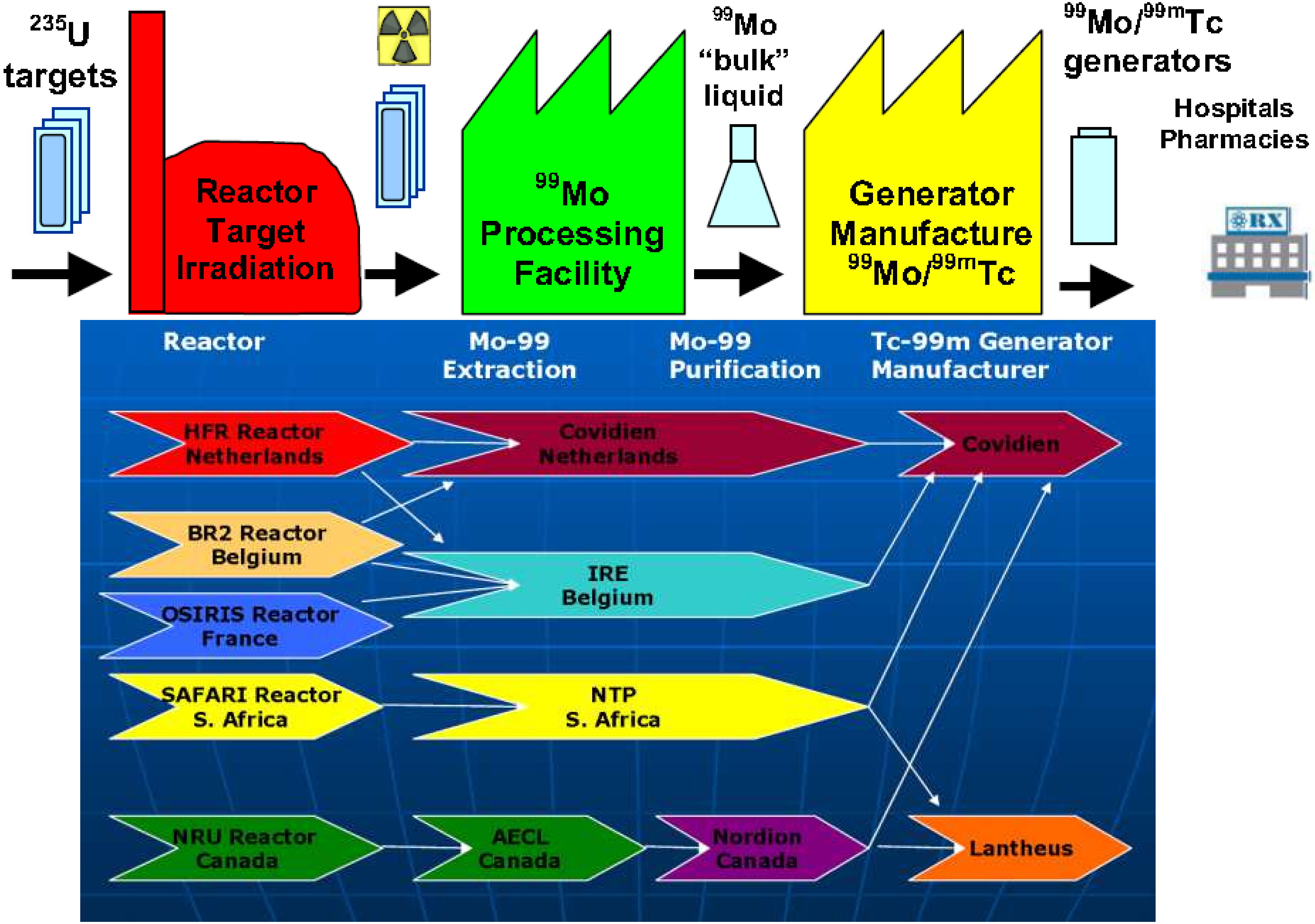
After irradiation, decay and chemical processing:

$^{99}Mo/^{all}Mo \approx$ 10%, i.e. 10% of theoretical specific activity 480 kCi/g

Extraction of fission-moly



The traditional supply chain of $^{99}Mo/^{99m}Tc$



Reactors presently used for ^{99}Mo production with HEU targets

Reactor	Location	Country	Power (MW)	Fuel	Operation (days per year)	Operation since	Typical ^{99}Mo world market share
NRU	Chalk River	Canada	135	LEU	315	1957	40%
HFR	Petten	Nether-lands	45	LEU	290	1961	30%
BR2	Mol	Belgium	100	HEU	115	1961	10%
OSIRIS	Saclay	France	70	LEU	220	1966	3%
SAFARI	Pelindaba	South Africa	20	HEU	315	1965	10%

European hospitals cope with Mo-99 supply crisis

Petten reactor shutdown disrupts nuclear medicine in 20 European countries and U.S. until mid-January

01 December 2008

EUROPE MOLYBDENUM SUPPLY REVIEW

L'inquiétante pénurie d'isotopes pour l'imagerie

Le 02 septembre 2010 à 00h 00 par A. P.

Engpässe in der Tumormedizin

SPIEGEL

Krebsärzten gehen die Diagnosemittel aus

Isotopes médicaux - Crise mondiale à l'horizon

Aucune solution n'existe pour résoudre le problème d'approvisionnement

Pauline Gravel 23 mai 2009 Santé

We Need to Expand Medical Isotope Production!

Isotope shortage means a healthcare crisis

Los Angeles Times

The radioisotope is needed to scan for heart disease and cancer. Two nuclear reactors that produce it have been shut down, severely limiting the supply, and alternatives are scant.

L'OCDE s'inquiète des risques de pénurie d'isotopes médicaux

Isotope shortage to get worse with closing of more reactors

Mangel an medizinisch verwendbaren Isotopen

Frankfurter Allgemeine

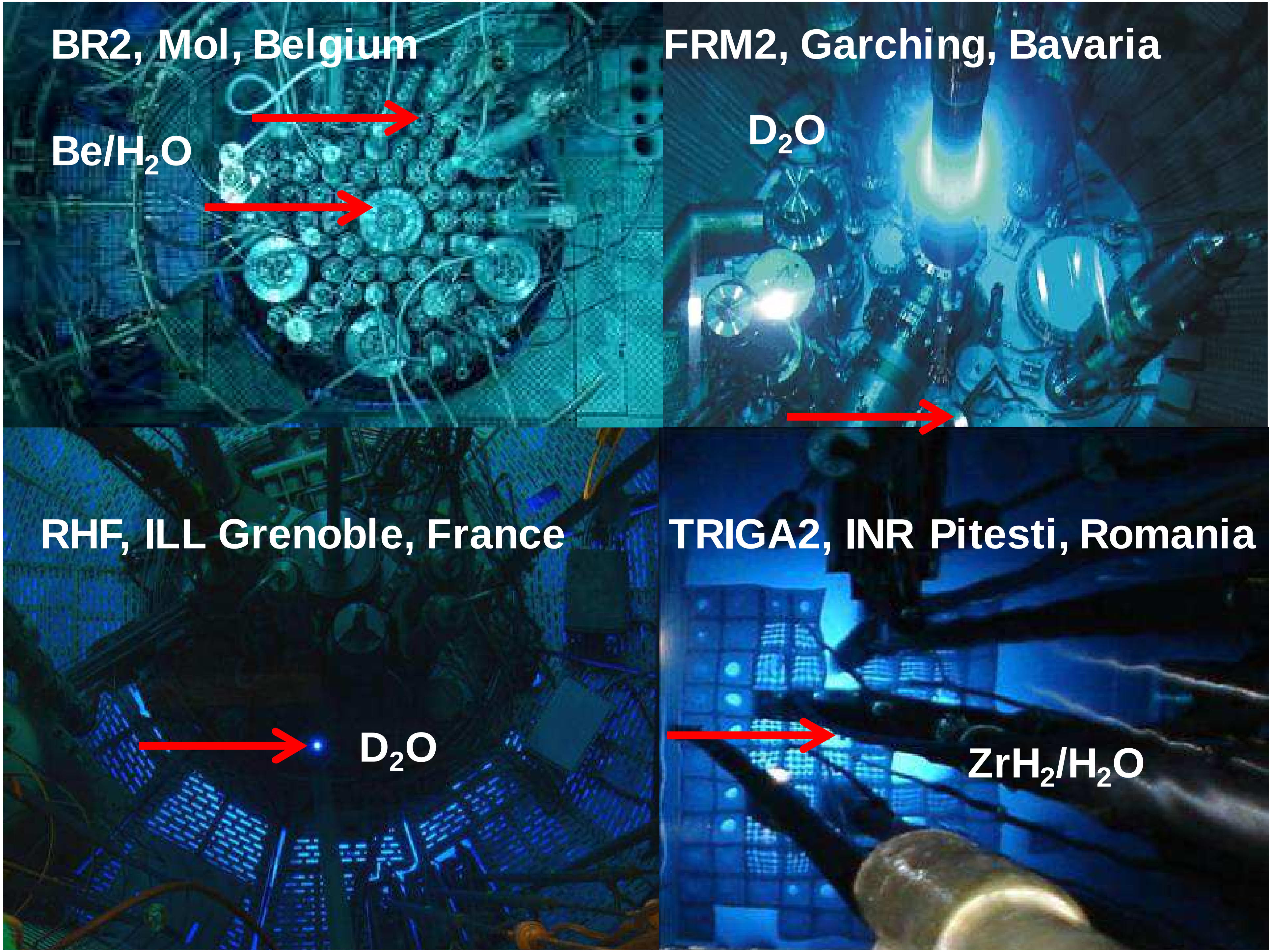
Szintigraphien fallen aus, für Februar droht der Notstand

Mo-99 crisis

^{99}Mo production by neutron capture

Due to very low (n_{th},γ) cross-section of 0.13 b a very high neutron flux is needed to reach the required specific activity!

2.2 Ci/g saturation activity in 1E14 n/cm^2/s flux



BR2, Mol, Belgium
Be/H_2O
FRM2, Garching, Bavaria
D_2O
RHF, ILL Grenoble, France
D_2O
TRIGA2, INR Pitesti, Romania
ZrH_2/H_2O

Results of test irradiations

Reactor	Power (MW)	Position	Thermal flux (cm^{-2}/s)	Irrad. time (d)	Specific activity at EOI (GBq/g)	(Ci/g)	Epi-thermal gain
ILL	54	V4 (3)	1.2E+15	6.8	951	26	22%
ILL	54	V4 (4)	1.1E+15	8	838	23	8%
BR2	68	H1 (300°)	1.0E+15	20.4	(2800)	(76)	(254%)
BR2	68	F46	3.6E+14	7	369	10	55%
TRIGA II	14	XC-1	2.6E+14	8.1	350	9.4	91%
FRM2	20	KBA1	1.3E+14	7	86	2.3	9%

How to produce 1000 "6-d-Ci" [50% of European weekly need]

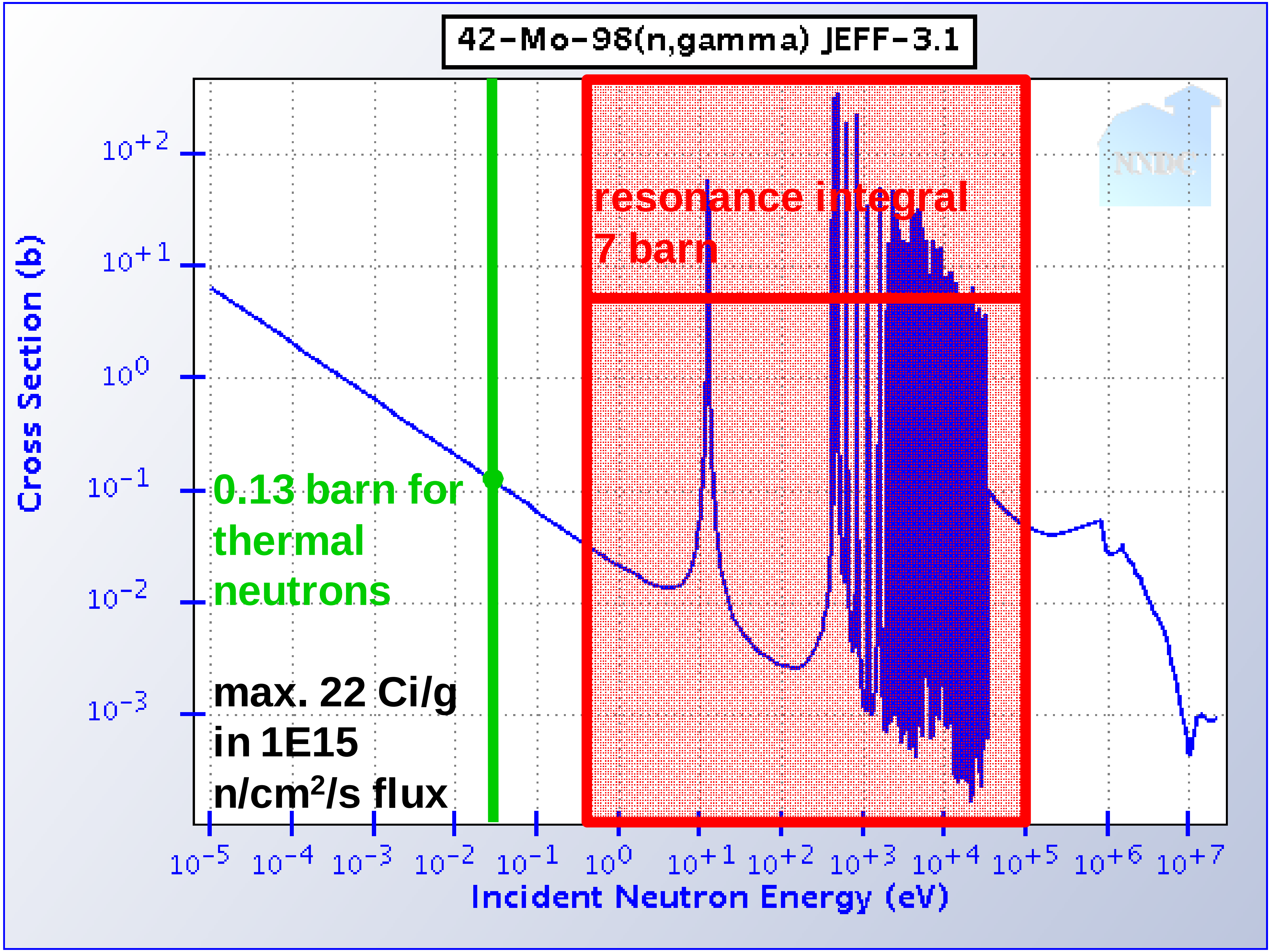
7 d irradiation, 2 d processing+shipping, 6 d use

360 g ^{98}Mo at ILL: 2 capsules metallic Mo or 8 caps. MoO_3

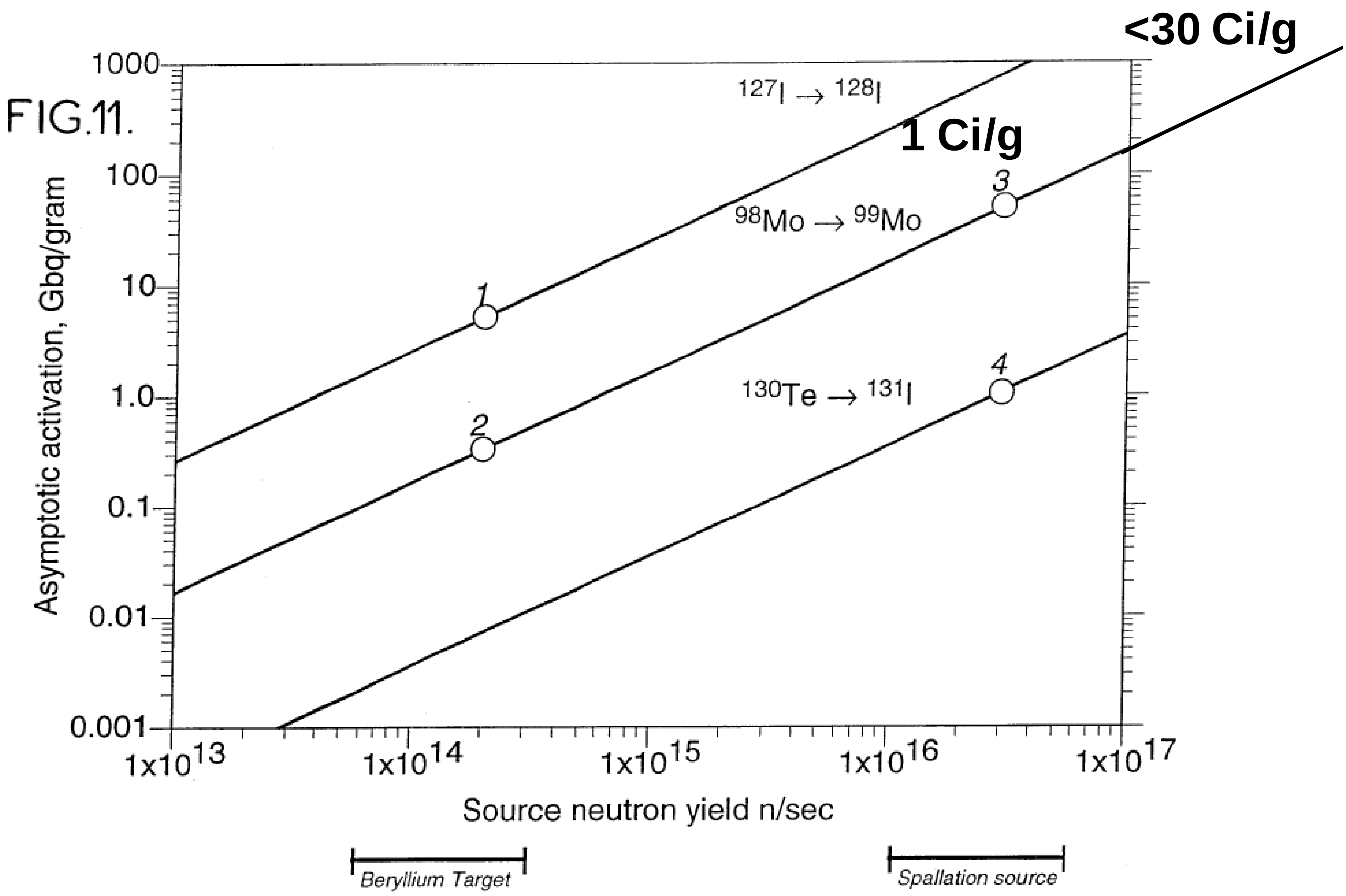
<400 g ^{98}Mo at BR2 (H1): 2 caps. metallic Mo or 8 caps. MoO_3

1200 g ^{98}Mo at BR2 (F46): 7 caps. met. Mo or 26 caps. MoO_3

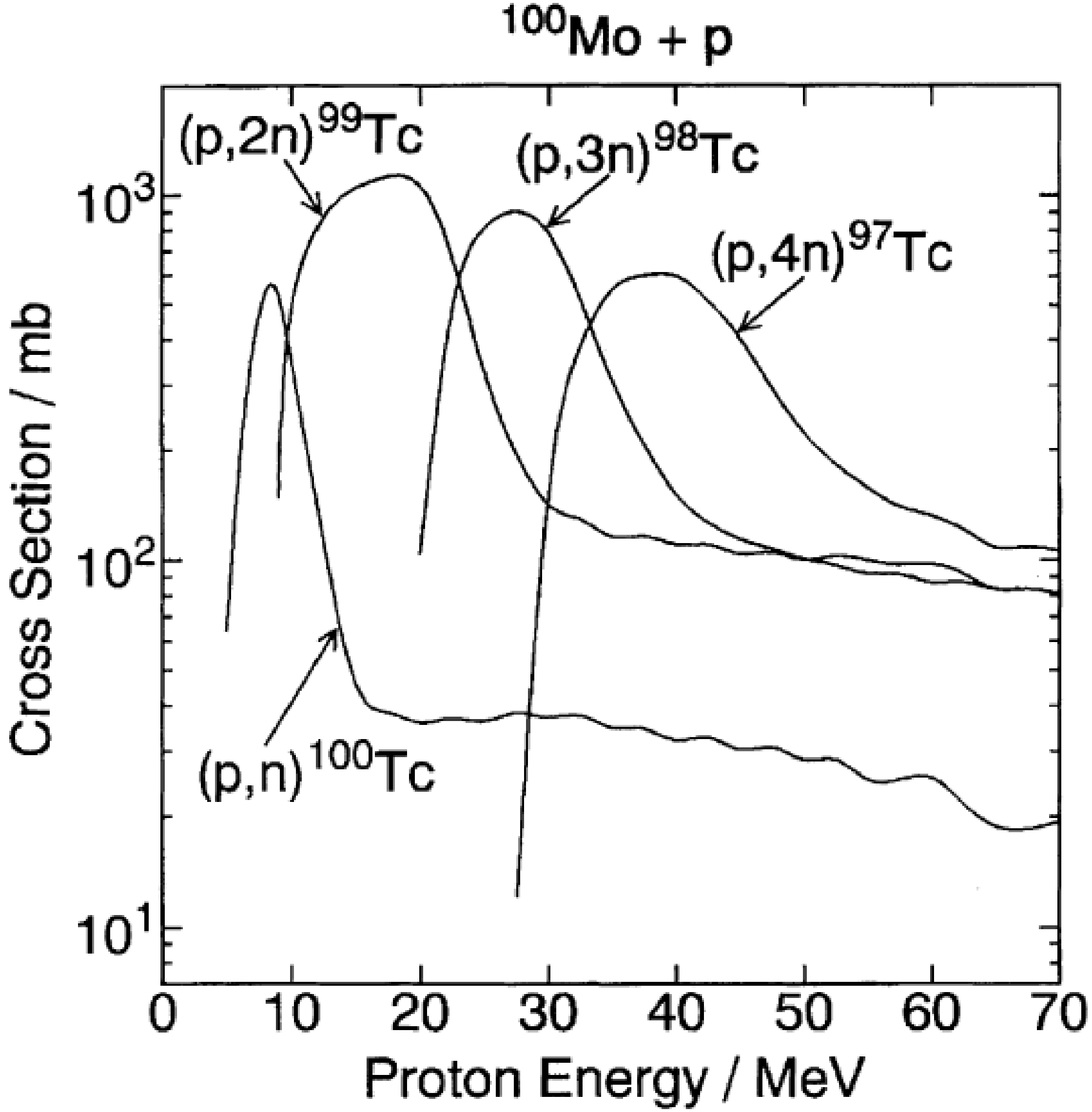
1600 g ^{98}Mo at TRIGA2: >9 caps. met. Mo or 36 caps. MoO_3


42-Mo-98(n,gamma) JEFF-3.1
Cross Section (b)
Incident Neutron Energy (eV)
resonance integral
7 barn
0.13 barn for
thermal
neutrons
max. 22 Ci/g
in 1E15
n/cm²/s flux
NNDC

Adiabatic Resonance Crossing



Ru 94 51.8 m
Ru 95 1.65 h
Ru 96 5.54
Ru 97 2.9 d
Ru 98 1.87
Ru 99 12.76
Ru 100 12.60
Ru 101 17.06
Ru 102 31.55
Ru 103 39.35 d
Tc 93
Tc 94
Tc 95
Tc 96
Tc 97
Tc 98 4.2 · 10^6 a
Tc 99
Tc 100 15.8 s
Tc 101 14.2 m
Tc 102
Mo 92 14.77
Mo 93
Mo 94 9.23
Mo 95 15.90
Mo 96 16.68
Mo 97 9.56
Mo 98 24.19
66.0 h
Mo 100 9.67
1.15 · 10^19 a
Mo 101 14.6 m
Nb 91
Nb 92
Nb 93
Nb 94
Nb 95
Nb 96 23.4 h
Nb 97
Nb 98
Nb 99
Nb 100
Zr 90 51.45
Zr 91 11.22
Zr 92 17.15
Zr 93 1.5 · 10^6 a
Zr 94 17.38
Zr 95 64.0 d
Zr 96 2.80
3.9 · 10^19 a
Zr 97 16.8 h
Zr 98 30.7 s
Zr 99 2.1 s
Y 89
Y 90
Y 91
Y 92 3.54 h
Y 93 10.1 h
Y 94 18.7 m
Y 95 10.3 m
Y 96
Y 97
Y 98

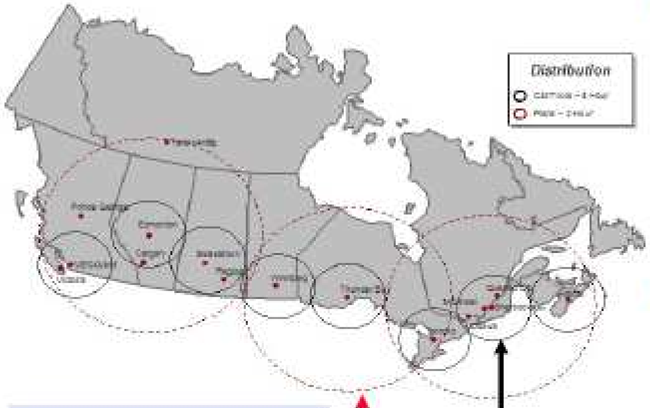


Direct, decentralized production of ^{99m}Tc requires enriched targets and <30 MeV protons.
22 MeV p, 0.1 mA: 10 Ci ^{99m}Tc at saturation.

SCK•CEN
STUDIECENTRUM VOOR KERNENERGIE
CENTRE D'ÉTUDE DE L'ÉNERGIE NUCLÉAIRE

4. New projects for Mo-99 and Tc-99m production

CANADA >>> Direct ^{99m}Tc production by cyclotron : ^{100}Mo(p,2n)^{99m}Tc



4 hours by car or by truck

2 hours by plane

- In July 2009, Advanced Cyclotron Systems Inc. (**ACSI**), together with several Canadian universities and research centres, proposed to develop commercial scale production of **Tc-99m in Canada** using cyclotrons as an alternative to the reactor produced ^{99}Mo/^{99m}Tc (NRU will stop producing Mo-99 in 2016).
- The research and development activities are focused on the development of commercial, cost efficient production of Tc-99m using high-current cyclotrons (18MeV/300µA) manufactured in Canada by ACSI.
  - Low cross sections
  - Mo-100 not yet commercially available, recycling mandatory
- The **network of cyclotron centres** would not only supply Tc-99m by direct route, but would also have the capacity to provide a full spectrum of PET and SPECT radioisotopes such as F-18, Cu-64, I-123, I-124, Ge-68.

Back to the roots ?

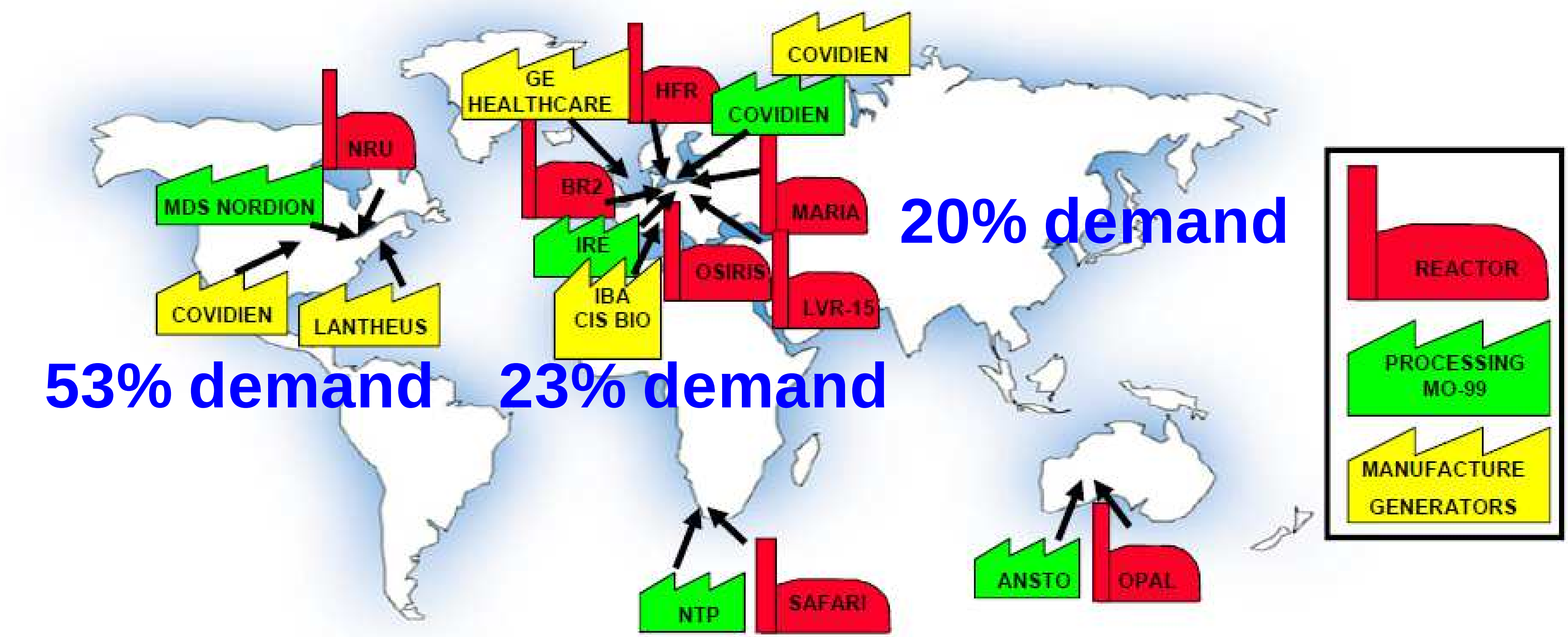
Original discovery of Tc in cyclotron-irradiated Mo !

C. Perrier, E. Segrè, J. Chem. Phys. 5 (1937) 712.

Alternative methods of producing ^{99}Mo

1. Neutron irradiation $^{98}Mo(n,\gamma)$
2. Liquid core reactor $^{235}U(n,f)$
3. Cyclotron bombardment $^{100}Mo(p,pn)$
4. Photo-nuclear reaction $^{100}Mo(\gamma,n)$
5. Photo-fission $^{238}U(\gamma,f)$
6. Fast neutrons $^{100}Mo(n,2n)$
7. Spallation source: $^{98}Mo(n,\gamma)$ with adiabatic resonance crossing
8. Accelerator driven subcritical assembly $^{235}U(n,f)$
9. Direct ^{99m}Tc production by $^{100}Mo(p,2n)$

2. The current Mo-99/Tc-99m supply situation



^{99}Mo Global Supply Chain

NEA
Nuclear Energy Agency

JUNE 2011

Nuclear Energy in Perspective

The Path to a Reliable Supply of Medical Radioisotopes

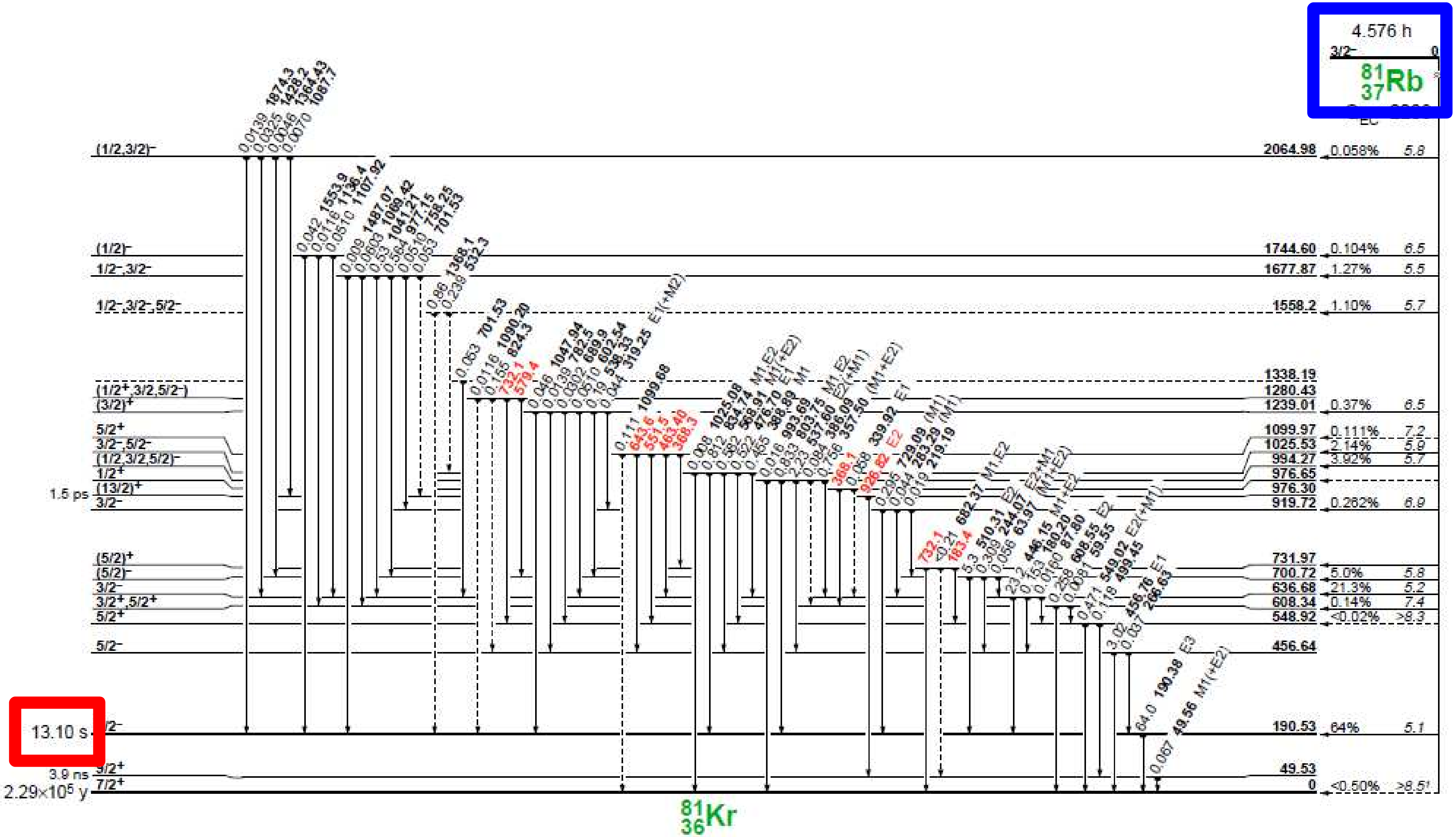
The producing reactor gets only 0.26 EUR per ^{99m}Tc patient dose, similar to the price of a single cheap pill.

	Irradiation value within final radiopharmaceutical price (EUR)	Irradiation value as % of final procedure costs
Pre-shortage situation	0.26	0.11
Required for economic sustainability	0.33-2.39	0.14-0.97

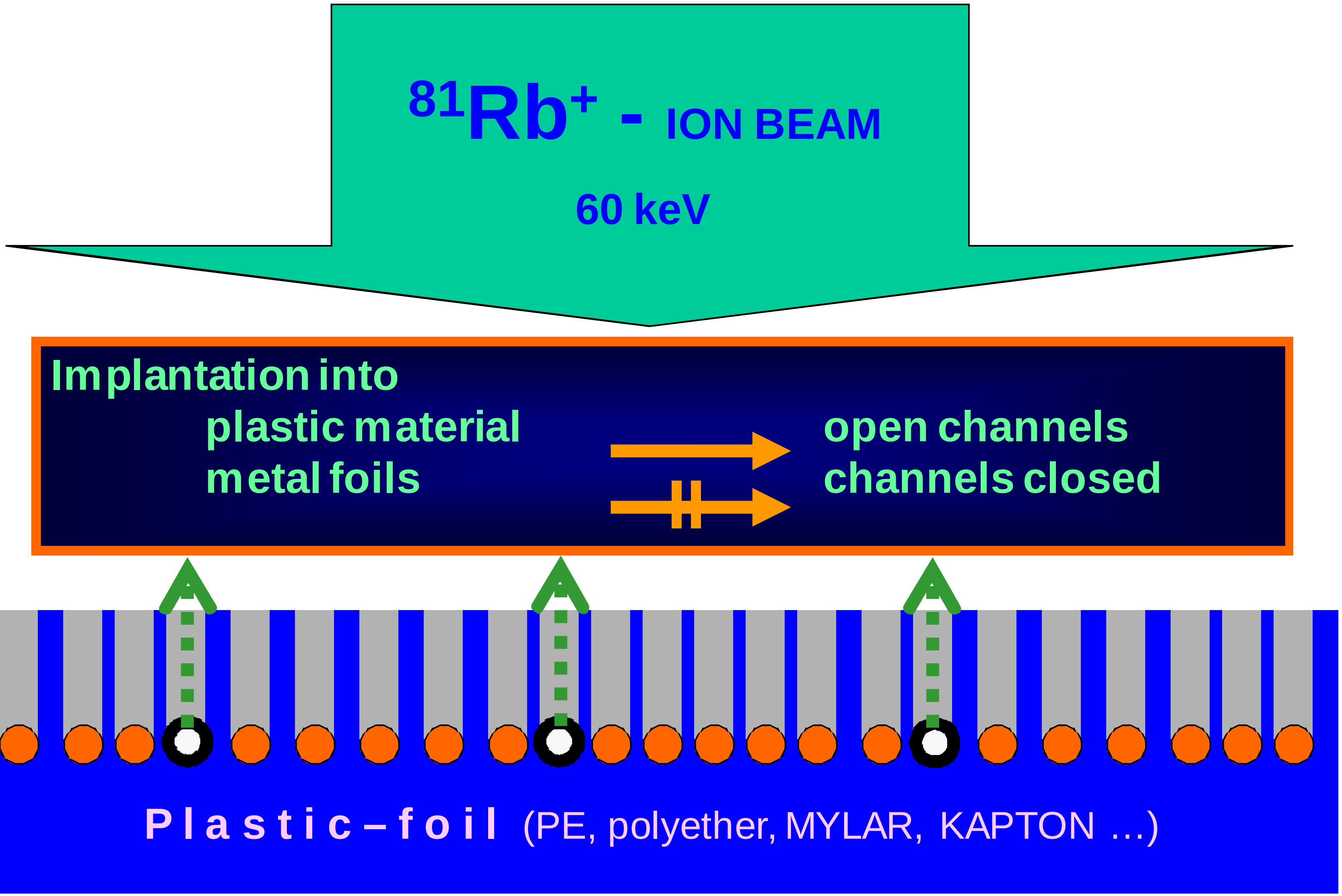
SPECT Tracer

Radio-nuclide	Half-life (h)	Eγ (keV)	Branching ratio γ (%)	Decay type
Ga-67	78	93	42	EC
Kr-81m	0.004	190	64	IT
Tc-99m	**6**	**141**	**89**	**IT**
In-111	**67**	**245**	**94**	**EC**
I-123	**13**	**159**	**83**	**EC**
Xe-133	126	81	38	β^-
Tl-201	**73**	**167**	**10**	**EC**
I-131	192	364	82	β^-
Lu-177	161	208	10.4	β^-

^{81}Rb/^{81m}Kr generator

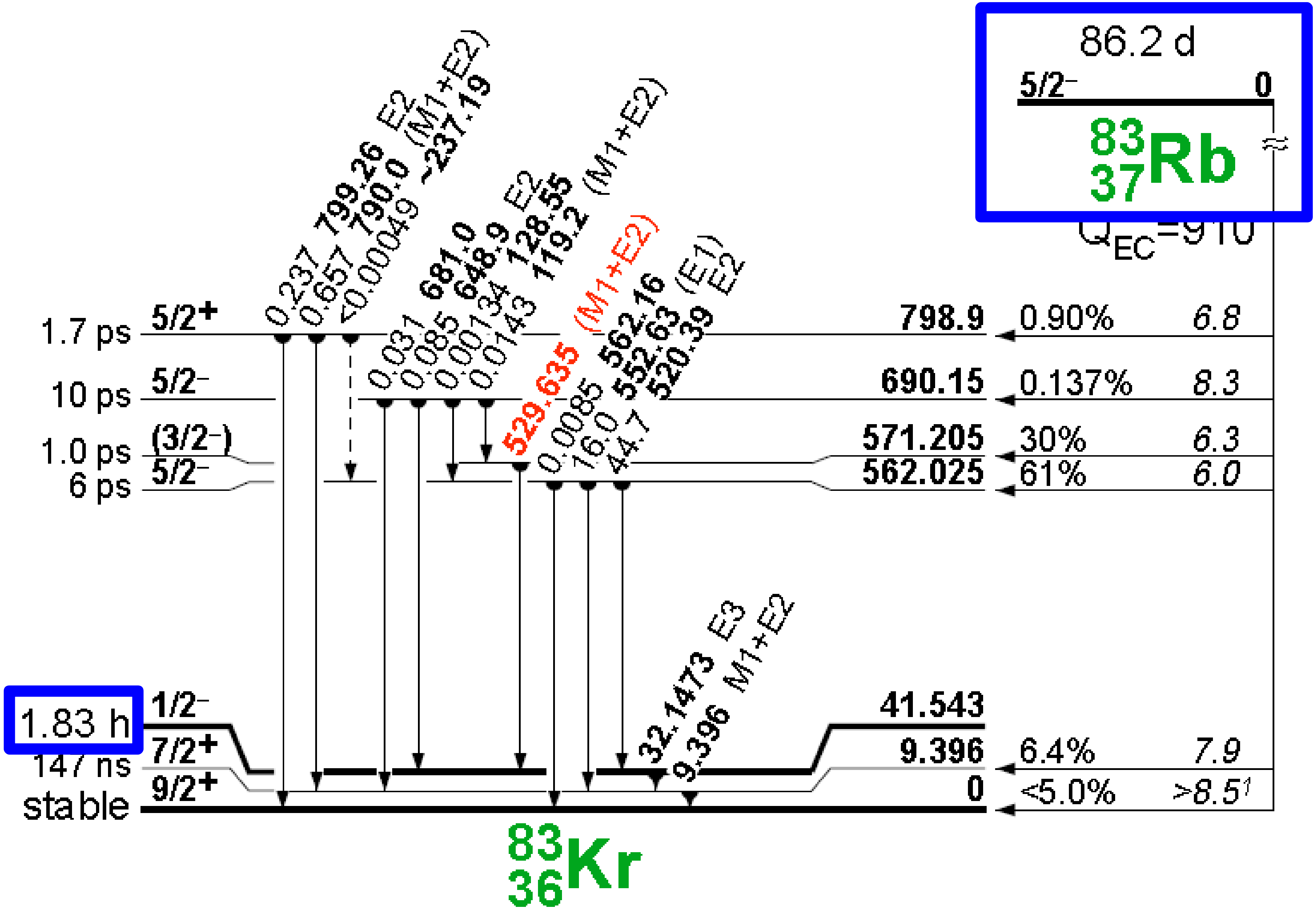


Implantation type ^{81}Rb / ^{81m}Kr generator



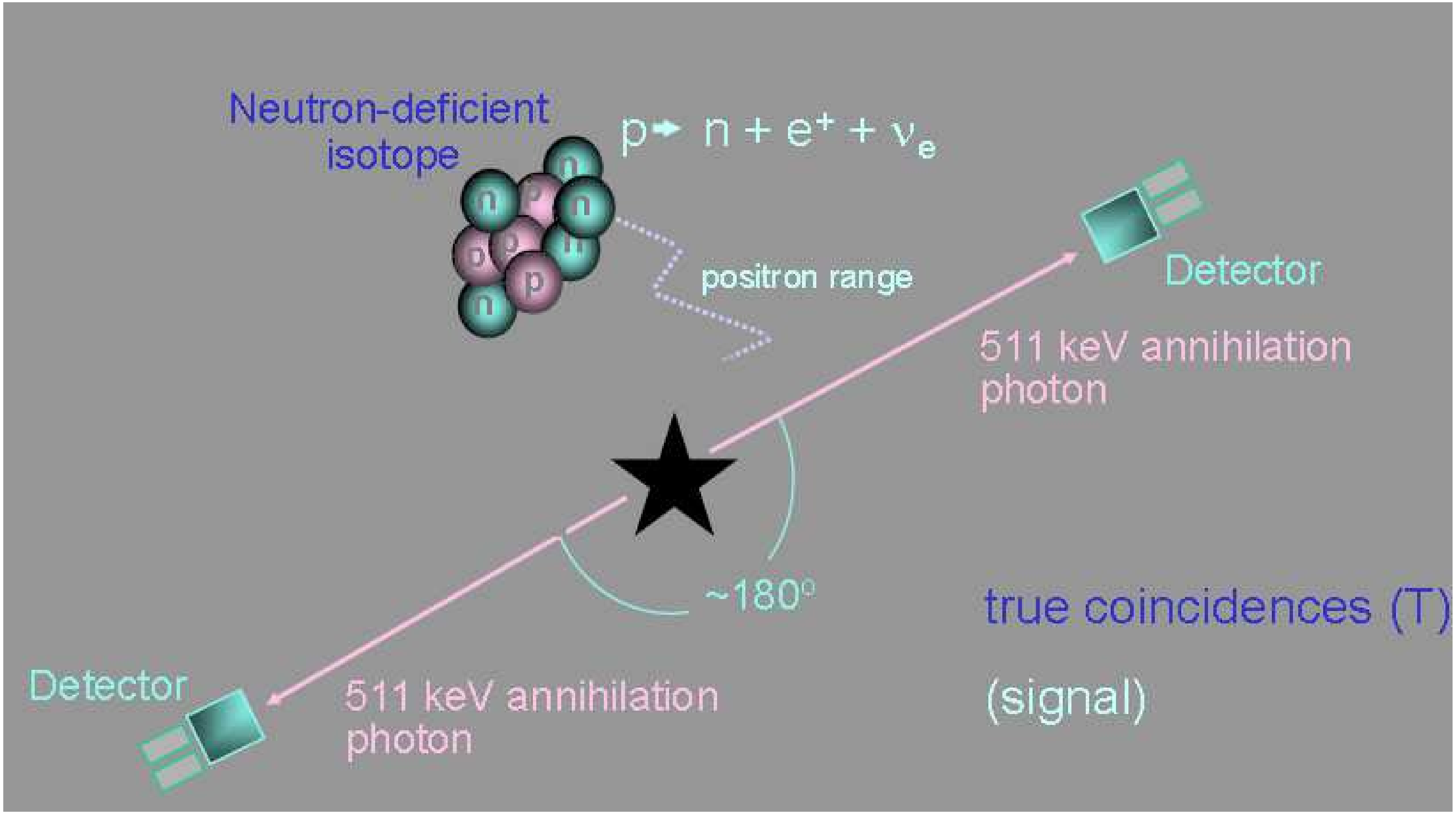
G.J. Beyer, H.L. Ravn, Y. Huang, Int. J. Appl. Radiat. Isot. 35 (1984) 1075.
G.J. Beyer, H.L. Ravn, Appl. Rad. Isot. 42 (1991) 141.

Implantation type ^{83}Rb/^{83m}Kr generator



^{83m}Kr for on-line calibration of large gas detectors

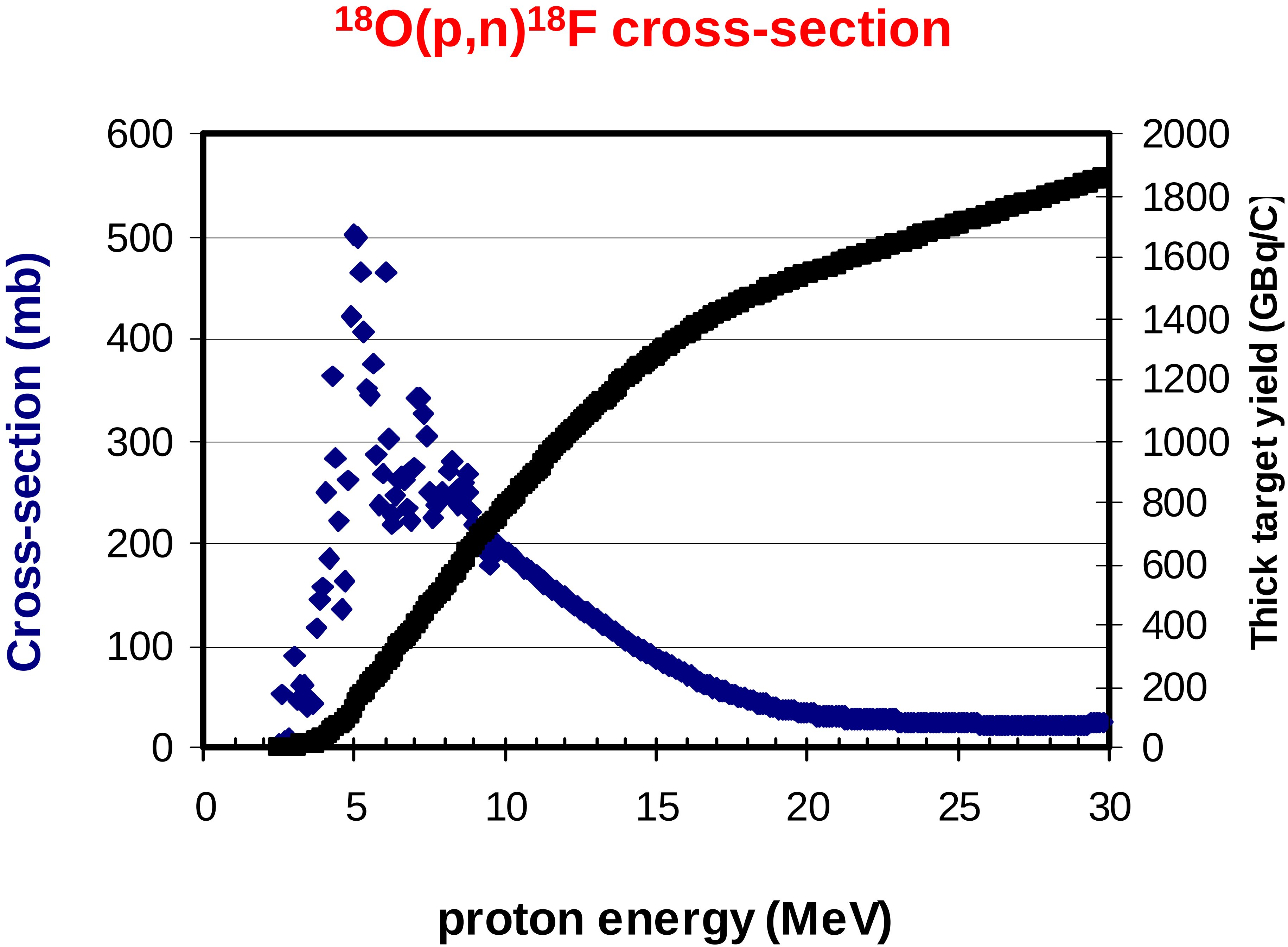
PET: Positron Emission Tomography



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

PET isotopes

Radio-nuclide	Half-life (h)	Branching ratio β^+ (%)	E mean (MeV)	Range (mm)
F-18	**1.83**	**96.7**	**0.25**	**0.7**
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



18O(p,n)18F cross-section
Cross-section (mb)
Thick target yield (GBq/C)
proton energy (MeV)
0
100
200
300
400
500
600
0
200
400
600
800
1000
1200
1400
1600
1800
2000
0
5
10
15
20
25
30

FLUORINE-18 PRODUCTION AT A 590 MeV SYNCHROCYCLOTRON: RADIOPHARMACEUTICAL SYNTHESIS AND BIODISTRIBUTION.

H. J. TOCHON-DANGUY, D. TOWNSEND, M. WENSVEEN, P. FREY, A. CHRISTIN, A. GEISSBUHLER, A. DONATH

Division of Nuclear Medicine, University Hospital, 1211 Geneva, (Switzerland).

H. RAVN

ISOLDE Group, CERN, Geneva (Switzerland)

R. DELTENRE

SC Group, CERN, Geneva (Switzerland)

J. Fluorine Chemistry 41 (1988) 33.

HIDAC camera

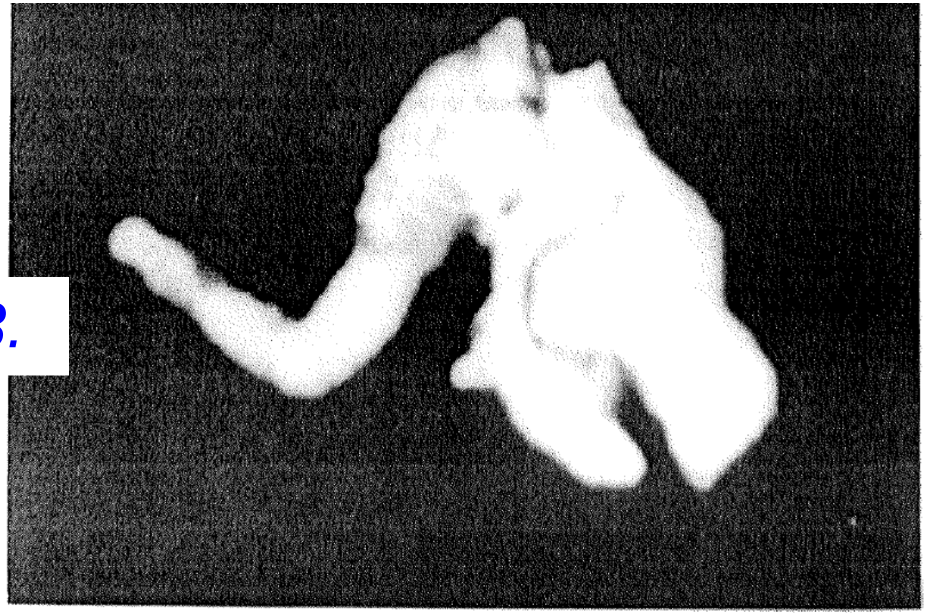
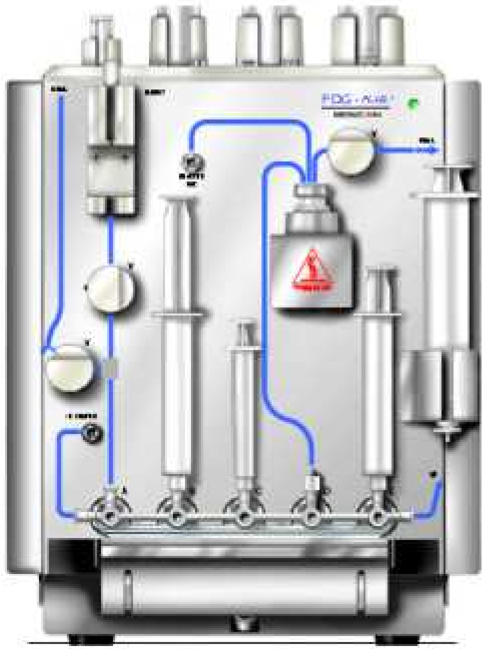
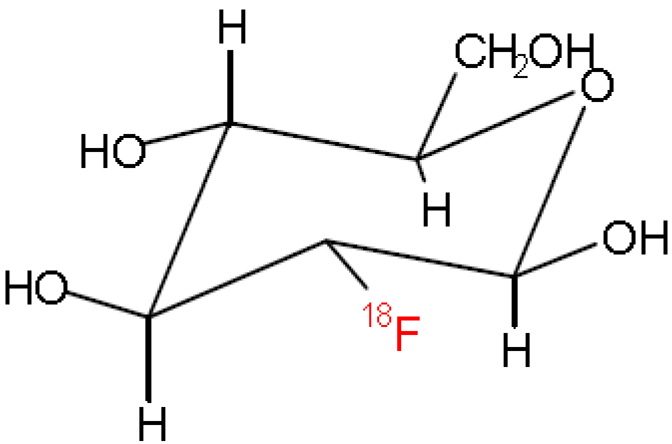


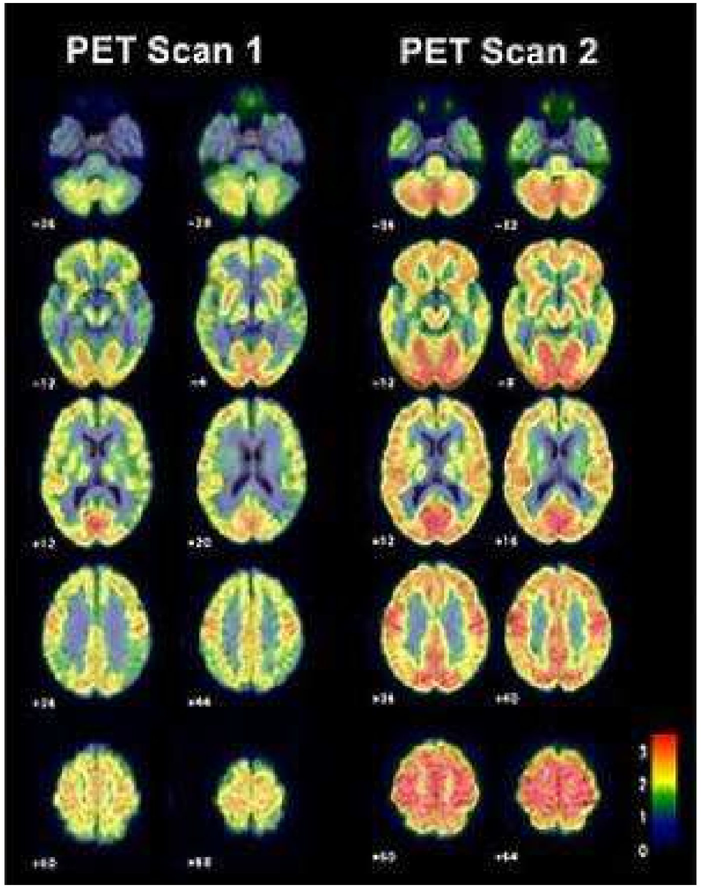
Fig. 3. Shaded-graphics display of the skull of a rabbit imaged 45 min after injection of a solution of $Na^{18}F$.


IBA

FDG





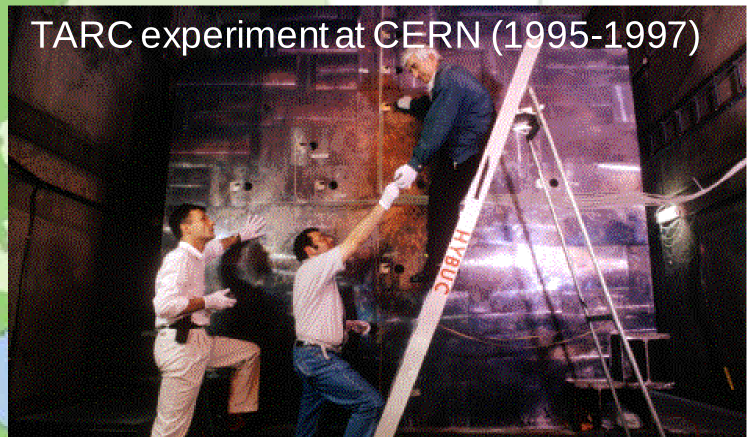


2-Deoxy-2-[^{18}F]fluoro-D-ß-glucose (2-FDG)

"Building a robust European PET infrastructure"

Advanced Accelerator Applications

- **12 production and R&D facilities**
- **more than 210 employees in 9 countries**
- **2011 revenues €36.4 million**


TARC experiment at CERN (1995-1997)

PET isotopes

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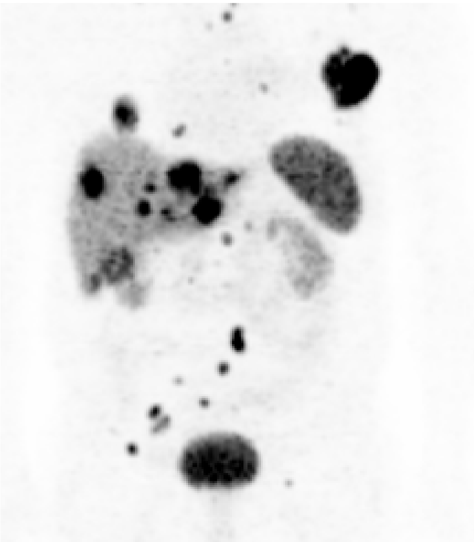
O-15	0.03	99.9	0.74	3.2
Ga-68	**1.13**	**89.1**	**0.83**	**3.8**
Rb-82	**0.02**	**95.4**	**3.38**	**20**
Sc-44	3.97	94.3	0.63	2.5

Use of ^{68}Ga as PET nuclide

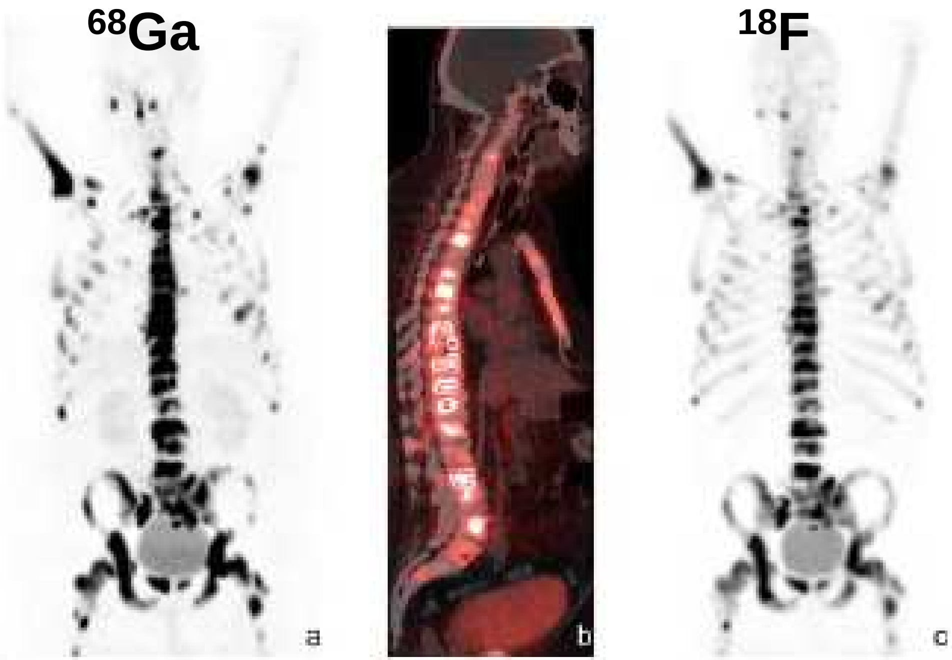
Somatostatin analogues



Galligas™

(Kotzerke et al.; Eur J Nucl Med Mol Imaging 2010)

Bisphosphonates (^{68}Ga vs. ^{18}F)

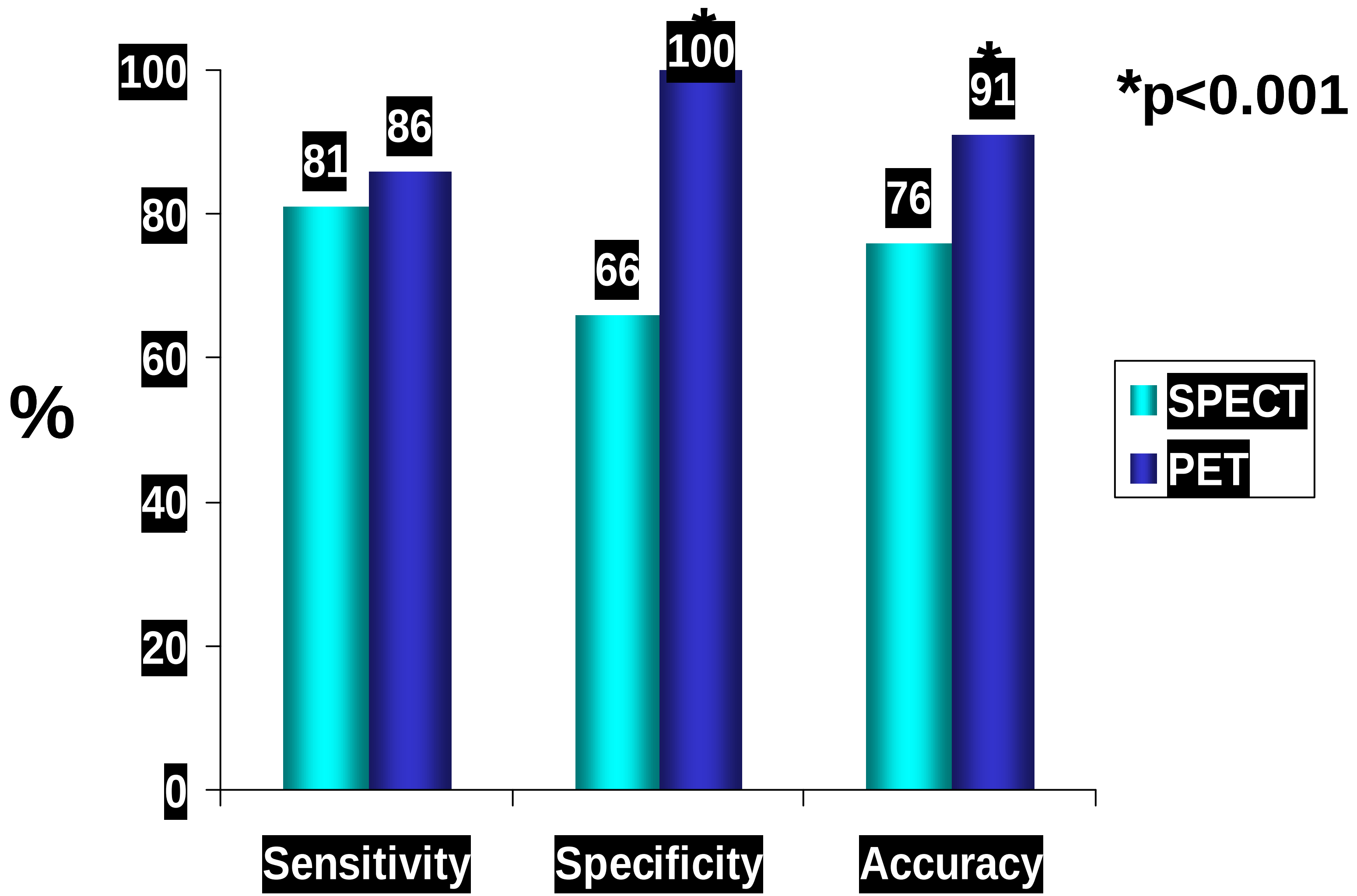


(Fellner et al.; Eur J Nucl Med Mol Imaging 2010)

Bombesin

Ga-microspheres

Diagnostic Accuracy: PET vs SPECT



D. Le Guludec, ICTR-PHE2012

Bateman et al, J Nucl Cardiol 2006

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O-15	0.03	99.9	0.74	[illegible]
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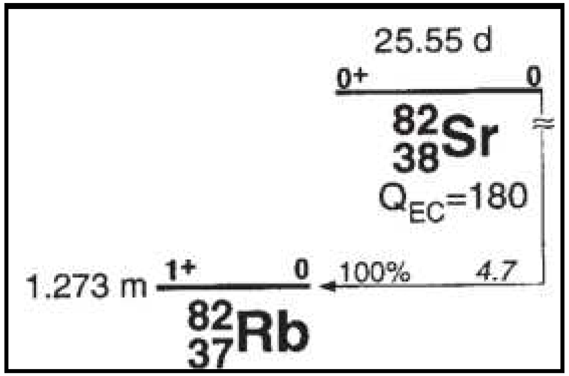
Rb-82	**0.02**	**95.4**	**3.38**	
Sc-44	3.97	94.3	0.63	

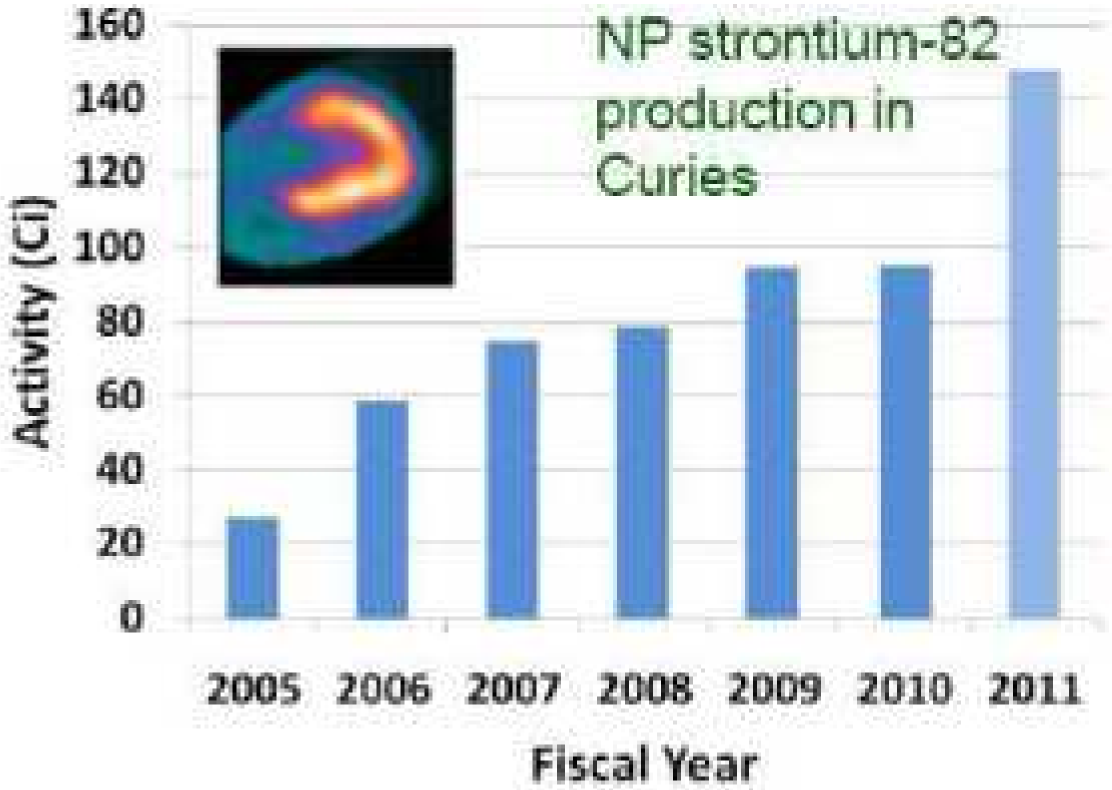
Mother isotope:
271 d
25 d
60 y

Transport of short-lived radioisotopes

^{82}Rb is used for PET in cardiology
→ ^{82}Sr/^{82}Rb generator



Evolution of ^{82}Sr demand in the USA



(source : Department of Energy, USA)

F. Haddad, Arronax Nantes

Facilities producing Sr-82 in the world

- LANL, USA –100 MeV, 200µA
- BNL, USA –200 MeV, 100µA
- INR, Russia –160 MeV, 120µA

BLIP

- iThemba, South Africa –66 MeV, 250µA
- TRIUMF, Canada –110 MeV, 70 µA

5 accelerators – 2 generator manufacturers – 1 generator

Mar - Jul 2011: outage of 2 accelerators > ^{82}Sr shortage
Jul '11 - Feb '12: generator recalled

Problem: Concentration on few players

New players

ARRONAX

Upcoming:

70 MeV cyclotrons in Legnaro, Texas,…

Two new $^{82}Sr/^{82}Rb$ generators (Draximage, Quanticardi)

Longer-lived PET isotopes

Radio-nuclide	Half-life (h)	Branching ratio 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**
Y-86	14.7	31.9	0.66	2.6
Zr-89	**78.4**	**22.7**	**0.40**	**1.4**
I-124	**100.2**	**22.8**	**0.82**	**3.8**
Tb-152	17.5	17	1.08	5

From diagnostics

to therapy

Cancer and efficiency of treatments

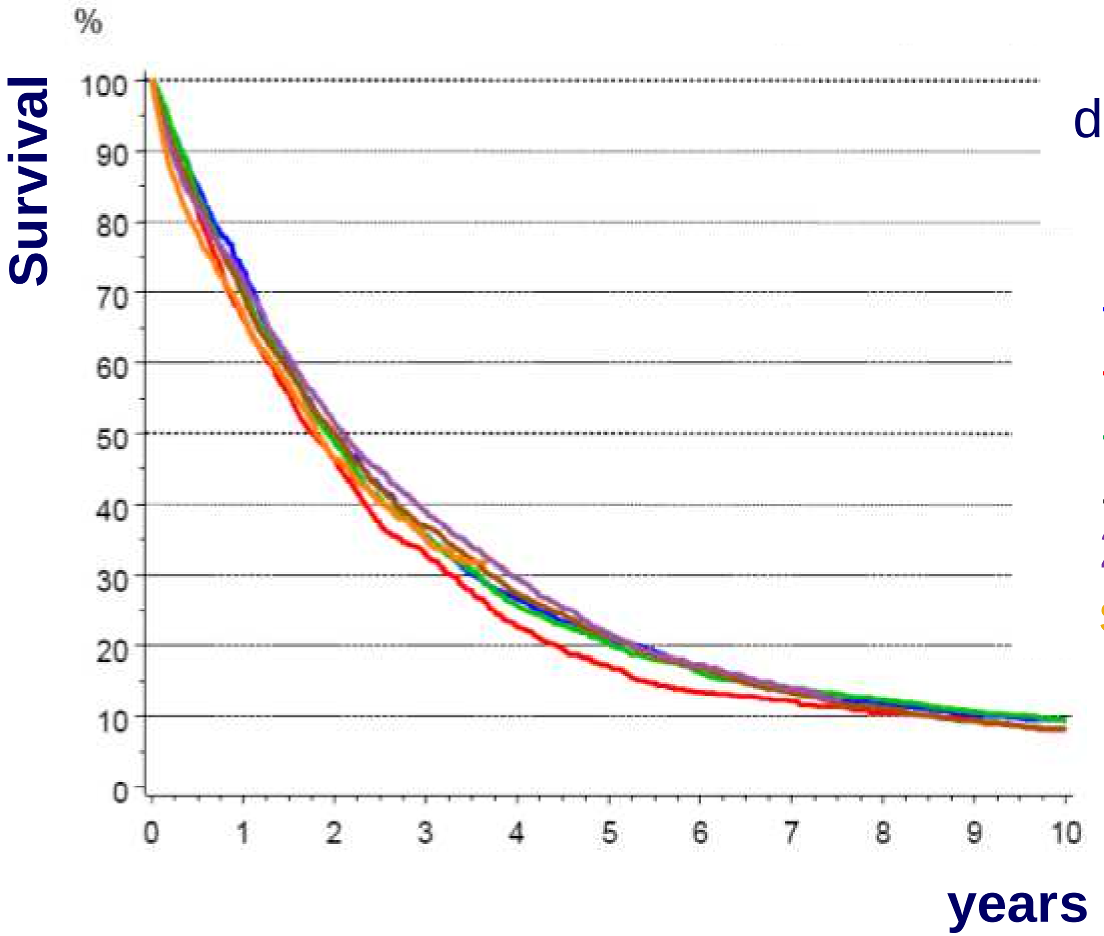
At time of diagnosis	Primary tumor	With metastases	Total
Diagnosed	58%	42%	100%
Cured by:			
Surgery	22%		
Radiation therapy	12%		
Surgery+radiation therapy	6%		
All other treatments and combinations incl. chemotherapy		5%	
Total cured	40%	5%	45%
Fraction cured	69%	12%	45%

Per year over one million cancer deaths in the EU.

⇒ improve early diagnosis

⇒ improve systemic treatments

Mammary Carcinoma
Survival time since diagnosis of metastases

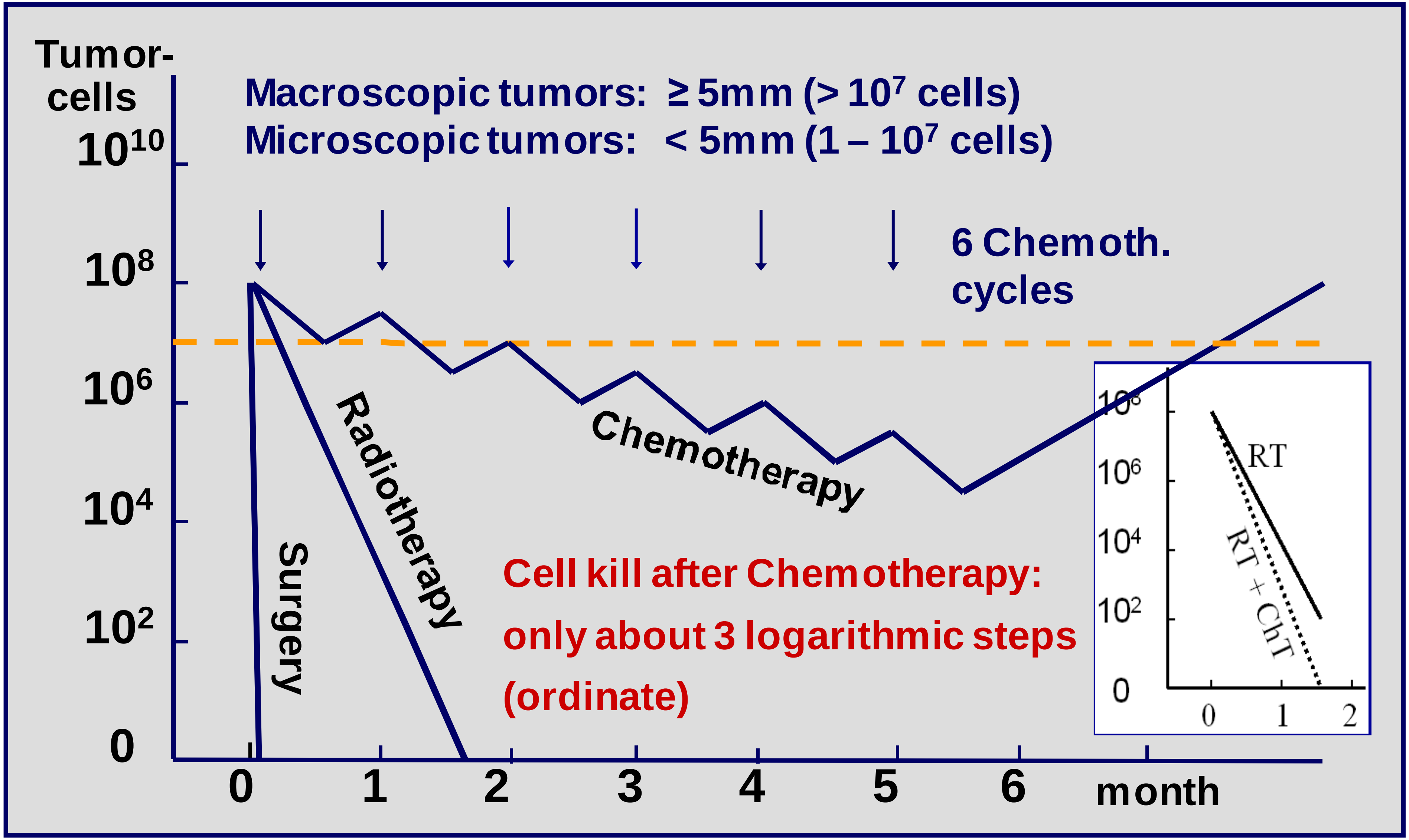


Results for 6 time periods
data from tumor centre Munich
n = 9228

1980-1984
1985-1989
1990-1994
1995-1999
2000-2003
since 2004

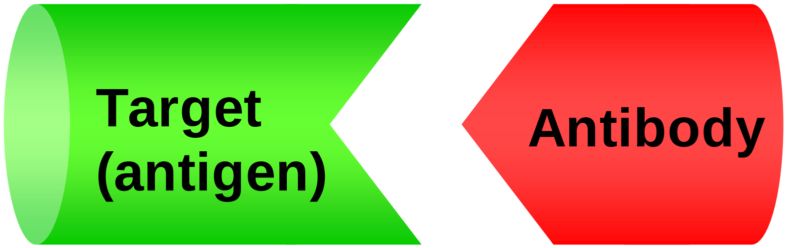
Little/no improvement with (modern) chemotherapies!

Comparison of Therapies

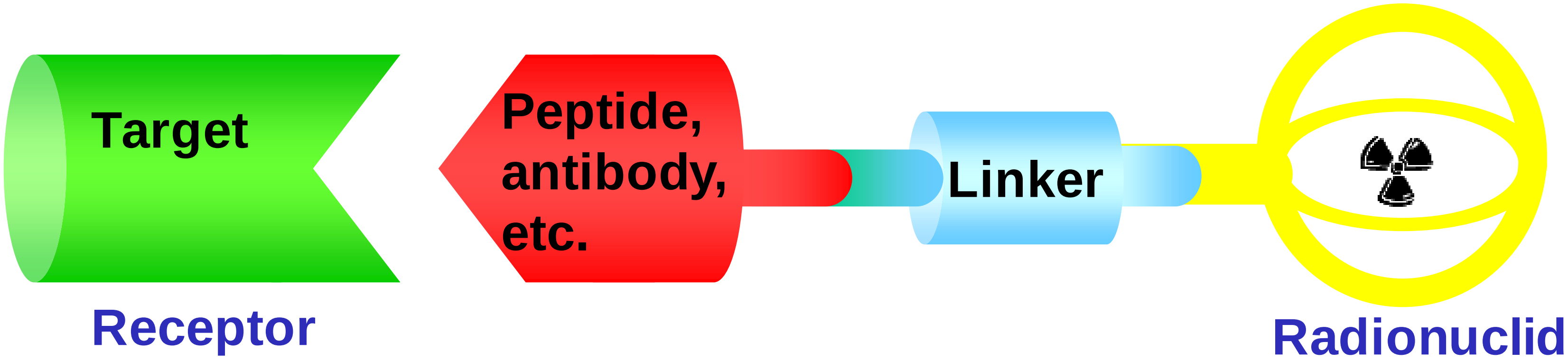


(Molls, TU München; according to Tannock: Lancet 1998, Nature 2006)

Immunology approach



Multidisciplinary collaboration to fight cancer

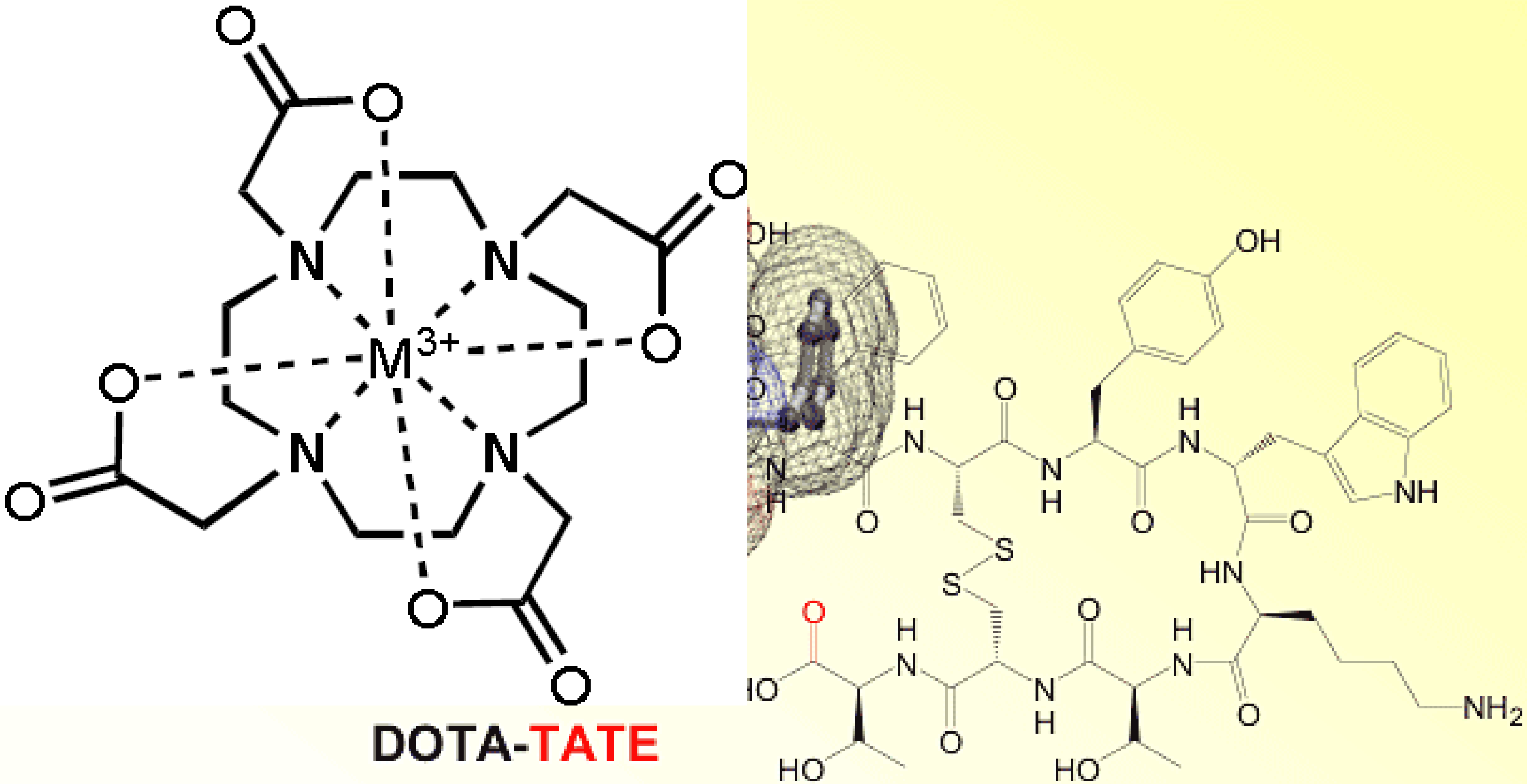


Immunology
Structural biology

Coordination chemistry

Nuclear physics and radiochemistry

Structural Formula of DOTA-TOC/TATE



DOTA-TATE

1,4,7,10-tetraazacyclododecantetraacetate

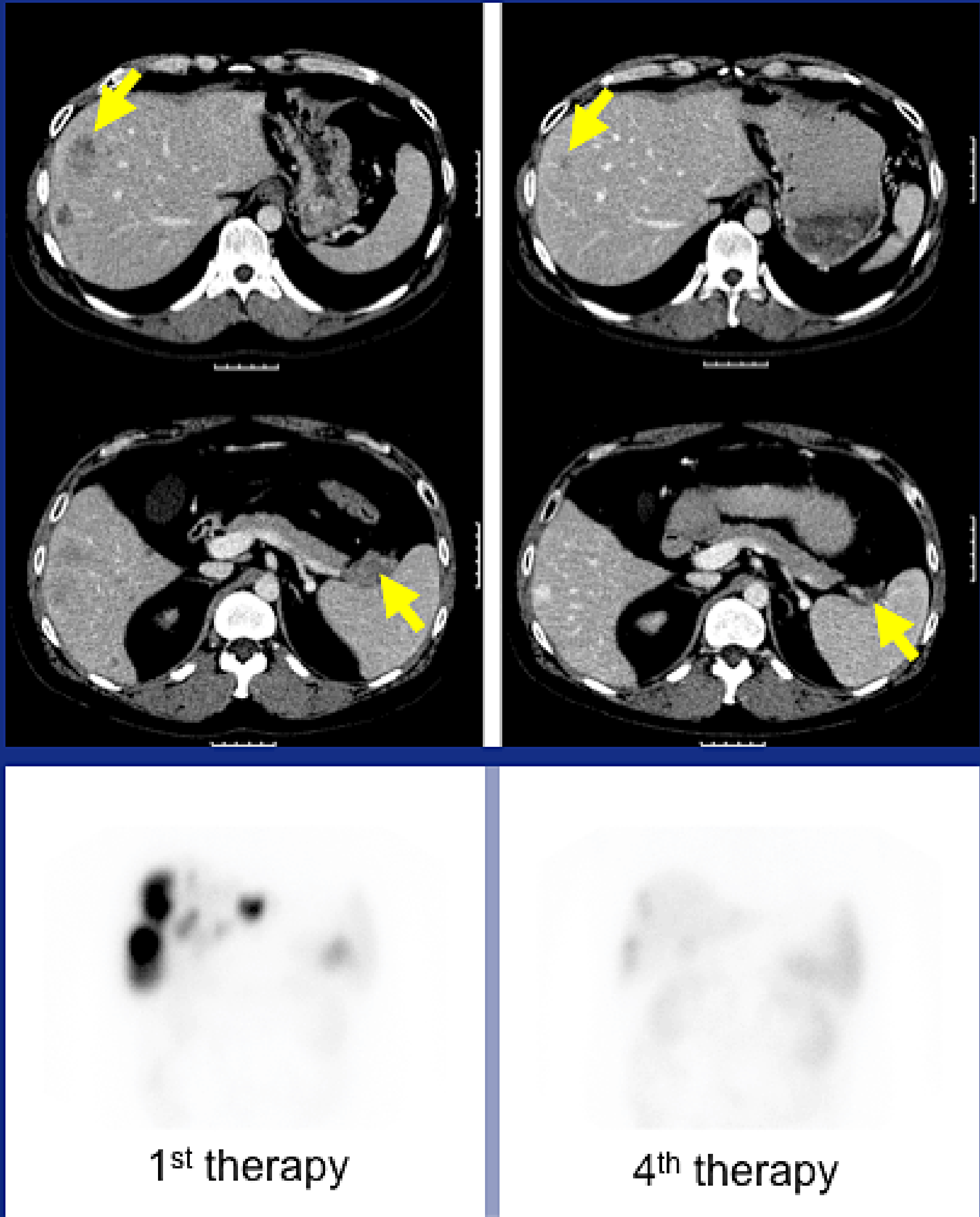
^{111}In ^{90}Y

^{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.

What success does PRRT offer?

- ✓ CR+ PR + MR in about 50% of patients: YES
- ✓ Reduce symptoms and improve quality of life: YES
- ✓ Increase survival time: YES
- ✓ Safety and tolerability: YES

Roelf Valkema, EANM-2008.

Erasmus MC

Lymphoma therapy: RITUXIMAB+^{177}Lu

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

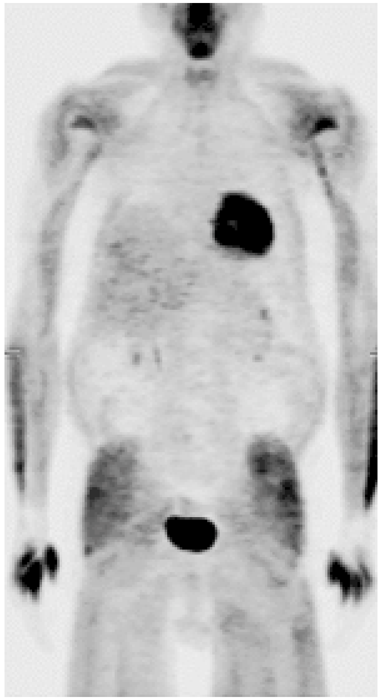
^{18}FDG PET

1.9.2002

^{177}Lu-Scan

13.9.2002

^{18}FDG PET

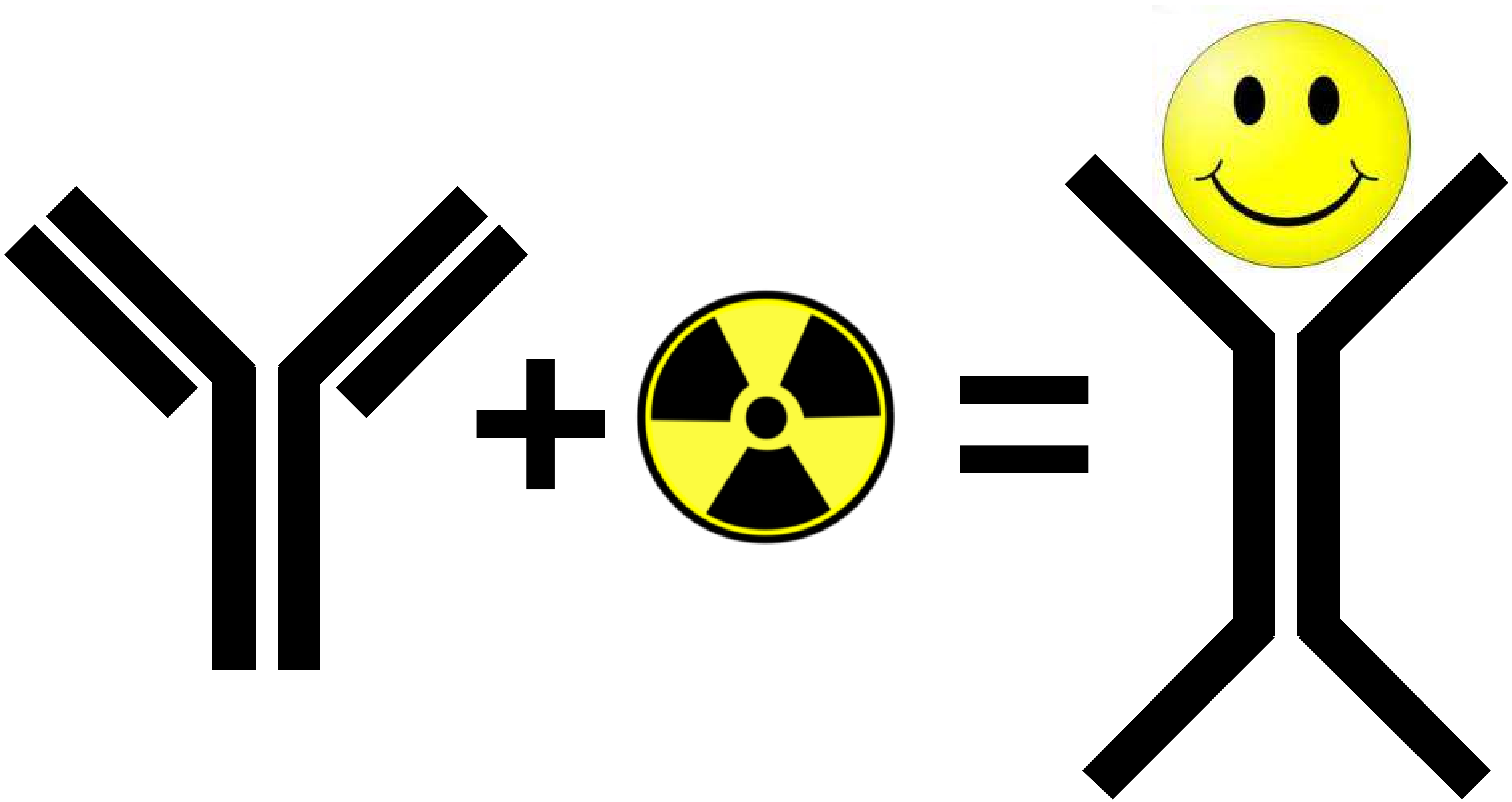


15.11.2002

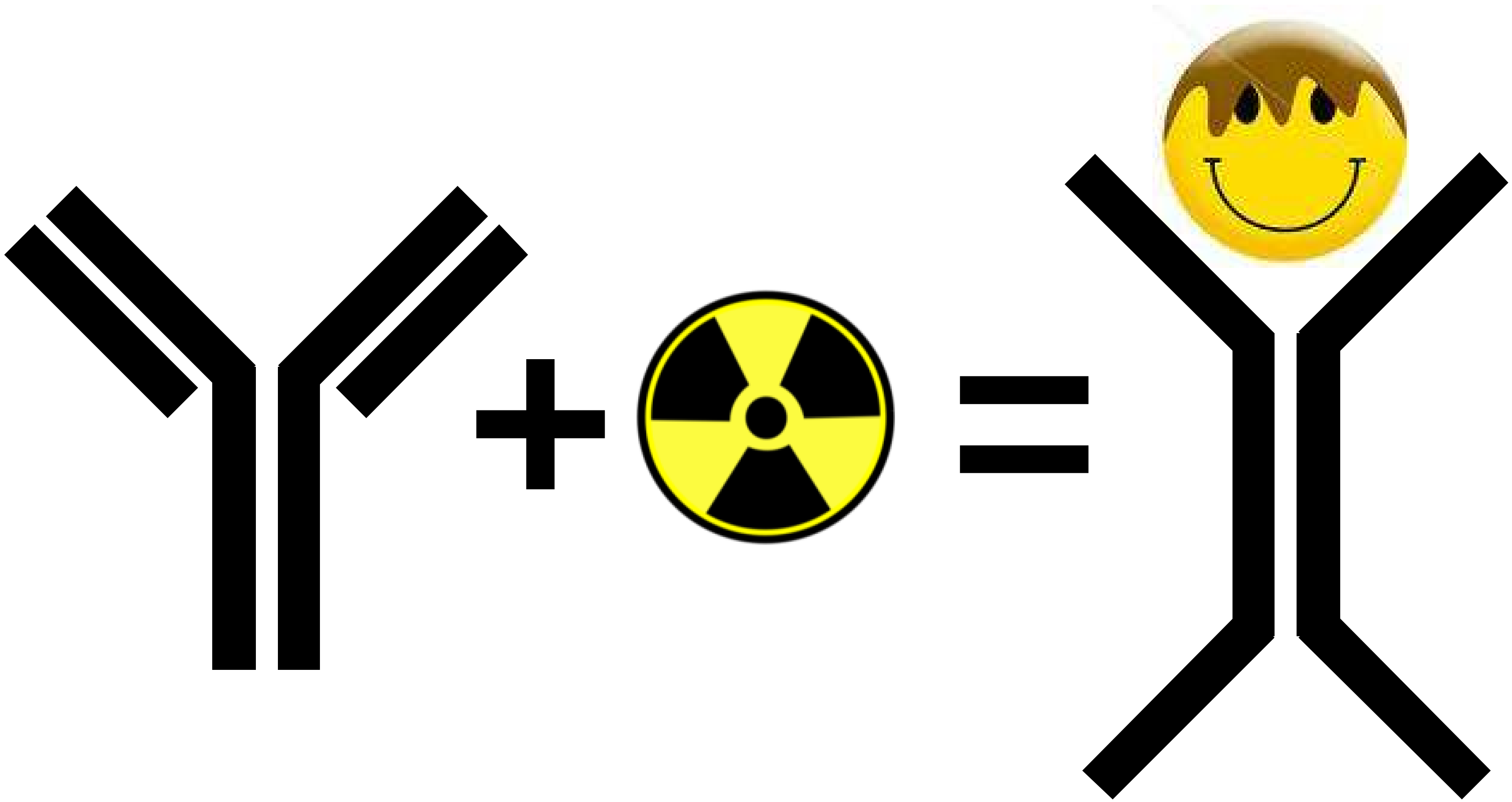
Still in CR

15.9.2009

Radioimmunotherapy



Radioimmunotherapy

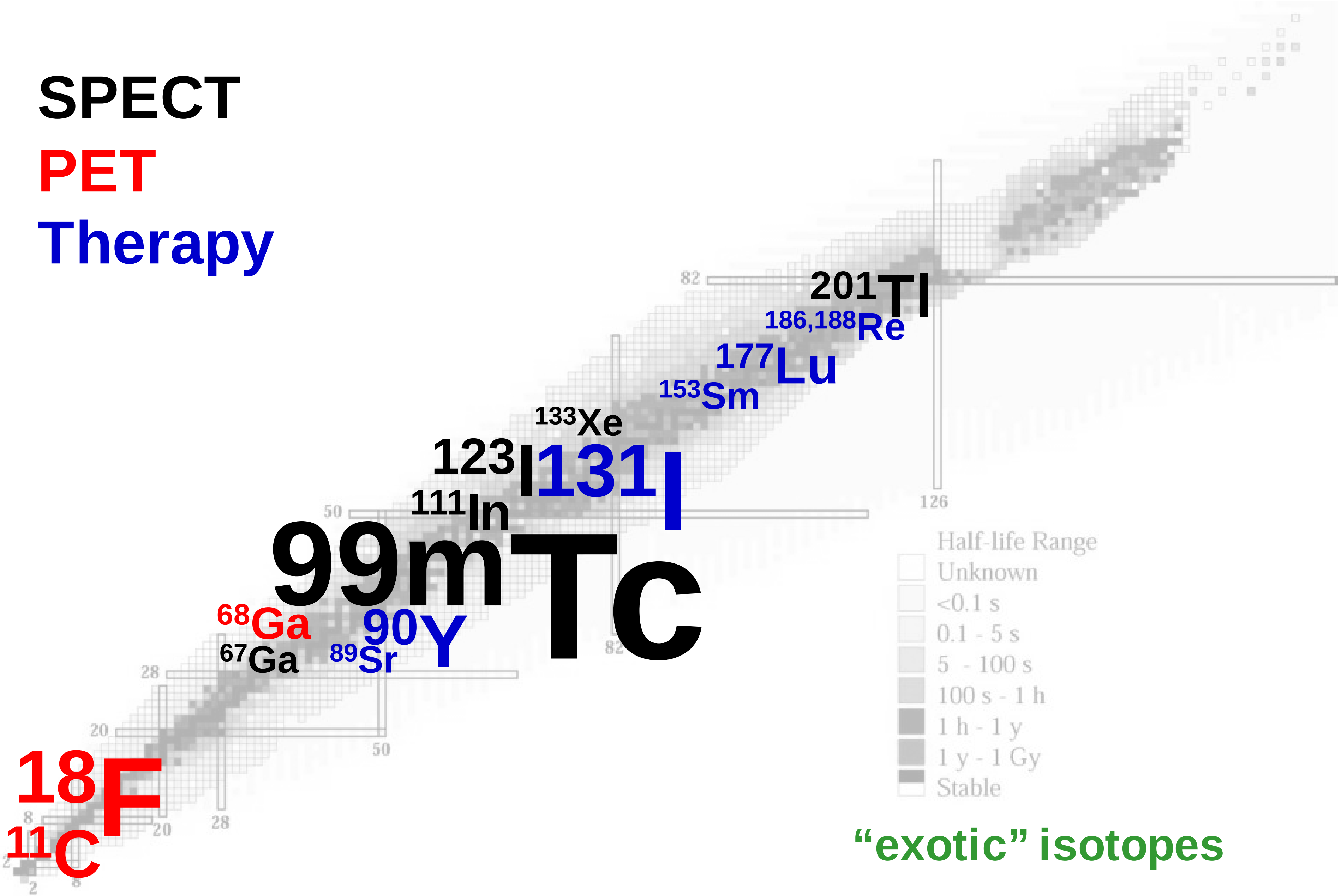


The chart of nuclides – nuclear medicine perspective

SPECT

PET

Therapy



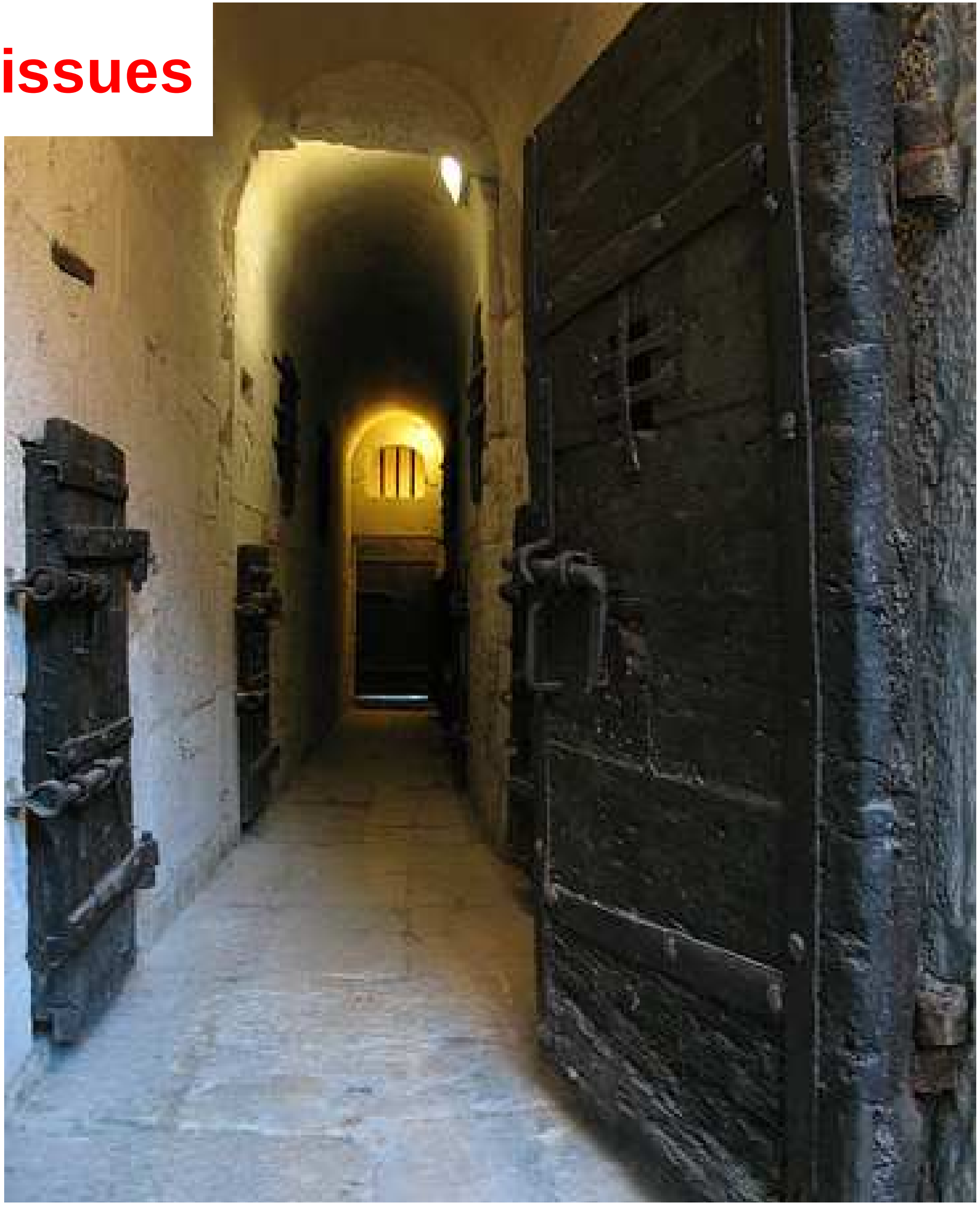
“exotic” isotopes

^{131}I: radioprotection issues

364 keV gamma ray emitted with 82% B.R.

3.7 GBq patient dose
$\Rightarrow$ 0.2 mSv/h at 1 m

requires dedicated shielded treatment rooms



^{90}Y: collateral damage from long range betas ?

$Q_{\beta -}$ = 2.28 MeV
up to 12 mm range

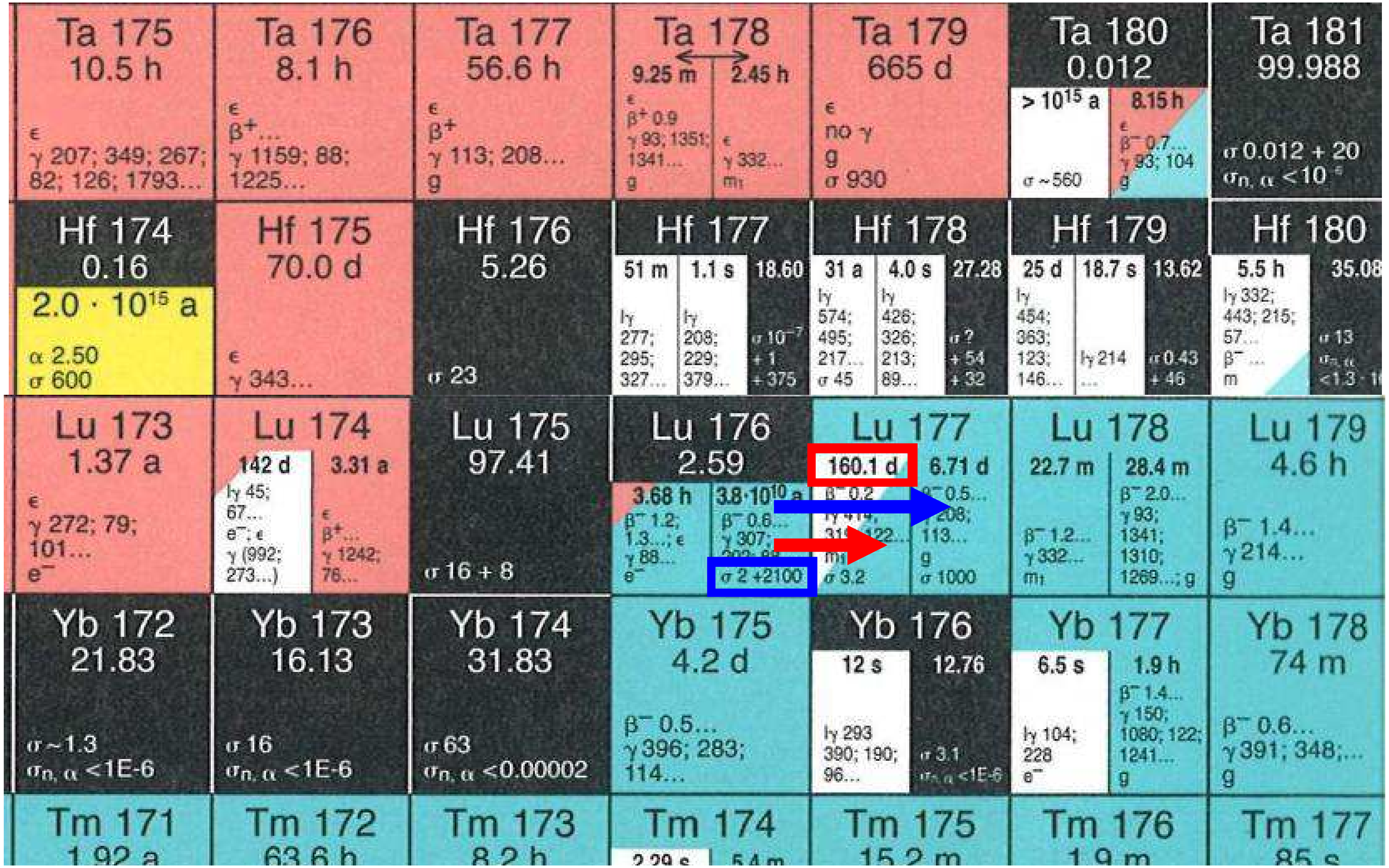
Radionuclides for RIT and PRRT

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

Emerging isotope

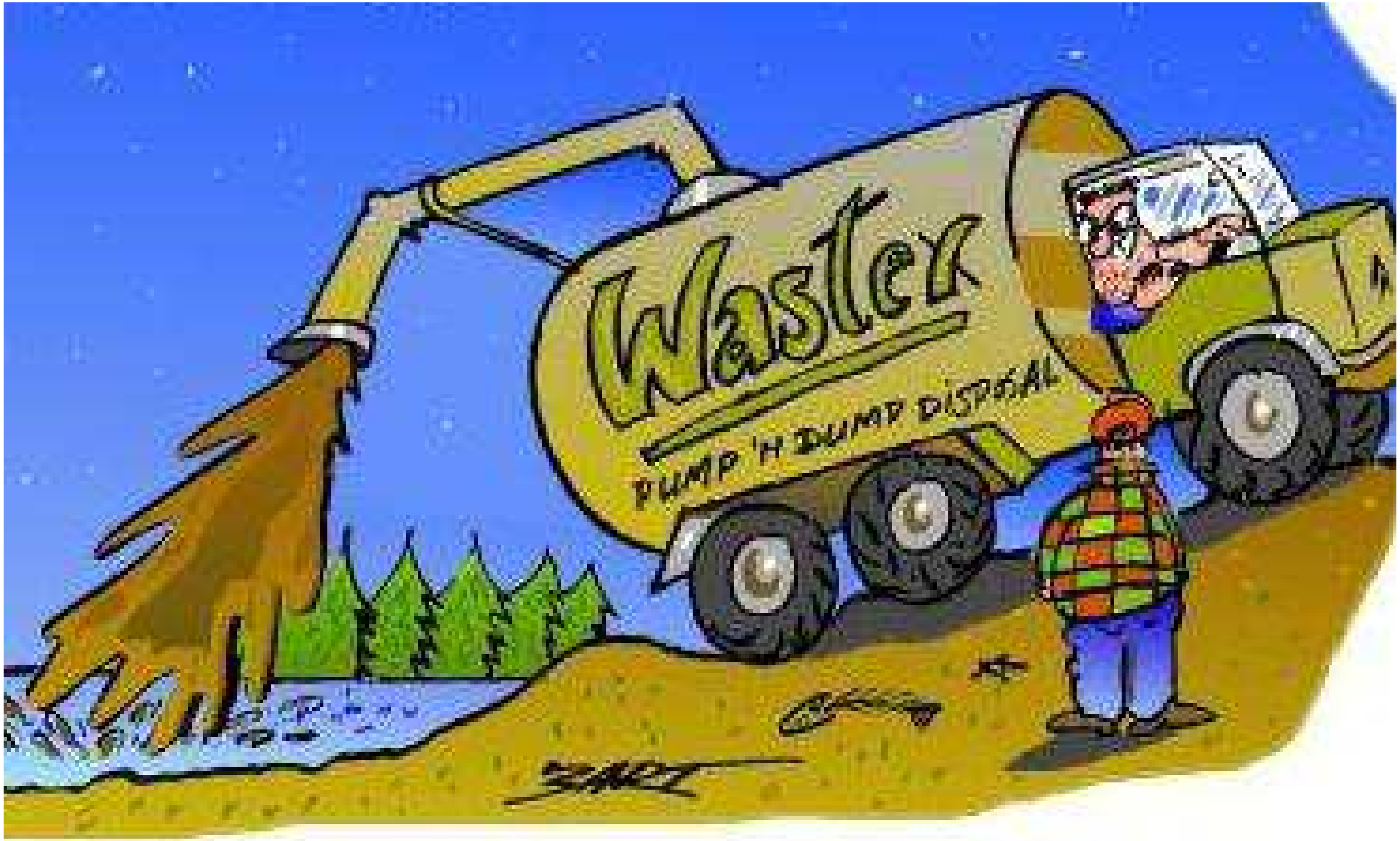
Production of ^{177}Lu



Waste problem for hospitals!

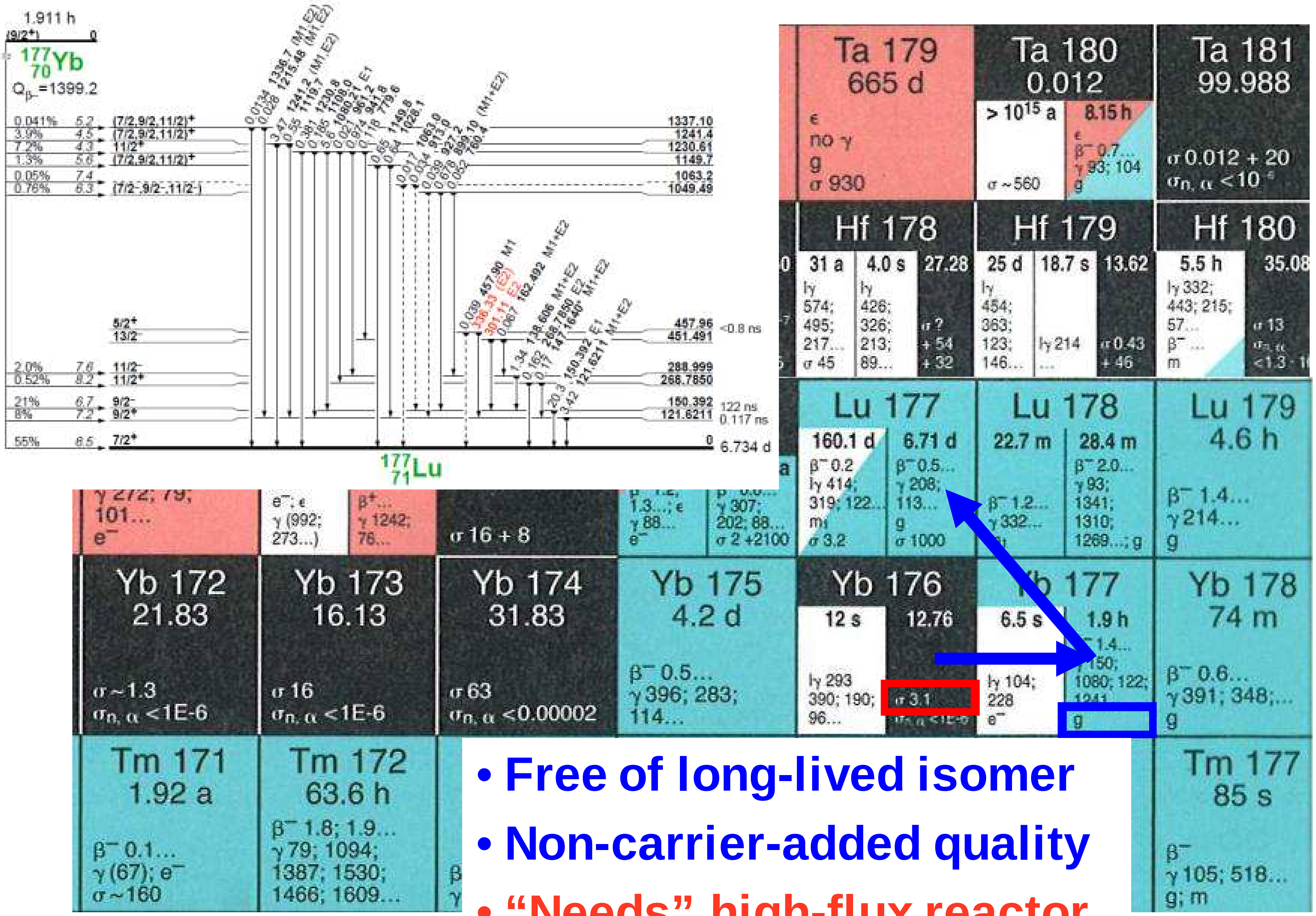
R. Henkelmann et al., Eur. J. Nucl. Med. Mol. Imag. 36 (2009) S260.

The curse of the *K*-isomer !

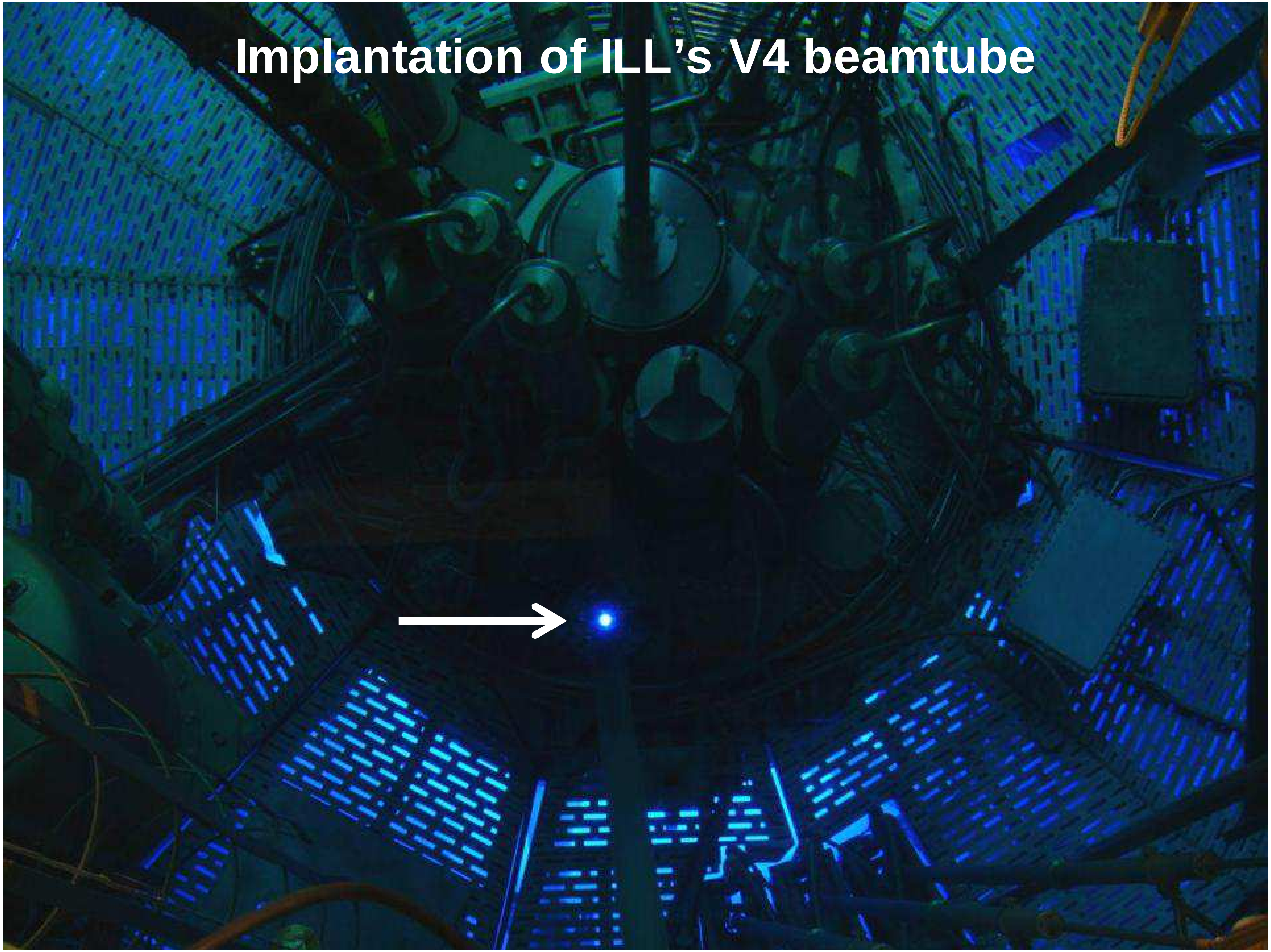


"So it'll pollute the lake. It will also make the fish glow in the dark when we go night-fishing !"

Alternative production route to ^{177}Lu



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


Implantation of ILL’s V4 beamtube

The rising star for therapy

The history of lutetium separation

1878 Separation of Yb in Geneva
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 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

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

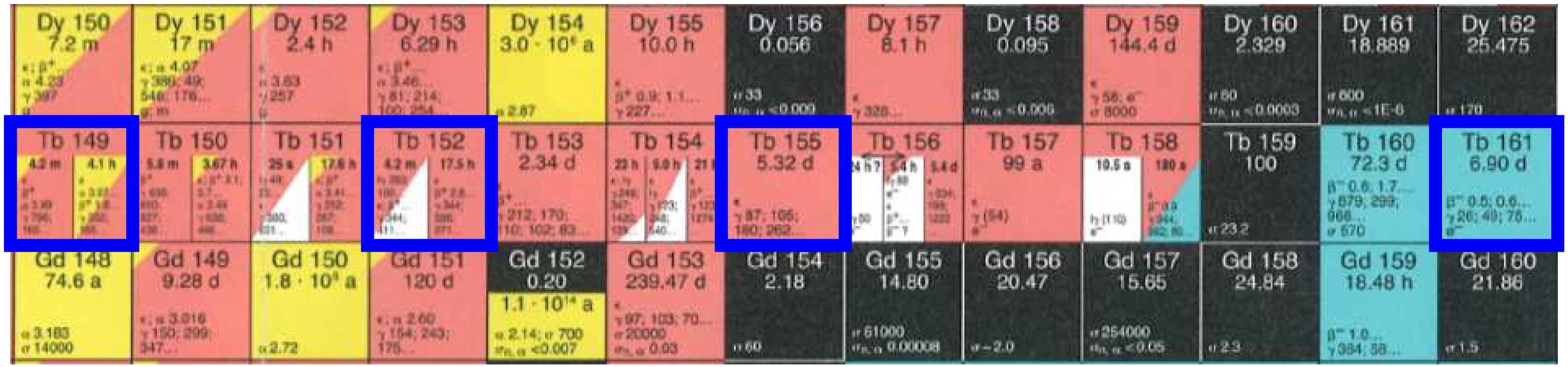
Emerging isotopes

R&D isotopes: supply-limited!

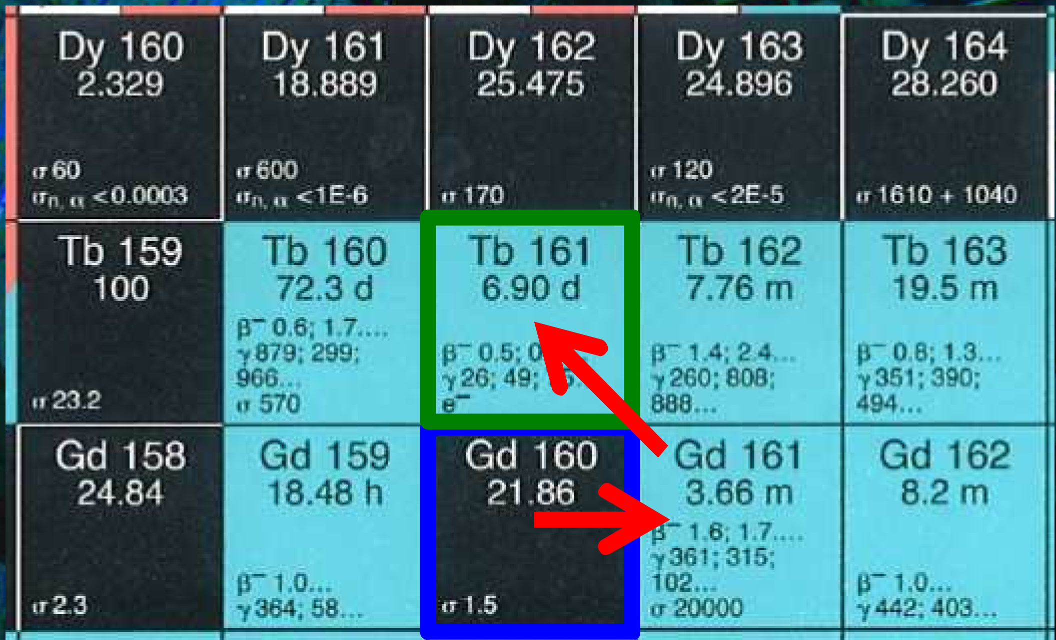
localized

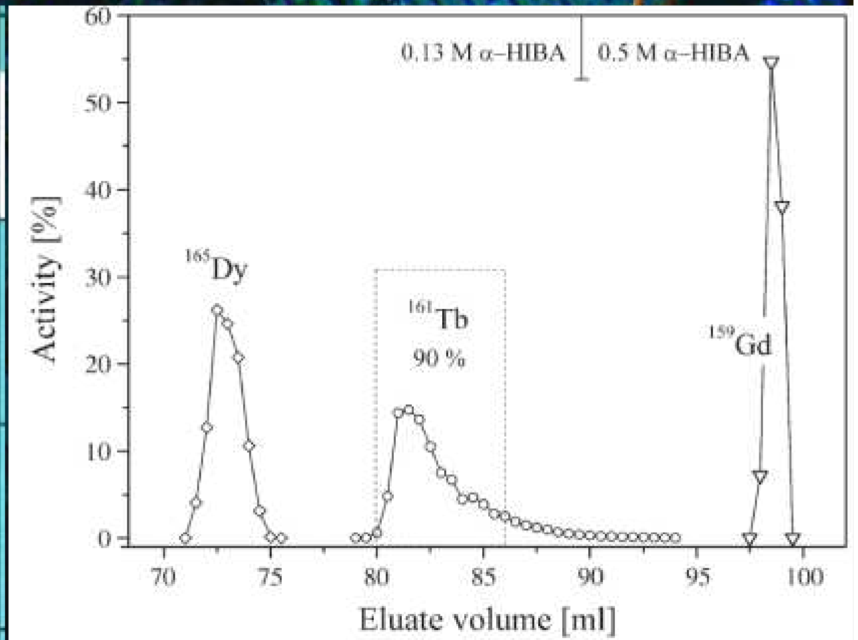
Modern, better targeted bioconjugates require shorter-range radiation ⇒ need for adequate (R&D) radioisotope supply.

Terbium: a unique element for nuclear medicine



Production of non-carrier-added ^{161}Tb

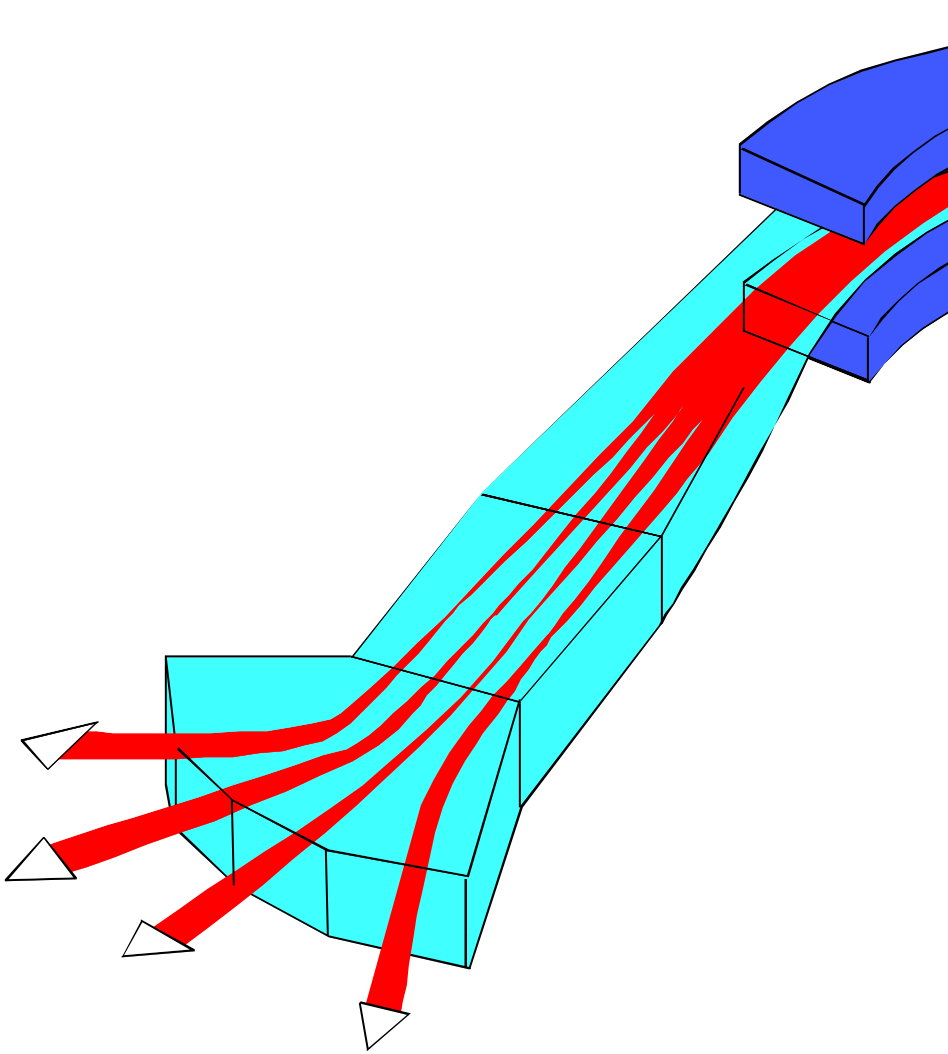




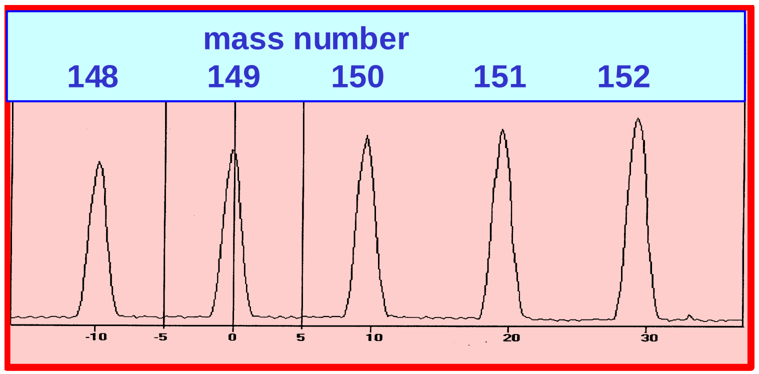
Irradiation in high flux reactor, then chemical separation

S. Lehenberger et al., Nucl. Med. Biol. 38 (2011) 917.

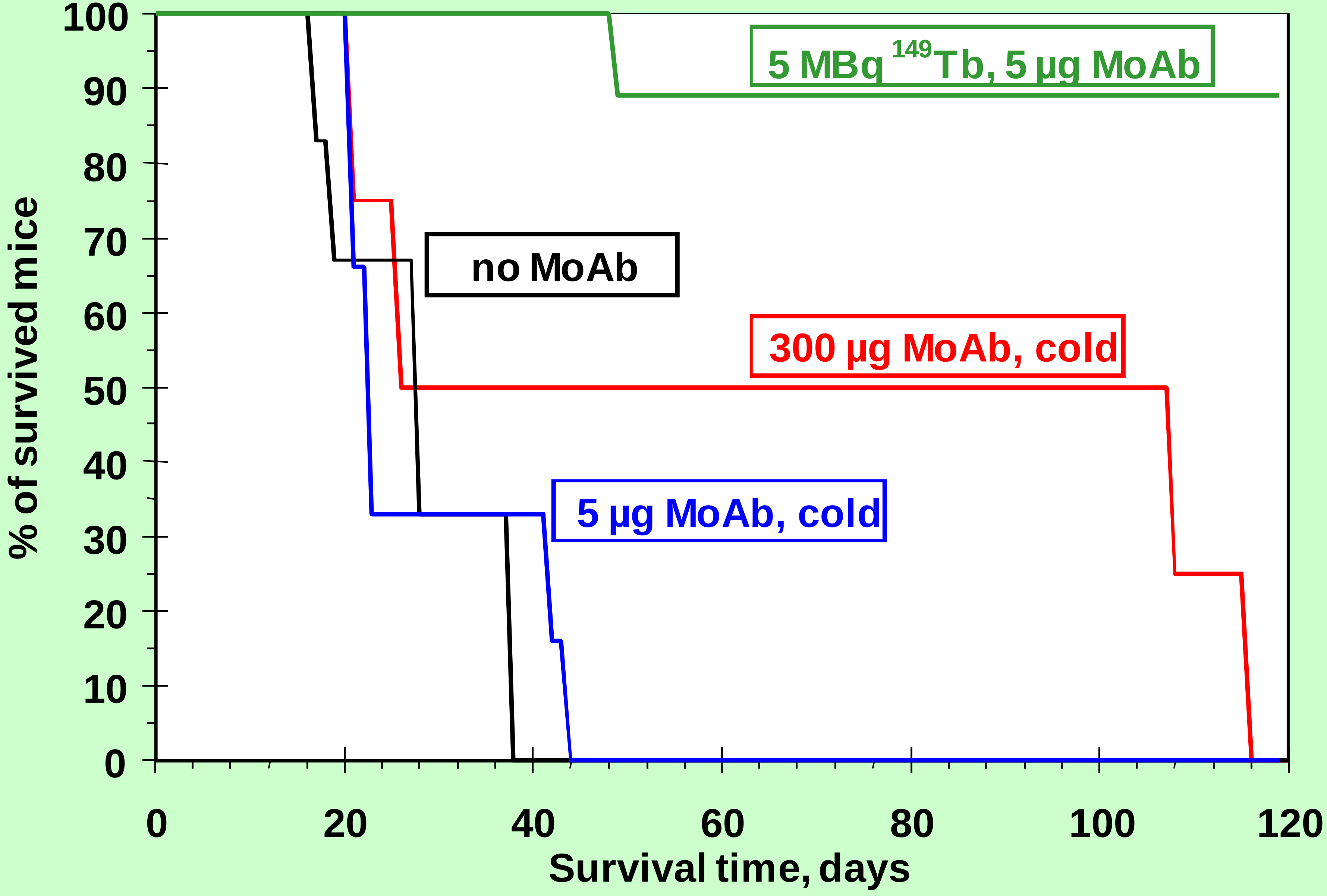
Production of ^{149}Tb, ^{152}Tb and ^{155}Tb at ISOLDE



radioactive ion beams



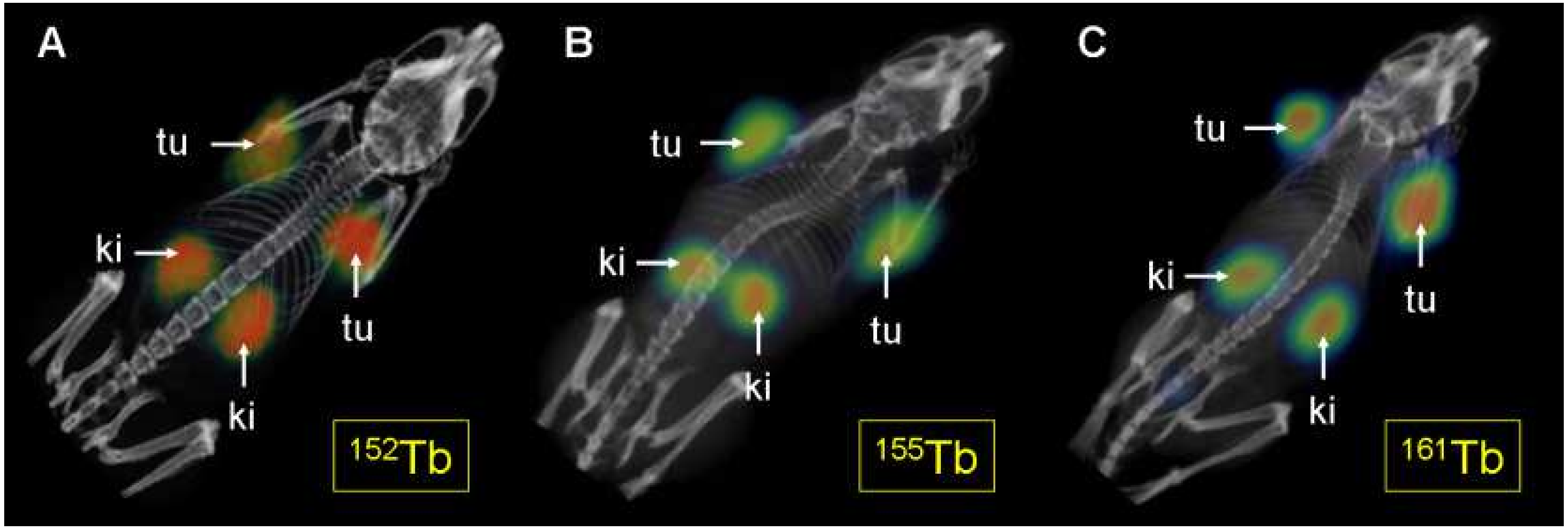
Targeted alpha therapy with ^{149}Tb from ISOLDE



G.J. Beyer et al., Eur. J. Nucl. Med. Molec. Imaging ***31*** *(2004) 547.*

Theranostics with terbium isotopes

PET *SPECT* *SPECT*



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

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

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

CERN ISOLDE

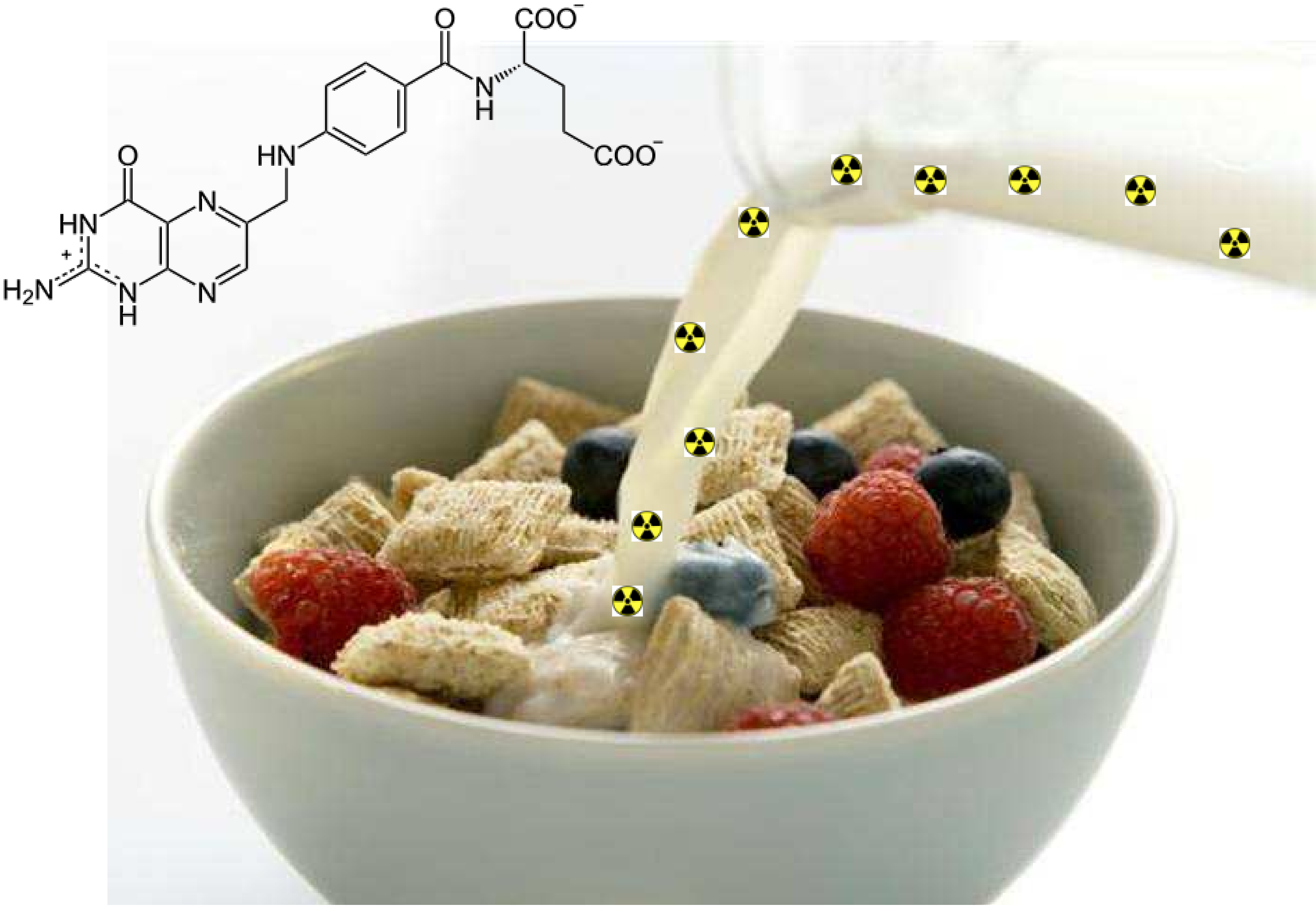
CERN ISOLDE

PAUL SCHERRER INSTITUT PSI

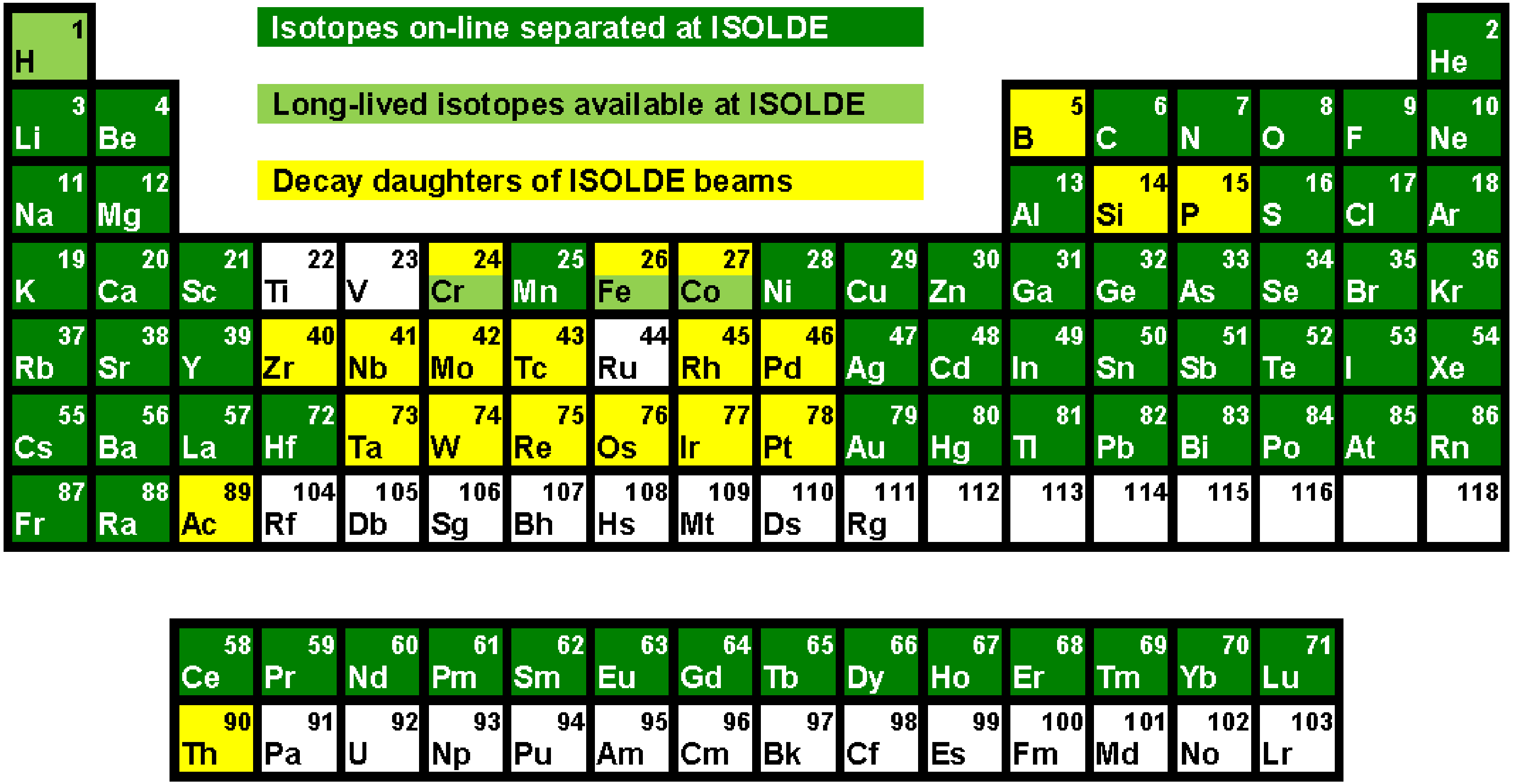
ILL NEUTRONS FOR SCIENCE

IS528 Collaboration: C. Müller et al., J. Nucl. Med. (2012), in press.

Folic acid



Radioisotopes available at ISOLDE-CERN

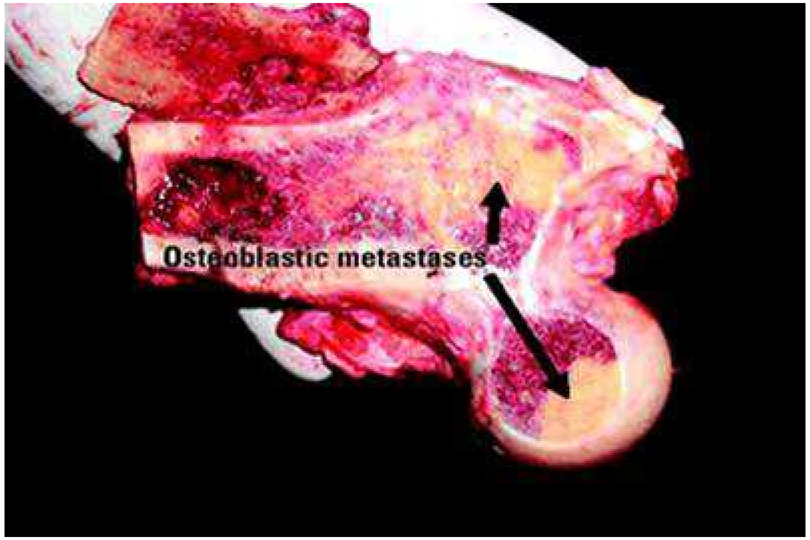


Currently available: more than 1000 different radioisotopes/-isomers

Saturation activities of longer-lived radioisotopes: GBq and more

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

Bone metastases



BM are a frequent complication of advanced prostate, breast, kidney, lung,… cancers

1.5 million patients worldwide suffer from BM:

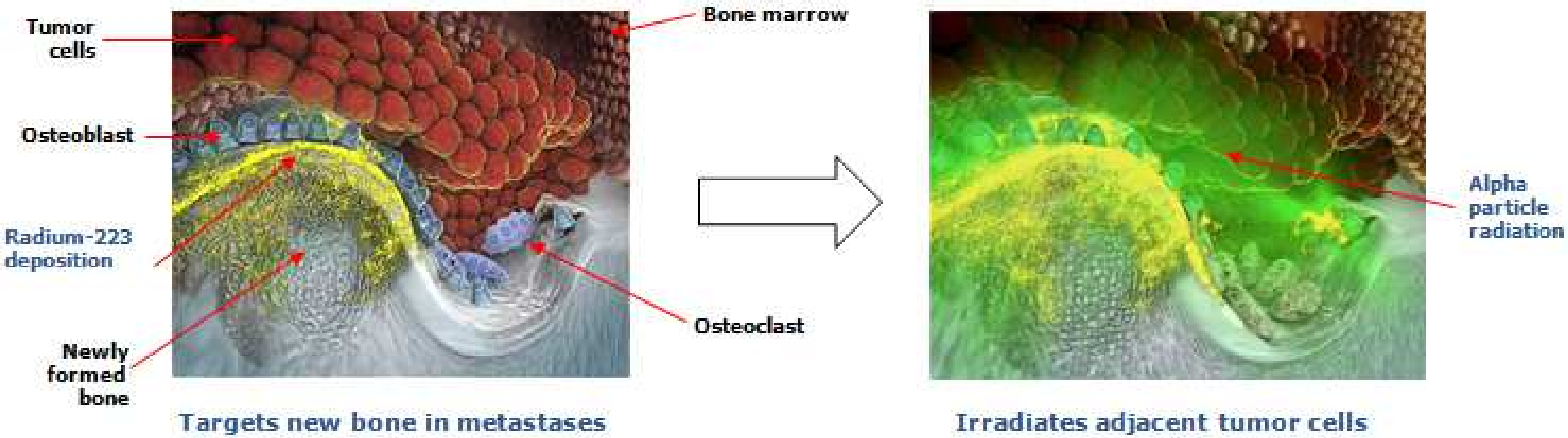
- severe pain
- weakened bones causing fracture
- damaged nerves
- red bone marrow produces less red/white blood cells

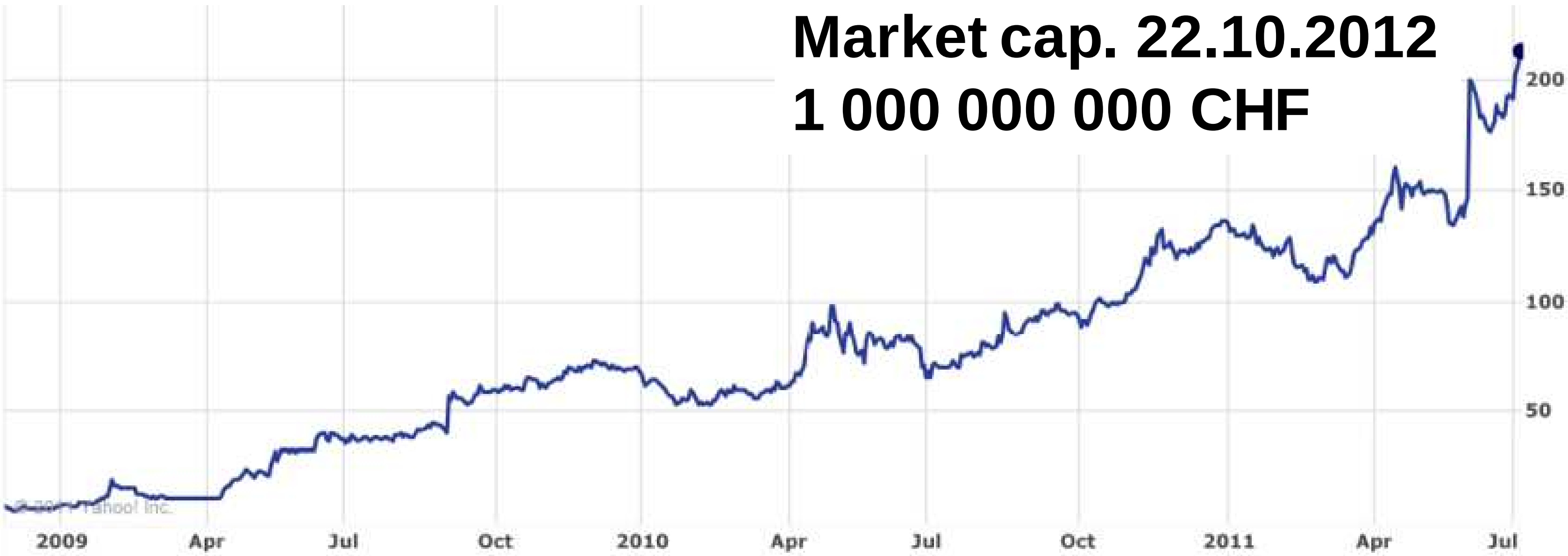
Isotopes for targeted alpha therapy

Isotopes for targeted alpha therapy

ALGETA: ^{223}Ra against bone metastases

Start-up company from Oslo University & Rikshospetalet
R&D on cancer therapies with alpha emitters





Market cap. 22.10.2012
1 000 000 000 CHF

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
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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

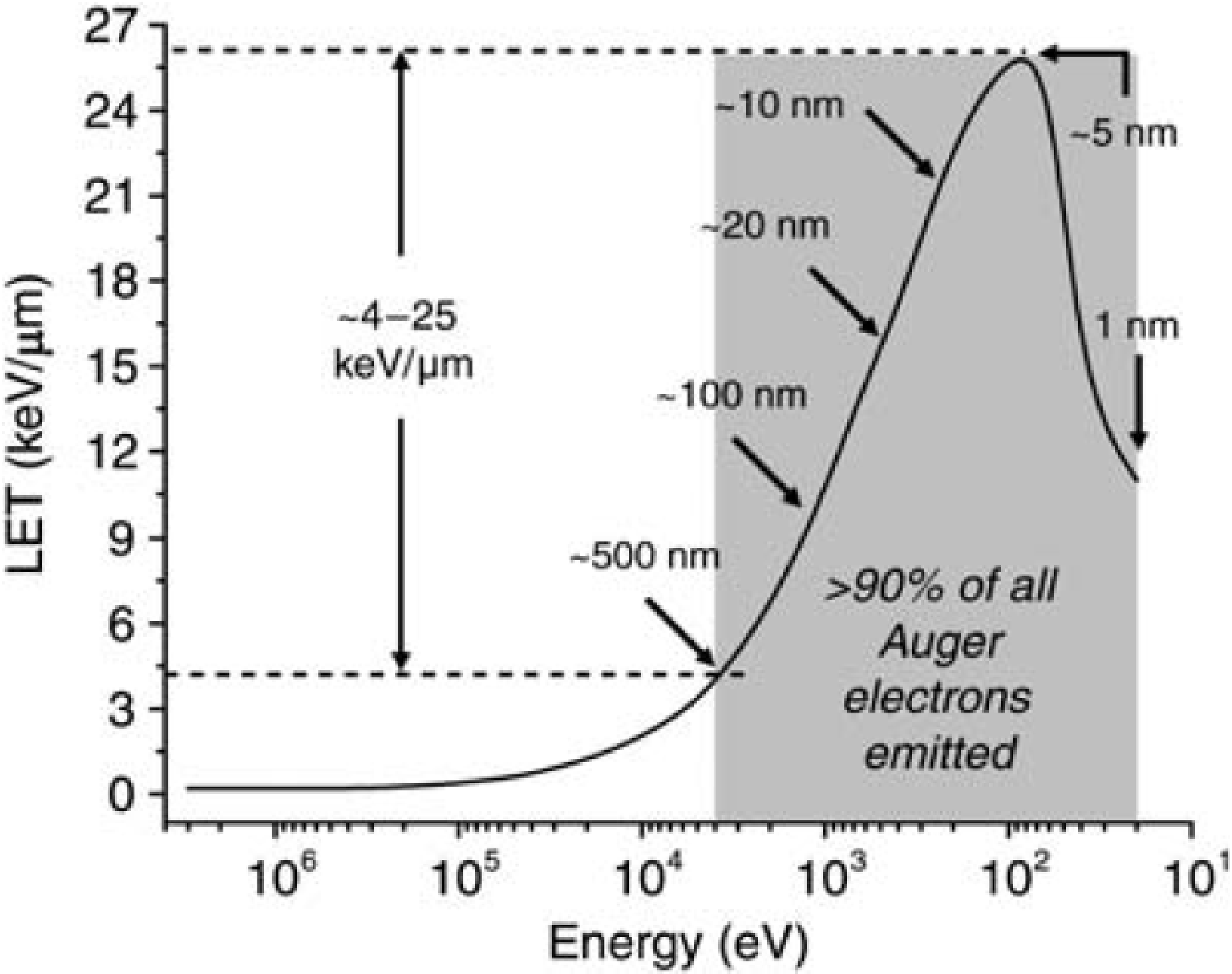
Emerging isotopes

R&D isotopes: supply-limited!

localized

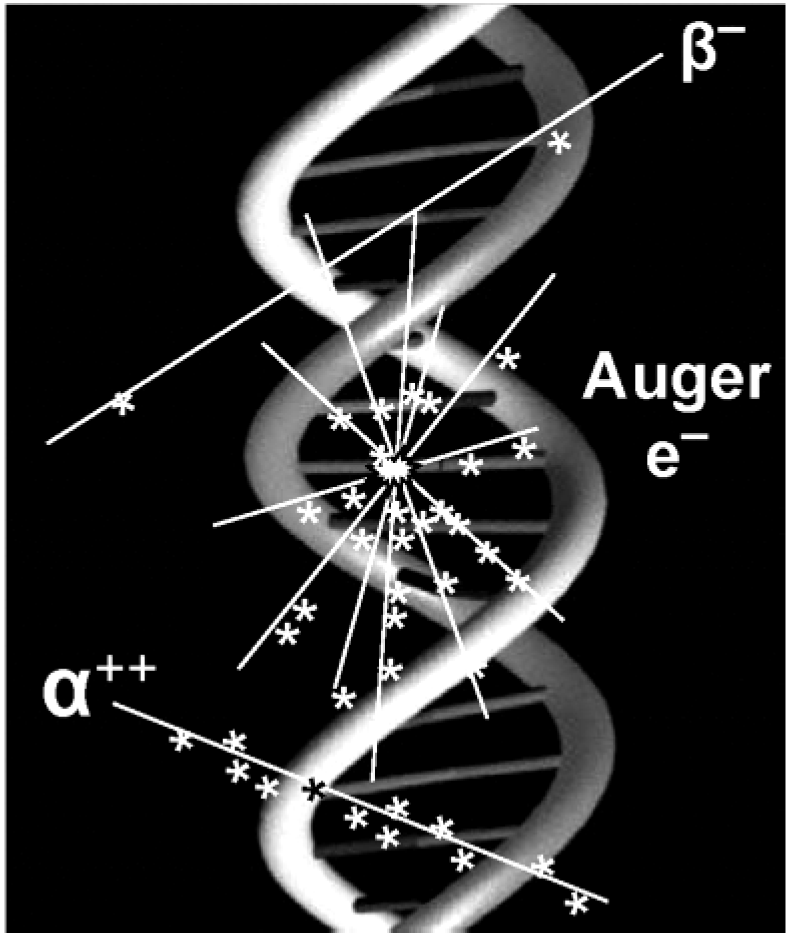
Modern, better targeted bioconjugates require shorter-range radiation ⇒ need for adequate (R&D) radioisotope supply.

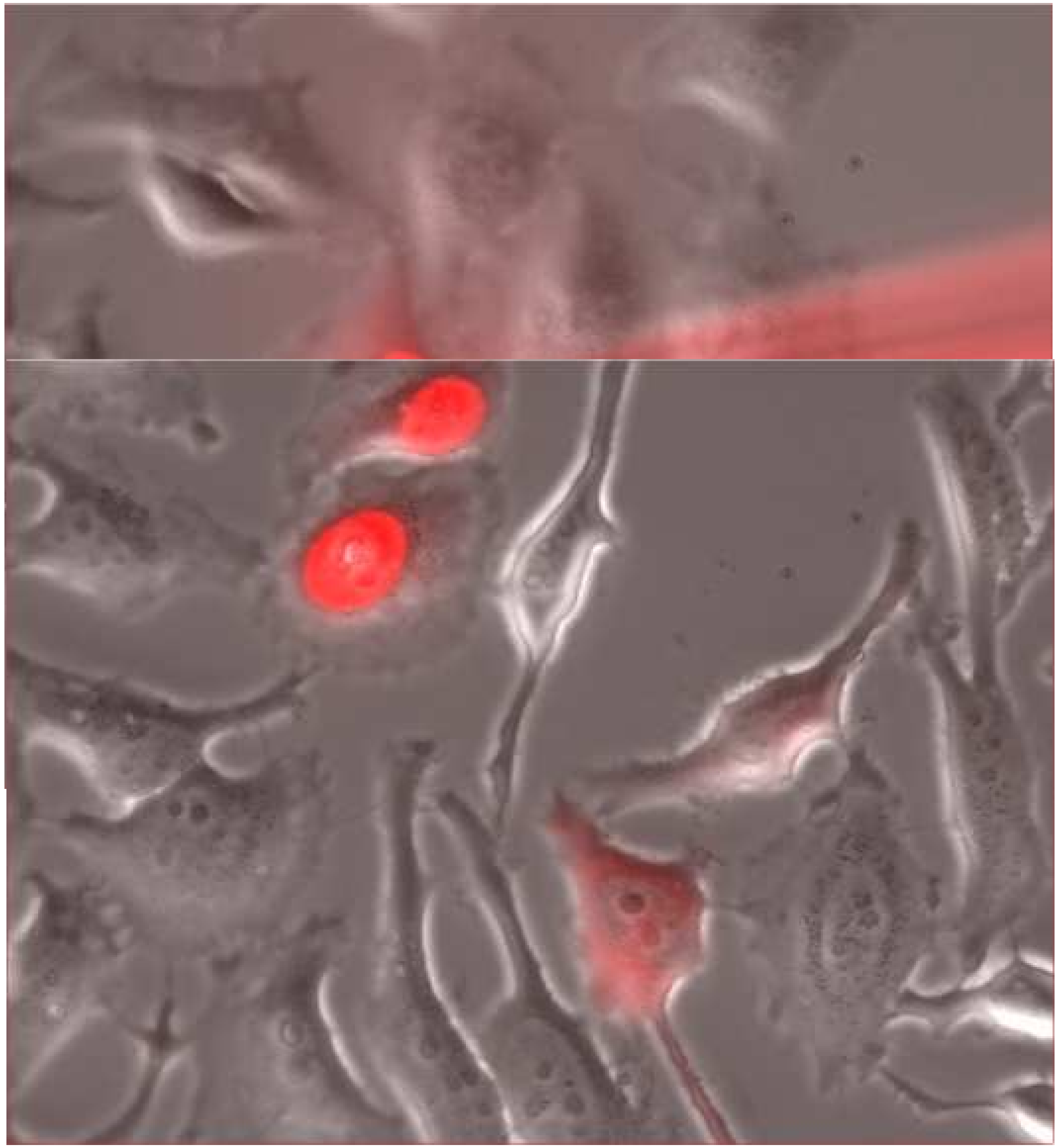
LET of Auger electrons



A.I. Kassis, Rad. Prot. Dosimetry 143 (2011) 241.

Radiobiology of Auger electron emitters ?





M. Jensen et al., DTU Risø

Outlook

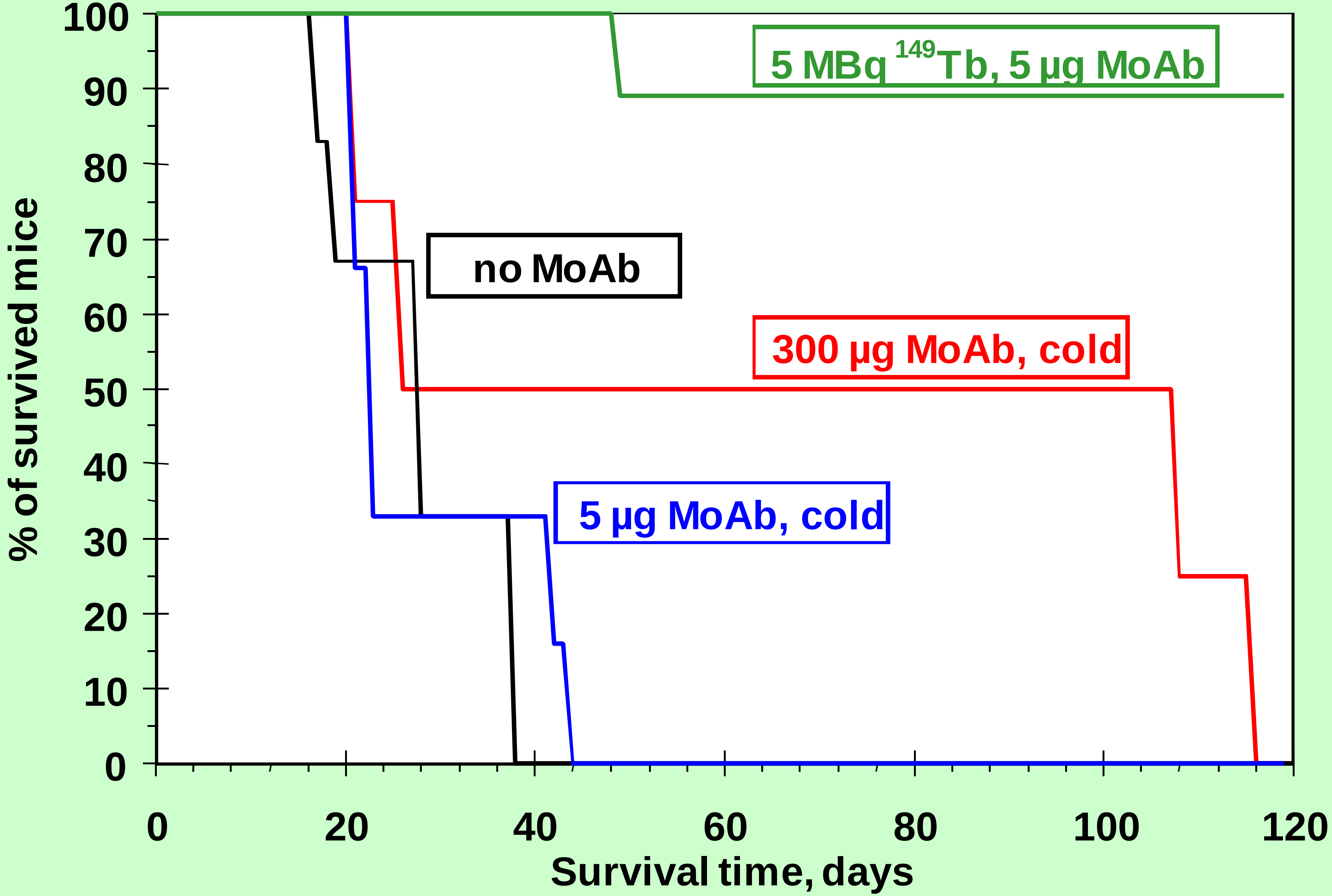
The ideal agent for cancer therapy would consist of heavy elements capable of emitting radiations of molecular dimensions, which could be administered to the organism and selectively fixed in the protoplasm of cells one seeks to destroy. While this is perhaps not impossible to achieve, the attempts so far have been unsuccessful.

*C. Regaud, A. Lacassagne, Radiophysiologie et Radiotherapie 1 (**1927**) 95.*
Translation : A.I. Kassis, Int. J. Radiat. Biol. 80 (2004) 789.

Today we are closer than ever to reach this goal !

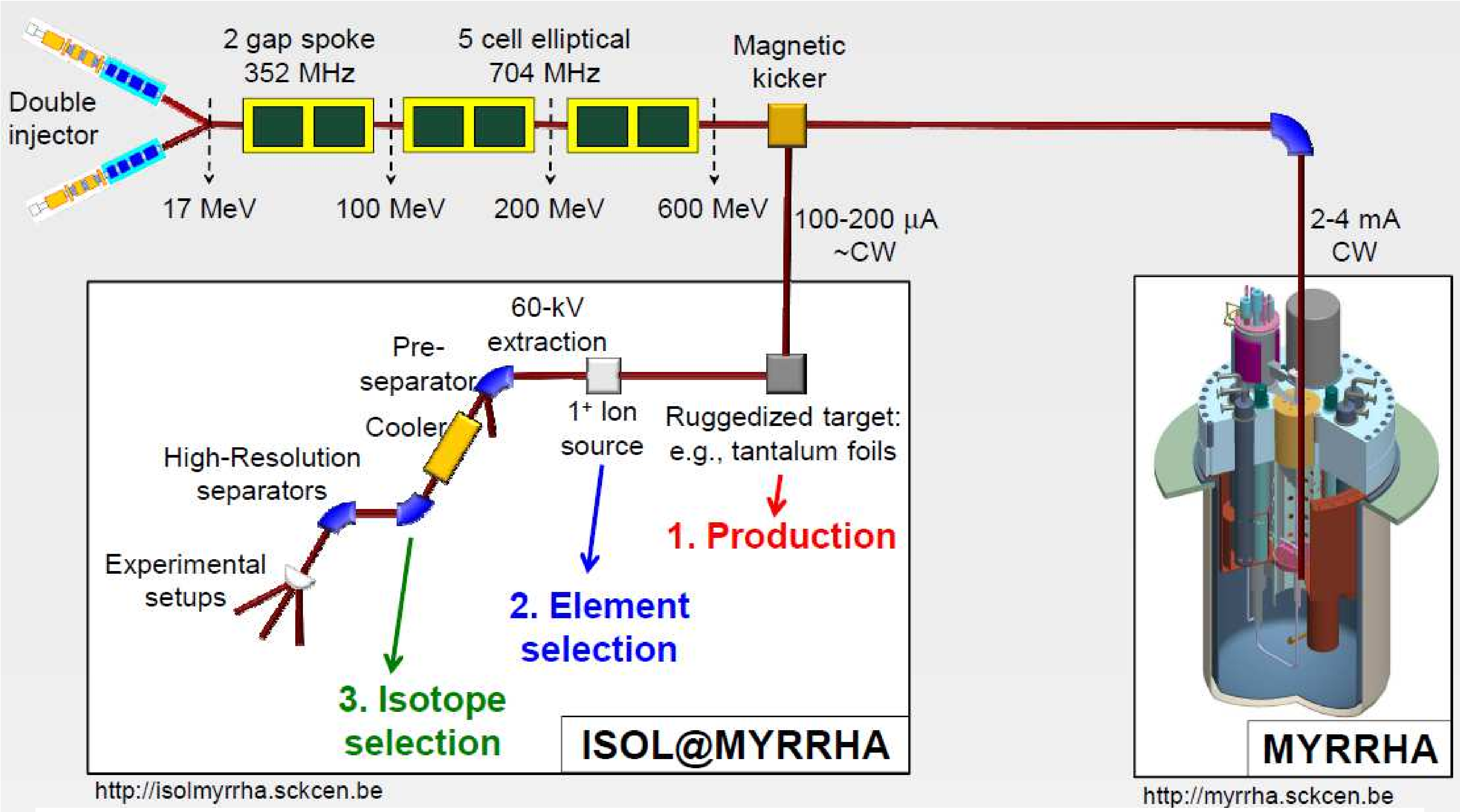
From lab to patient

Idea: Targeted alpha therapy with ^{149}Tb



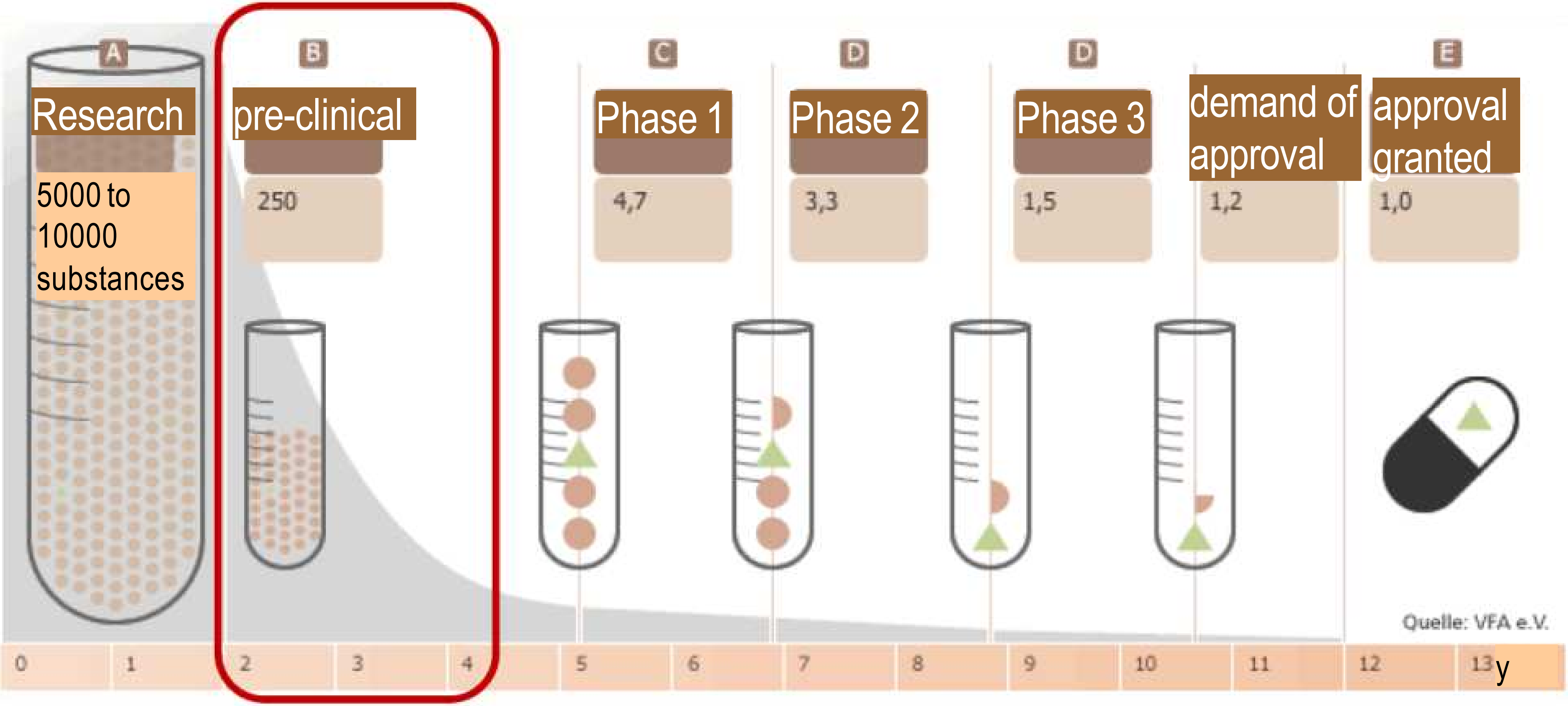
G.J. Beyer et al., Eur. J. Nucl. Med. Molec. Imaging ***31*** *(2004) 547.*

Vision: large-scale production possible



Also possible at:
PSI, ISIS, SNS, LANL, J-PARC, ESS, SPL, EURISOL,…

Endurance: Development of pharmaceuticals



Screening in vitro tests
animal exp.

tests with humans

toxicity
side effects

wanted effect

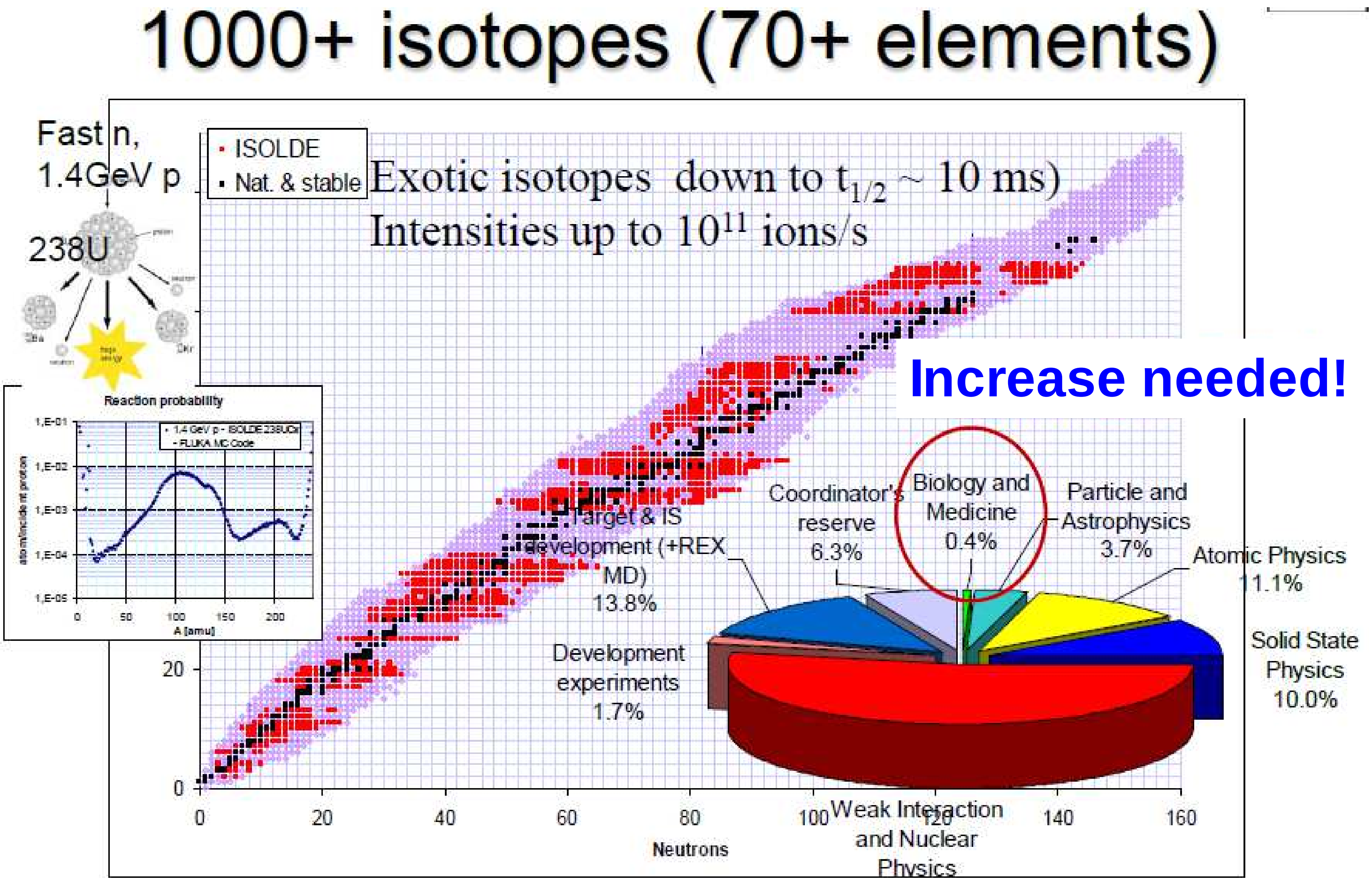
comparison with standard

20-80 healthy volunteers

100-300 patients

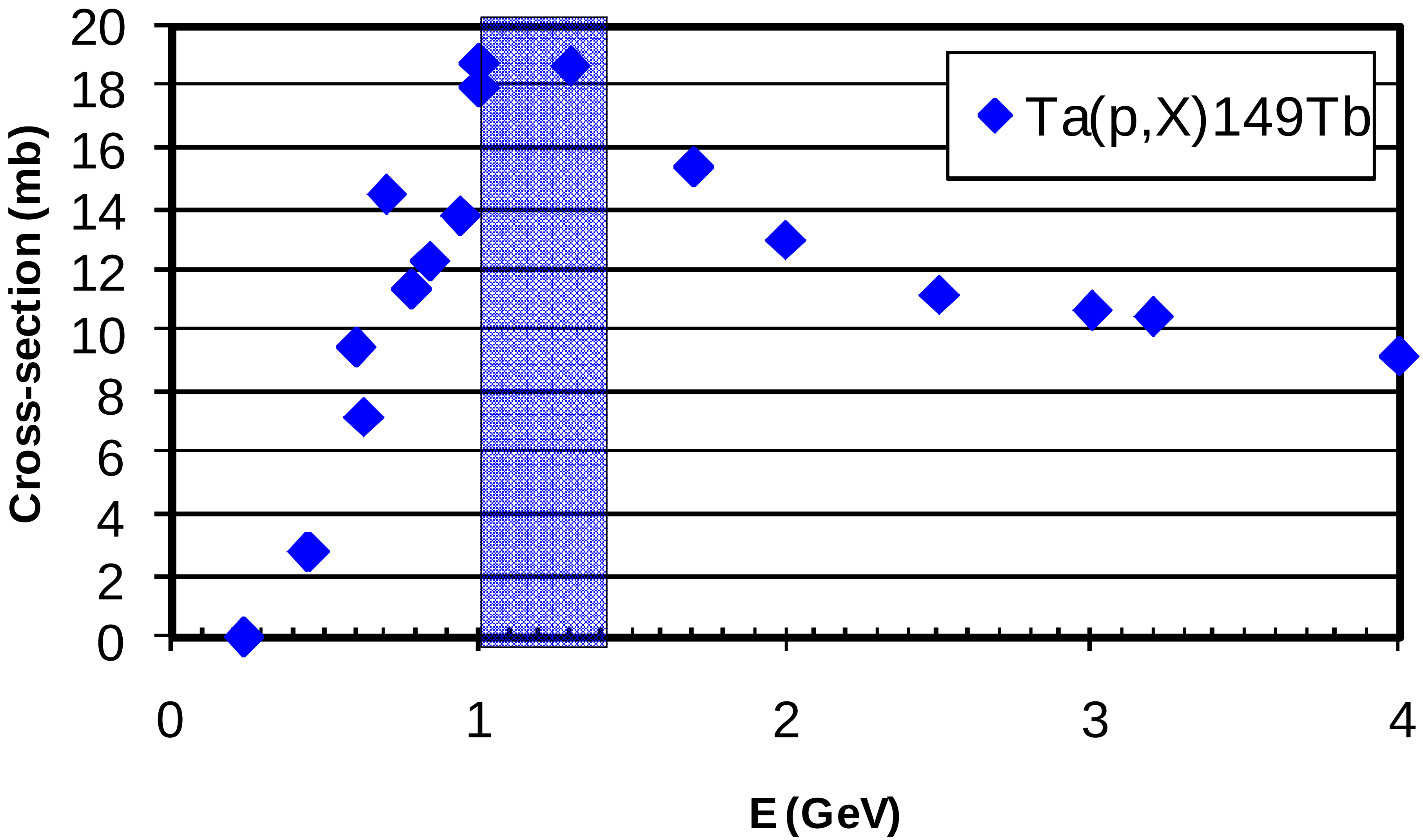
x00-x000 patients

Isolde: a multi-use facility



Accelerator Wishlist

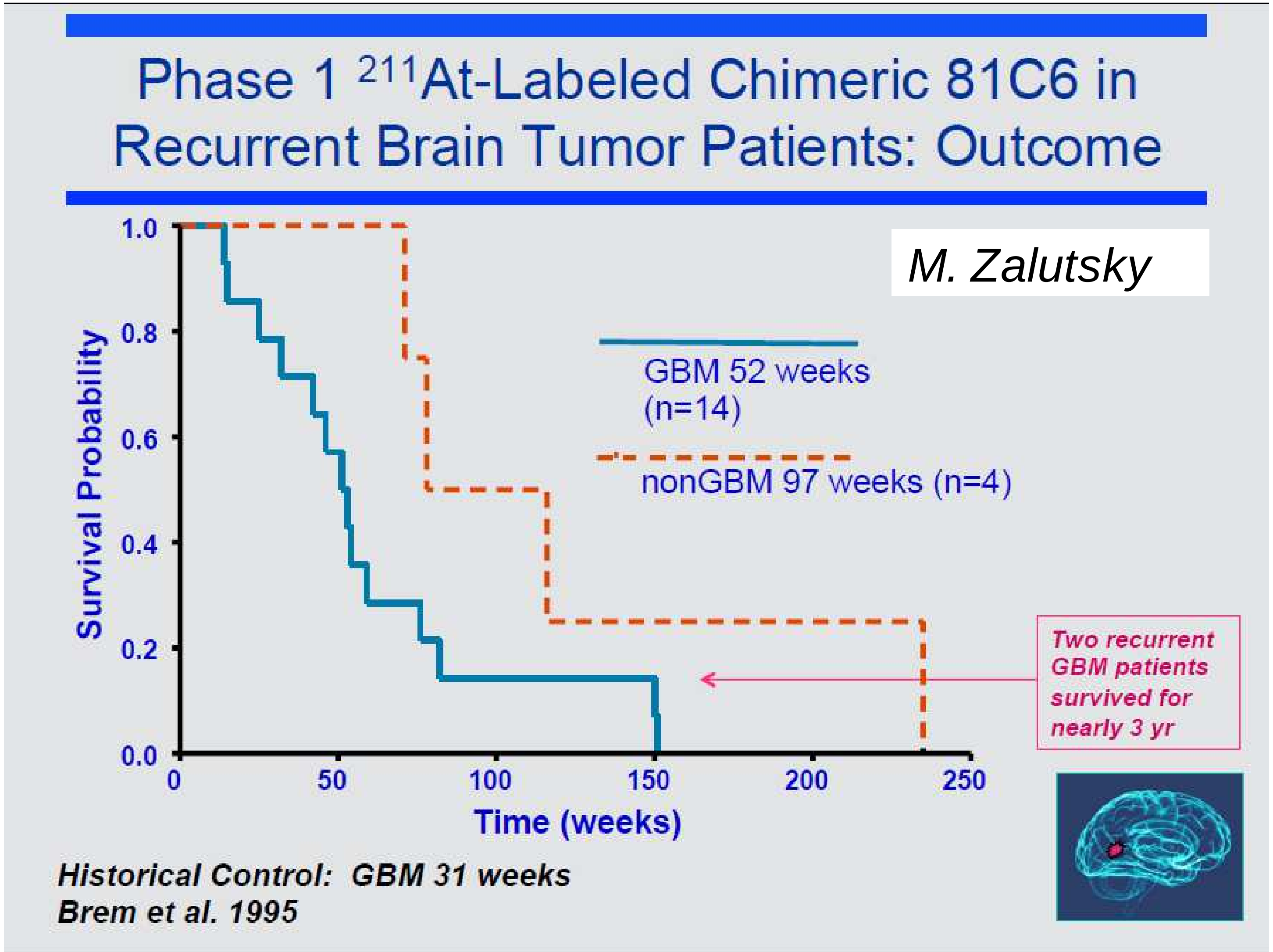
GeV protons for spallation production



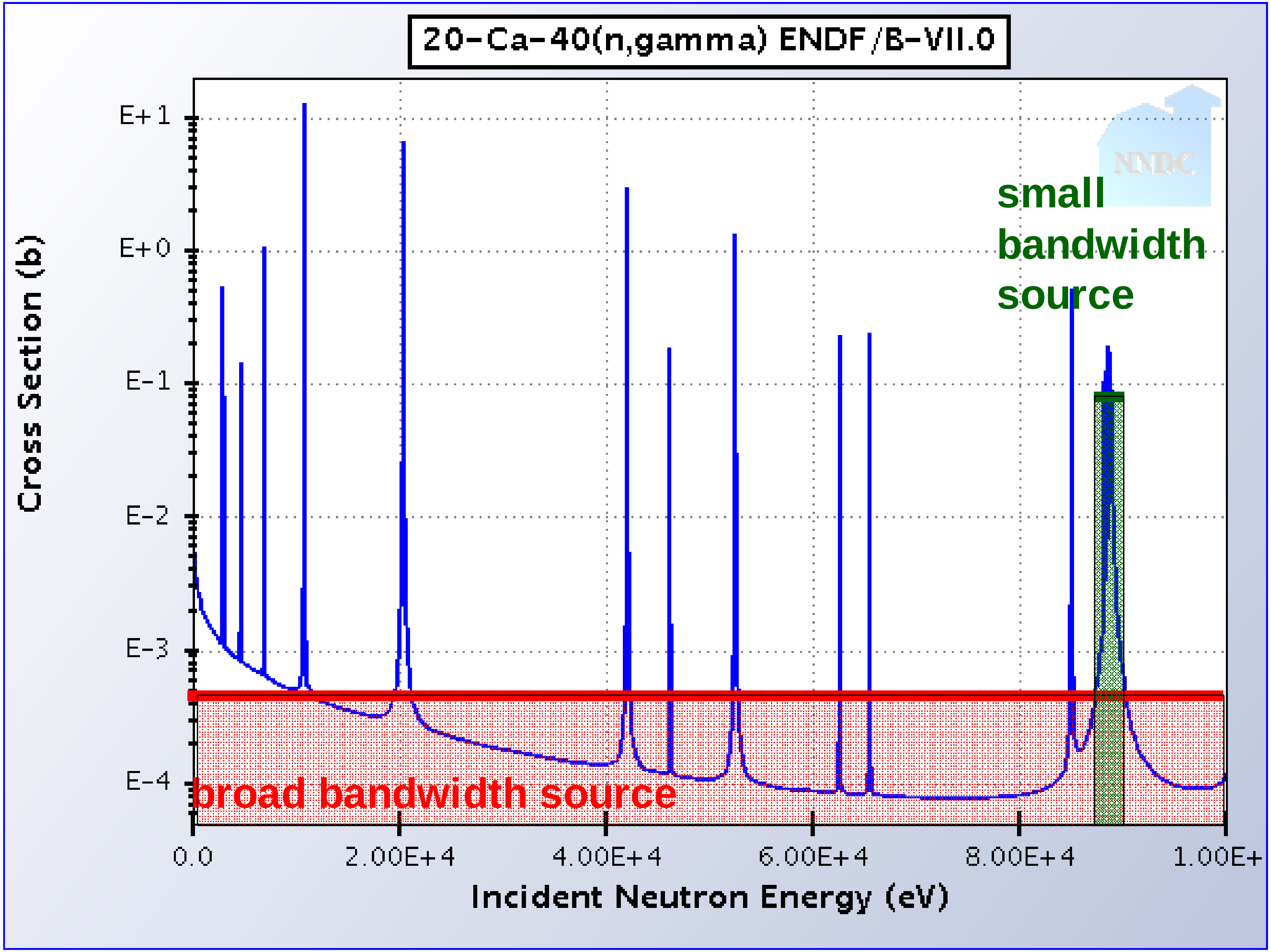
> 1 GeV, ≈100 μA, "parasitic use"

also > 100 MeV in beam dumps (^{44}Ti)

^{4}He beams with tens of MeV



≈100 μA, 29 MeV $^{4}He^{2+}$ for $^{209}Bi(\alpha,2n)^{211}At$
tens of MeV for other (α,xn) reactions

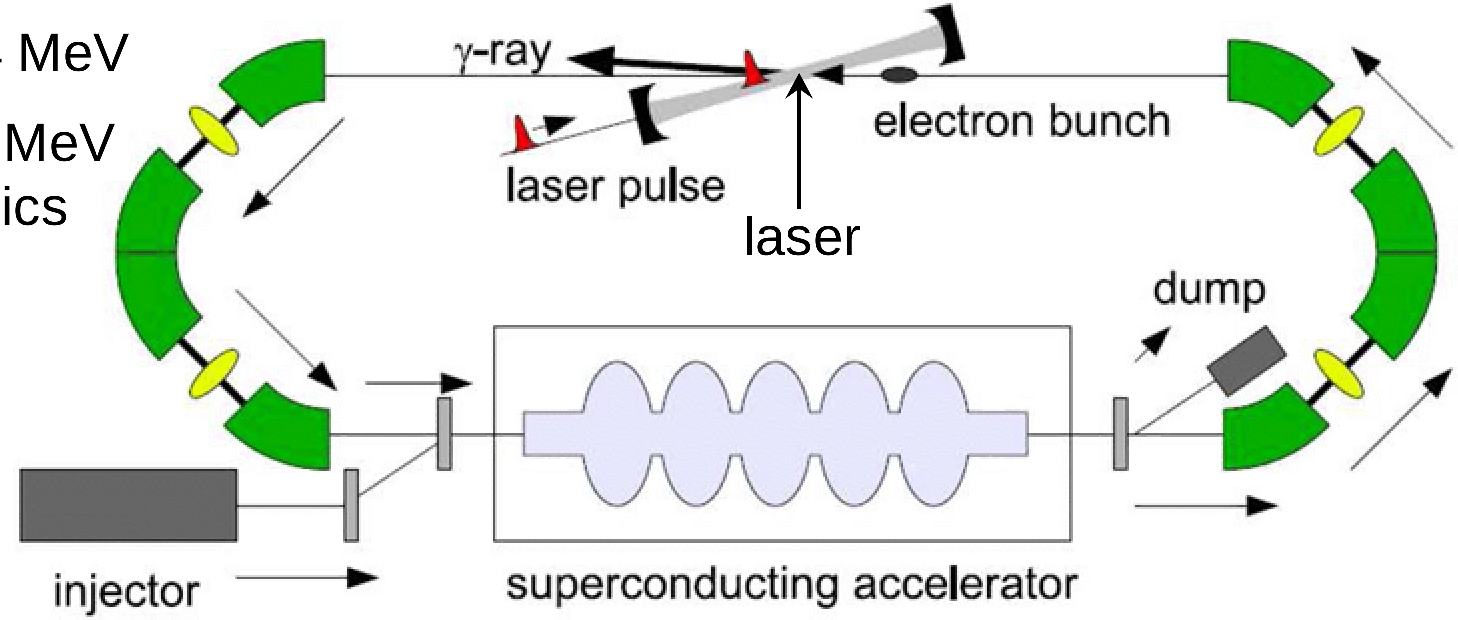


20-Ca-40(n,gamma) ENDF/B-VII.0
Cross Section (b)
E+1
E+0
E-1
E-2
E-3
E-4
0.0
2.00E+4
4.00E+4
6.00E+4
8.00E+4
1.00E+
Incident Neutron Energy (eV)
small bandwidth source
broad bandwidth source
NNDC

Energy recovery linac (ERL)

E_γ = 0.2 – 14 MeV

E_γ = 1 – 100 MeV
high harmonics



100's MeV e^-, 1 – 100 mA ERL, 10's μm interaction area

$^{226}Ra(\gamma,n)^{225}Ra$ 1 Ci/day using few mCi ^{226}Ra targets
$^{195}Pt(\gamma,\gamma')^{195m}Pt$ 2 Ci/mg
$^{170}Er(\gamma,n)^{169}Er$ 20 Ci/mg
etc.

D. Habs and U. Köster, Appl. Phys. B103 (2011) 501.

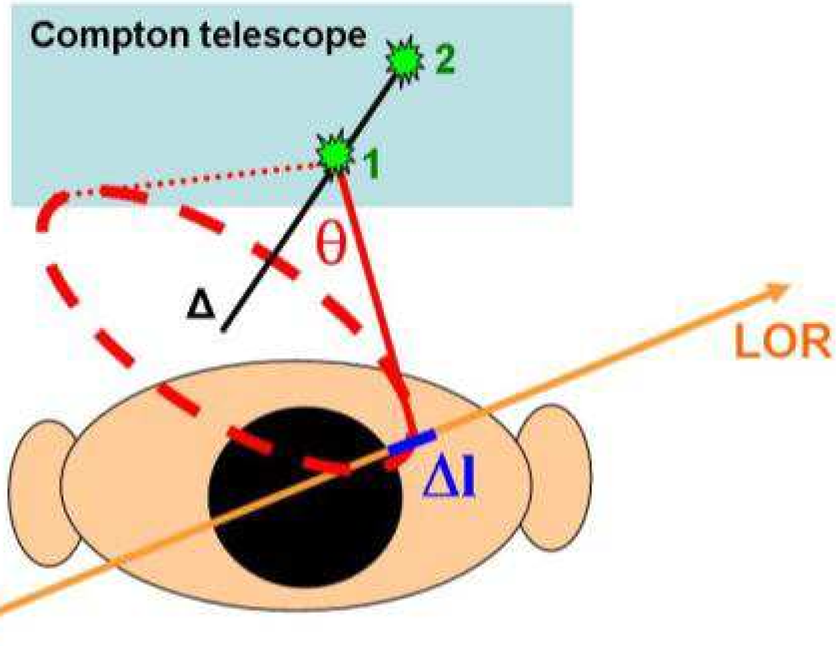
Detector Wishlist

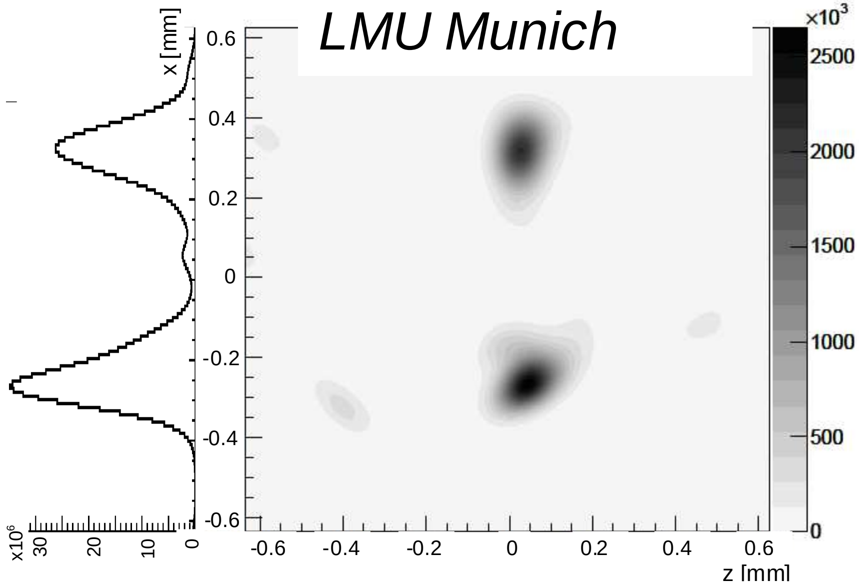
Longer-lived PET isotopes

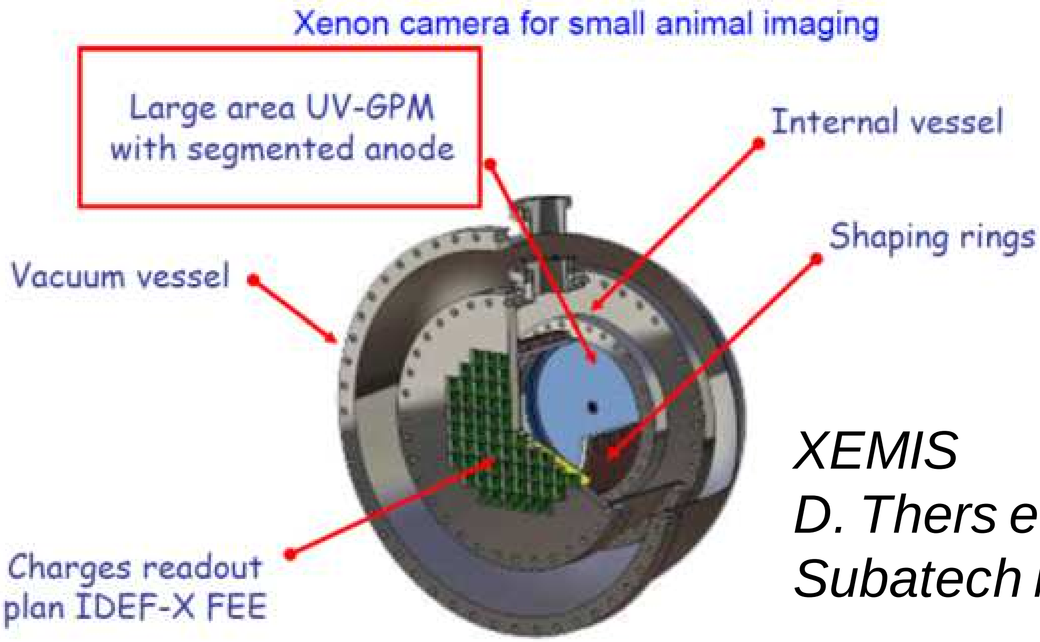
Radio-nuclide	Half-life (h)	Branching ratio β⁺ (%)	Branching ratio γ (%)	h_{10} (mSv/h/GBq)
Sc-44	3.97	94.3	101	0.324
Cu-64	**12.7**	**17.6**	**0.5**	**0.03**
Y-86	14.7	31.9	320	0.515
Zr-89	**78.4**	**22.7**	**100**	**0.182**
I-124	**100.2**	**22.8**	**99**	**0.17**
Tb-152	17.5	17	142	

3-photon-cameras

Compton camera
C. Lang et al.
LMU Munich







XEMIS
D. Thers et al.,
Subatech Nantes

Applications:

- ^{34m}Cl
- ^{44}Sc
- ^{52m}Mn
- ^{86}Y
- $^{94(m)}Tc$
- ^{124}I
- ^{152}Tb

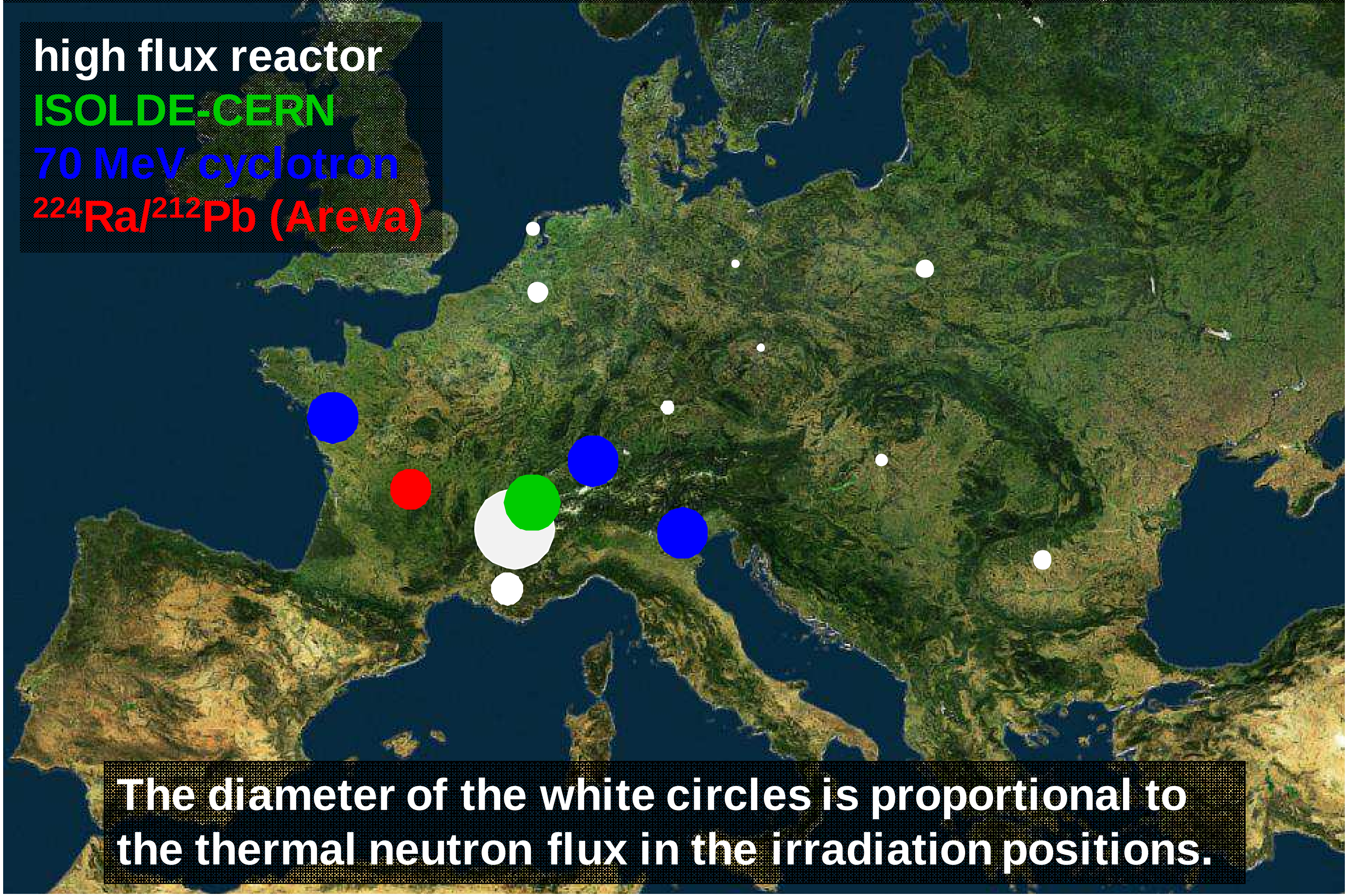
Summary: Radioisotopes for Medicine

1. **Trends**
   - alternative ^{99m}Tc production (economic question, not technical)
   - more PET isotopes, more generators, more “big” accelerators
   - molecular therapy of cancer ⇒ better isotopes (^{177}Lu,…)
   - Theranostics (personalized medicine) ⇒ need of radiometals
   - earlier treatment ⇒ shorter range ⇒ new isotopes (alpha, Auger)

2. **Highly interdisciplinary**
   - physics (accelerator, target) + radiochemistry (target, separation, labeling) + biochemistry (vectors) + pharmacy (QC, QA) + medicine (preclinical and clinical trials)
   - need for interdisciplinary education and training, in particular metal (radio-)chemistry

3. **Very long leadtimes**
   - shortage of R&D isotopes ⇒ eventually affects many patients
   - unusual technologies must be nurtured by research facilities
   - facilitate facility access for physicians (“mail-out-users”)

Production of innovative radioisotopes in 2016



The diameter of the white circles is proportional to the thermal neutron flux in the irradiation positions.