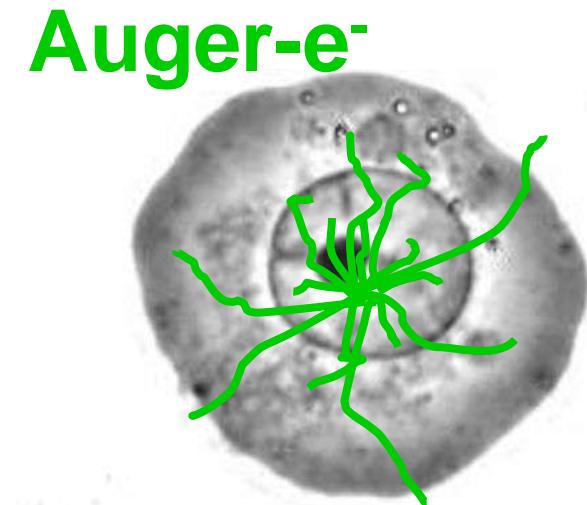
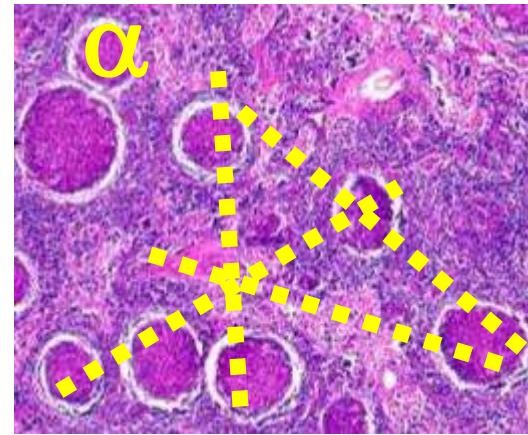
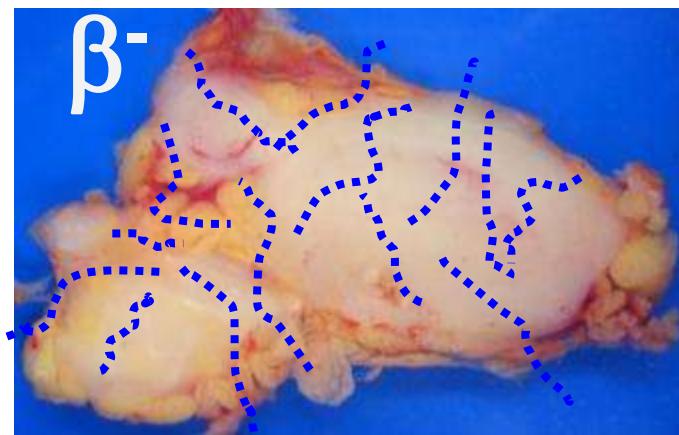
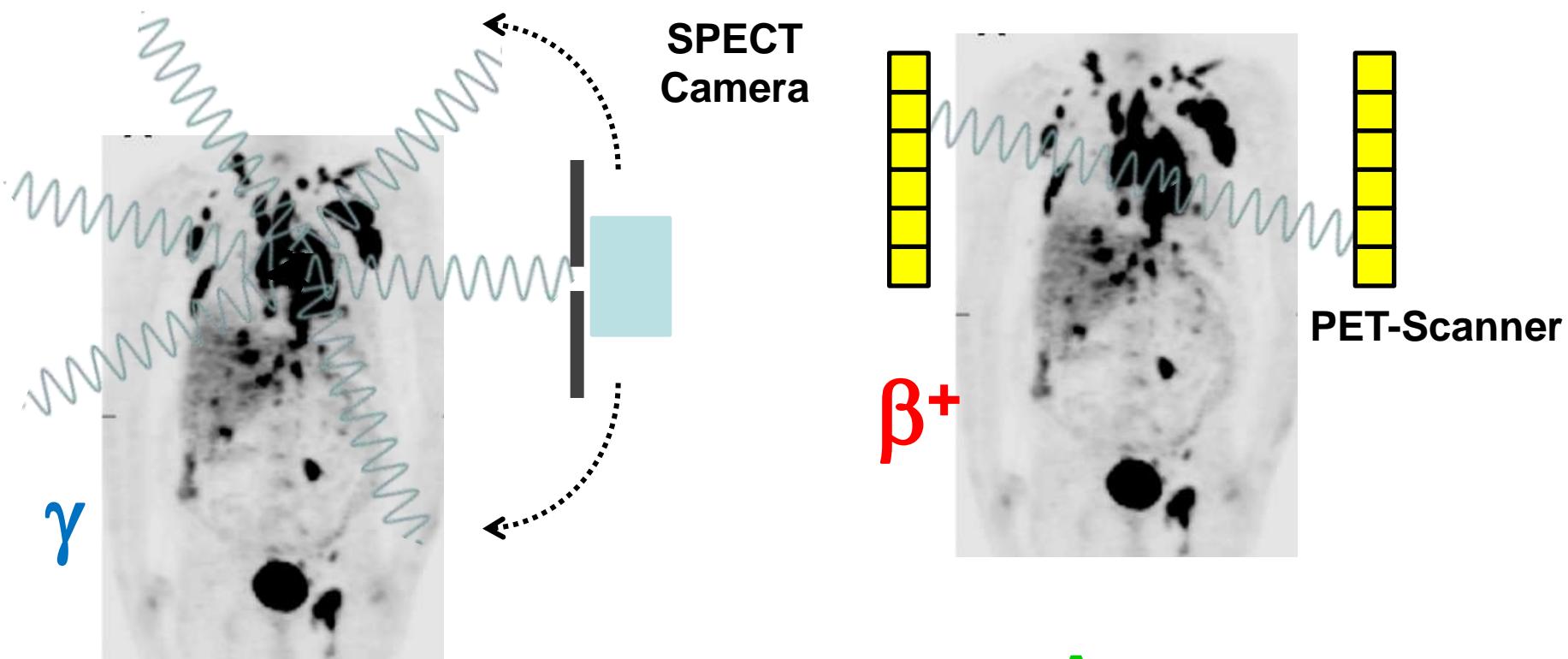
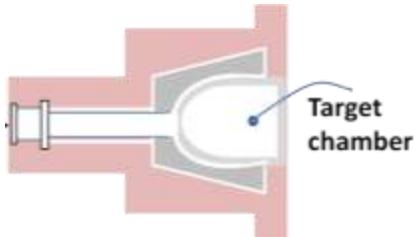


Radioisotopes production and use

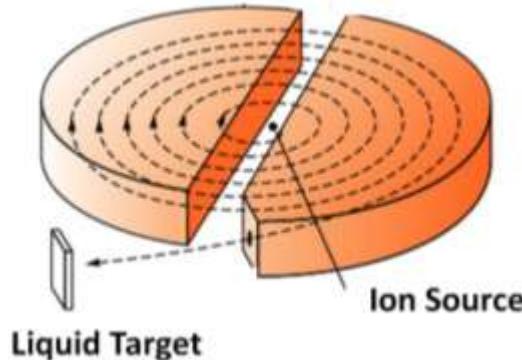
The Nuclear Medicine Alphabet



Cyclotron versus reactor production



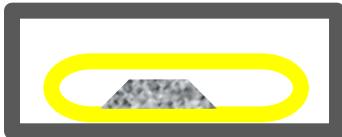
H_2^{18}O water
(liquid target)



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



Transformation into FDG
by automated synthesis
modules in shielded hot cell



$^{176}\text{Yb}_2\text{O}_3$
(powder in quartz
ampoule & Al capsule)

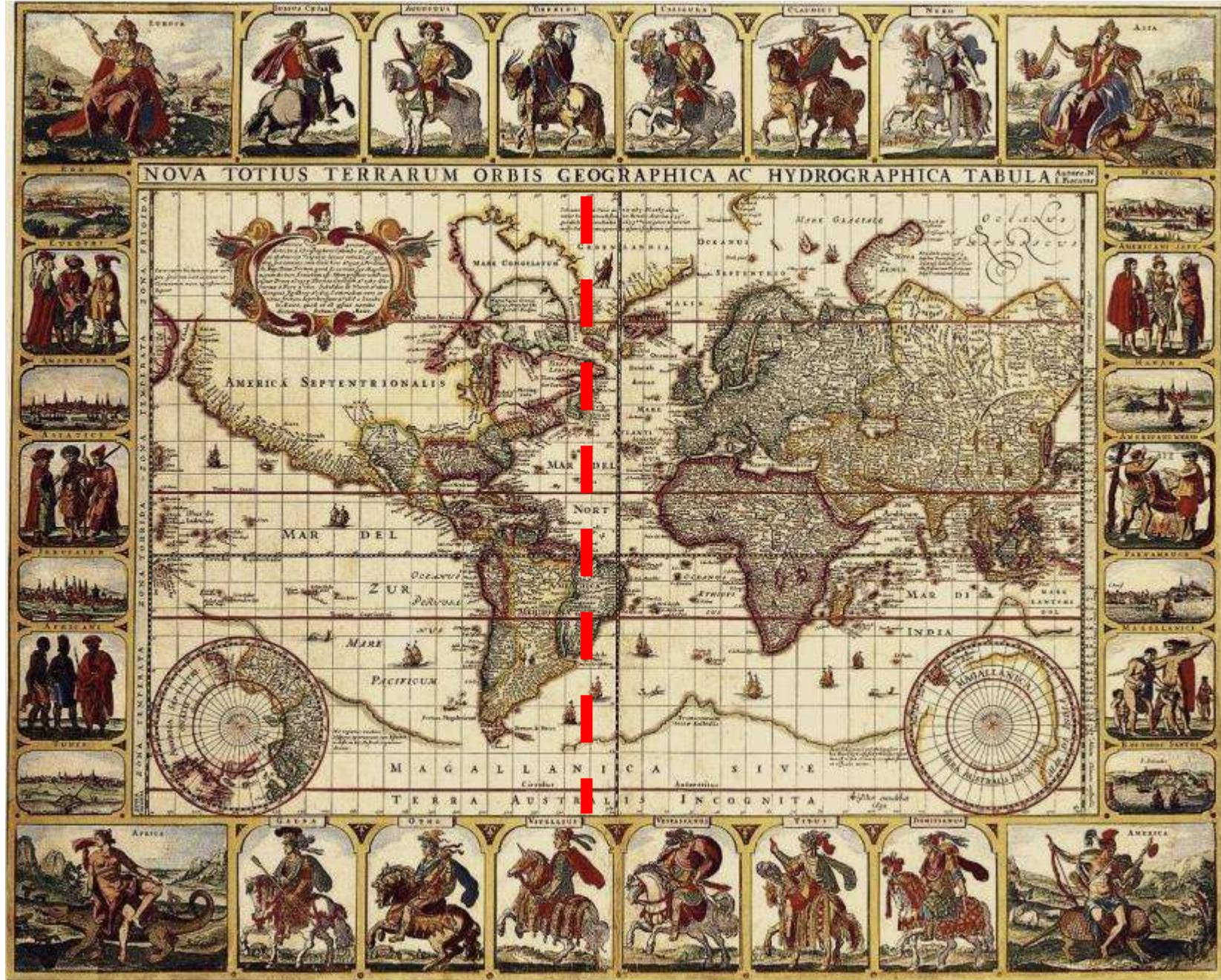


Reactor irradiation
 $^{176}\text{Yb}(\text{n},\gamma)^{177}\text{Yb}(\beta^-)^{177}\text{Lu}$
produces $[^{177}\text{Lu}/^{176}\text{Yb}]$ oxide

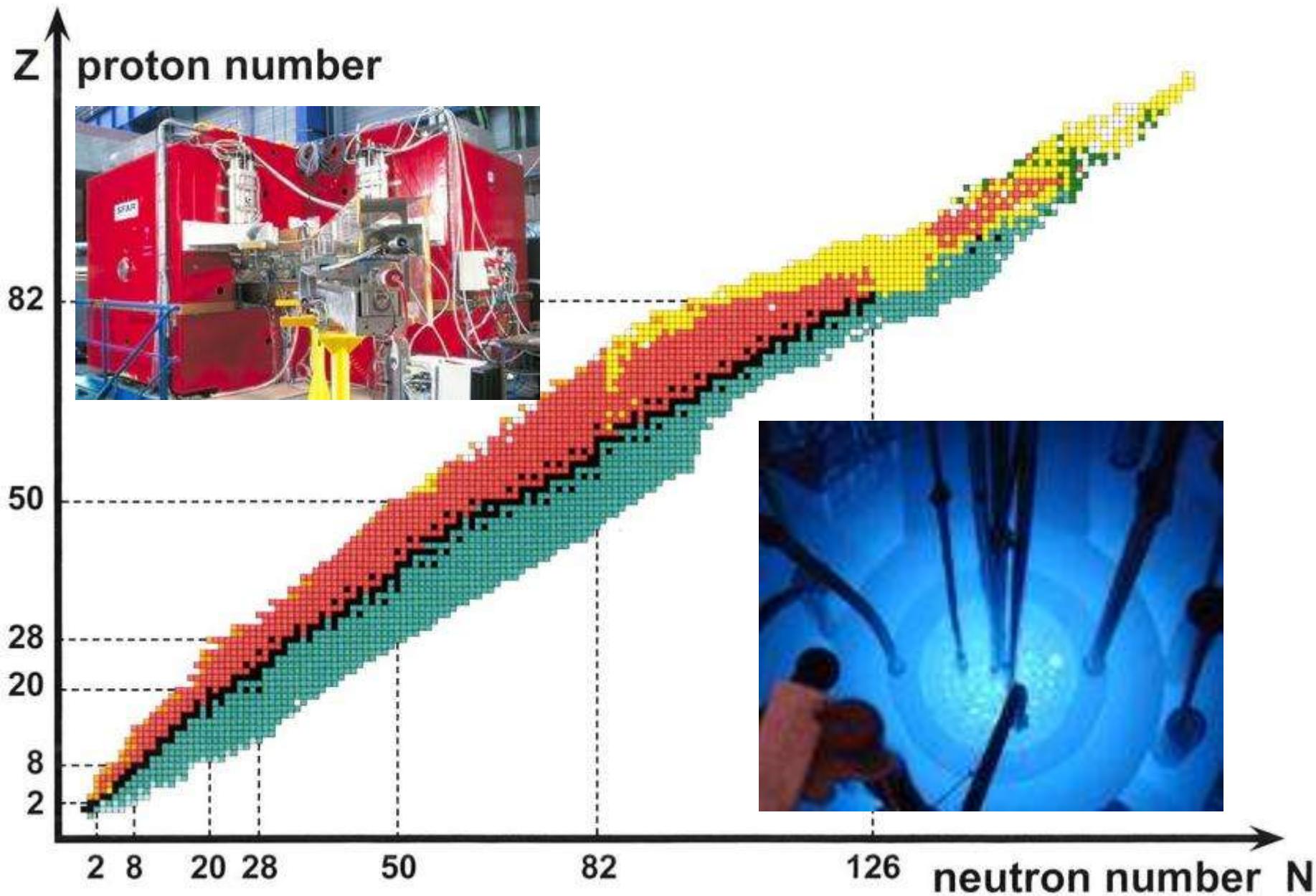


Radiochemical separation
of Lu from Yb
in shielded hot cells

The Tordesillas meridian



The Tordesillas meridian of radioisotope production



Reactor vs. cyclotron

Ge 64 64 s β^+ 3.0, 3.3... γ 427, 667 128...	Ge 65 31 s β^+ 4.6, 5.2... γ 650, 62, 809 191... $\beta\bar{\nu}$ 1.28...	Ge 66 2.3 h β^+ 0.7, 1.1... γ 382, 44, 109 273...	Ge 67 18.7 m β^+ 3.0, 3.2... γ 167, 1473...	Ge 68 270.82 d ϵ no β^+ no γ σ 1.0	Ge 69 39.0 h β^+ 1.2... γ 1107, 574 872, 1336...	Ge 70 20.57 σ 3.0	Ge 71 11.43 d ϵ no γ	Ge 72 27.45 β 0.9
Ga 63 31.4 s β^+ ~4.5... γ 637, 627, 193 650...	Ga 64 2.62 m β^+ 2.9, 6.1... γ 992, 808 3366, 1387 2195...	Ga 65 15 m β^+ 2.1, 2.2... γ 115, 61, 153 752...	Ga 66 9.304 h β^+ 4.2... γ 1039, 2752 834, 2190 4296...	Ga 67 78.278 h ϵ no β^+	Ga 68 67.63 m β^+ 1.9... γ 93, 185, 300... γ 1077, (1833...)	Ga 69 60.108 σ 1.68	Ga 70 21.15 m β^- 1.7... ϵ γ (1040, 176)	Ga 71 39.892 σ 4.7
Zn 62 9.13 h ϵ β^+ 0.7 γ 41, 597, 548 508...	Zn 63 38.1 m β^+ 2.3... γ 670, 962 1412...	Zn 64 49.17 σ 0.74 $\sigma_{n,\alpha}$ 1.1E-5 $\sigma_{n,p}$ < 1.2E-5	Zn 65 244.3 d ϵ , β^+ 0.3 γ 1115...	Zn 66 27.73 σ 0.9 $\sigma_{n,\alpha}$ < 2E-5	Zn 67 4.04 σ 6.9 $\sigma_{n,\alpha}$ 0.0004	Zn 68 18.45 σ 0.072 ± 0.8 $\sigma_{n,\alpha}$ < 2E-5	Zn 69 13.8 h β^- 439 β^- ... γ (319...)	Zn 70 56 m β^- 0.9... γ (319...) σ 0.0081 ± 0.083
Cu 61 3.4 h β^+ 1.2... γ 283, 656, 67 1186...	Cu 62 9.74 m β^+ 2.9... γ (1173...)	Cu 63 69.15 σ 4.5	Cu 64 12.7004 h ϵ β^- 0.6, β^+ 0.7 γ (1346) σ ~270	Cu 65 30.85 ϵ β^- 2.6... γ 1039, (834...)	Cu 66 5.1 m σ 2.17 σ 140	Cu 67 61.9 h β^- 0.4, 0.6... γ 185, 93, 91...	Cu 68 3.8 m β^- 526, 85 β^- 11... β^- 1.7, 1.9 γ 1077... γ 1261...	Cu 69 3.0 m β^- 2.5... γ 1007, 834 531... 9
Ni 60 26.223 σ 2.9	Ni 61 1.1399 σ 2.5 $\sigma_{n,\alpha}$ 3E-5	Ni 62 3.6346 σ 15	Ni 63 100 a β^- 0.07 no γ σ 20	Ni 64 0.9255 σ 1.6	Ni 65 2.52 h β^- 2.1... γ 1482, 1115 366... σ 22	Ni 66 54.6 h β^- 0.2 no γ	Ni 67 21 s β^- 3.8... γ (1937, 1115 822...)	Ni 68 29 s β^- 758, 84 9
Co 59 100 σ 20.7 + 16.5	Co 60 10.5 m β^- 0.3 γ 59, e^- β^- 1.5... γ (1332...) γ 1173... σ 58 σ 2.0	Co 61 1.65 h β^- 1.2... γ 67, 909... σ 2.0	Co 62 14.0 m β^- 2.9... γ 1173... 1163 2003... 1129...	Co 63 27.5 s β^- 3.6... γ 87, 982...	Co 64 0.3 s β^- 7.0... γ 1346, 931	Co 65 1.14 s β^- 6.0... γ 1141, 310 963...	Co 66 0.18 s β^- 7.2, 8.5... γ 1426, 1246 1805	Co 67 329 ms β^- 8.0... γ 694...

Crossing the meridian ?

**Report of an International Atomic
Energy Agency's Consultants' Meeting
on Fluorine 18: Reactor Production
and Utilization**

HERNAN VERA RUIZ

Department of Research and Isotopes, IAEA, P.O. Box 100, A-1400 Vienna, Austria

H. Vera Ruiz, Appl Radiat Isot 1988;39:31.

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

Transport of short-lived radioisotopes

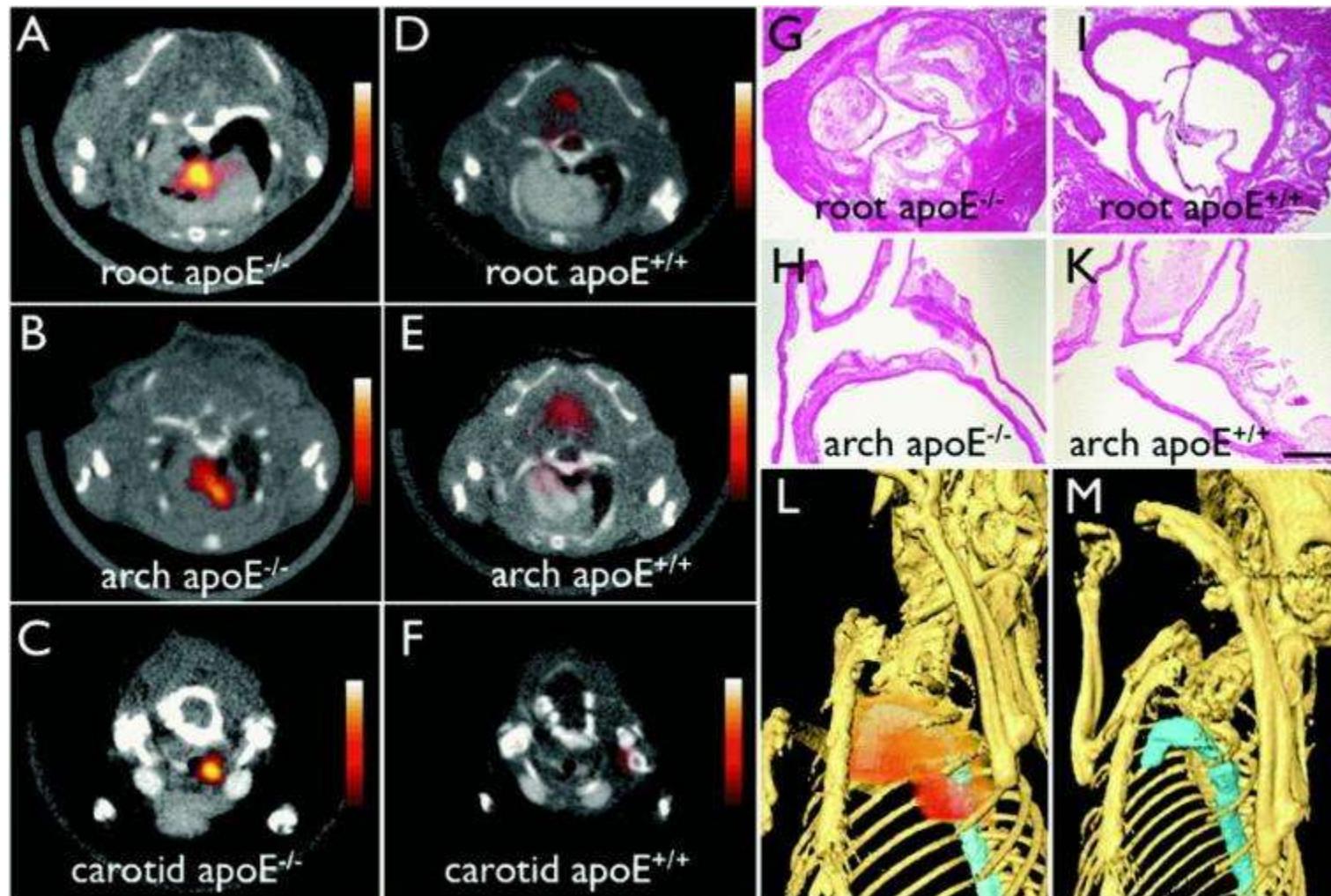


PET isotopes

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O-15	0.03	99.9	0.74	3.2
F-18	1.83	96.7	0.25	0.7
Ga-68	1.13	271 d generator		3.8
Rb-82	0.02	25 d generator		20

Nanoparticle PET-CT Imaging of Macrophages in Inflammatory Atherosclerosis

^{64}Cu -TNP



Longer-lived PET isotopes

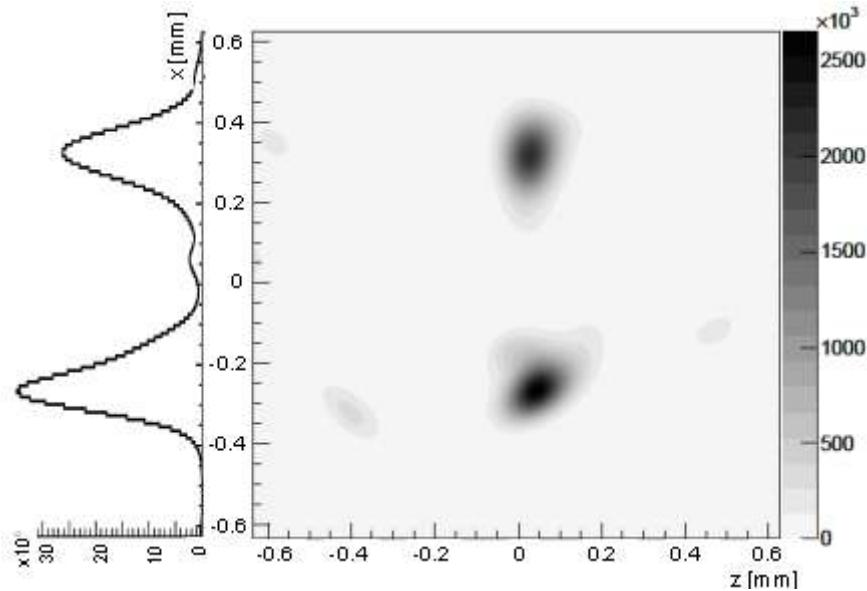
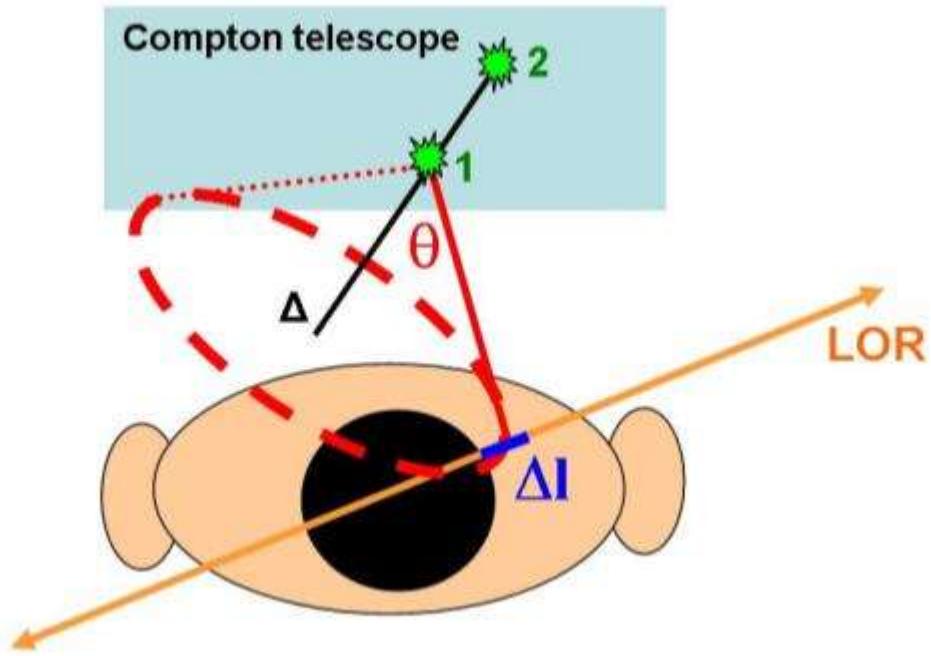
Radio-nuclide	Half-life (h)	Intensity β^+ (%)	E mean (MeV)	Range (mm)
Sc-44	3.97	94.3	0.63	2.5
Cu-64	12.7	17.6	0.28	0.8
Br-76	16.2	55	1.18	6
Y-86	14.7	31.9	0.66	2.6
Zr-89	78.4	22.7	0.40	1.4
I-124	100	22.8	0.82	3.8

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				$\frac{3.927 \text{ h}}{2^+} \approx 0$
Y-86				
Zr-89				
I-124				
Tb-152				

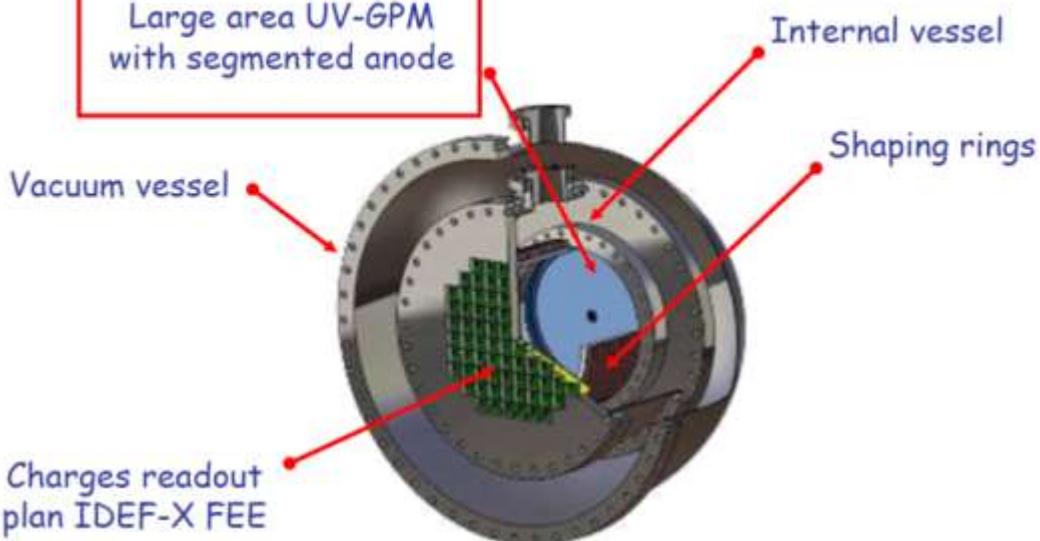
44
20**Ca**

3-photon-cameras



Xenon camera for small animal imaging

Large area UV-GPM
with segmented anode



Applications:

^{34m}Cl

^{44}Sc

$^{52m}\text{Mn}, ^{52g}\text{Mn}$

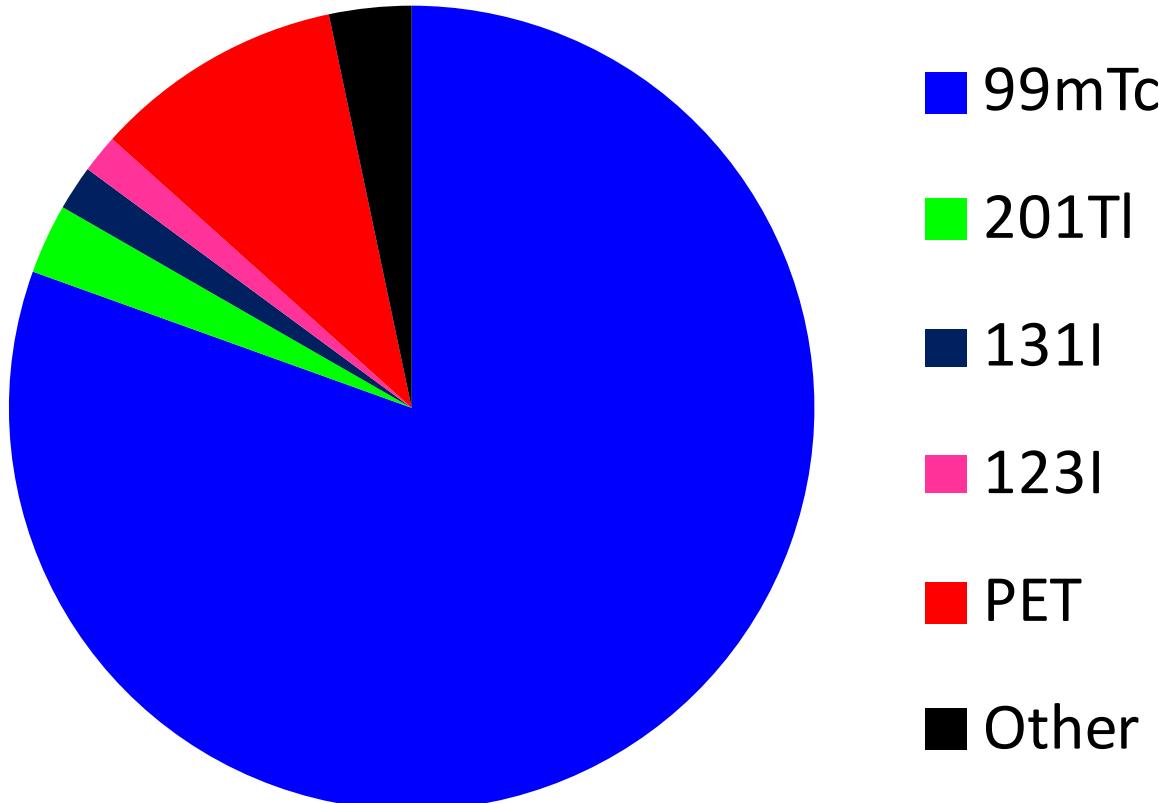
^{86}Y

$^{94(m)}\text{Tc}$

^{124}I

^{152}Tb

The leading radioisotopes



Dose Datamed 2 project; update by NuPECC working group.

All ways lead to Rome; many ways lead to ^{99m}Tc

^{99}Mo production (for generator)

$^{235}\text{U}(\text{n}_{\text{th}}, \text{f})$

$^{238}\text{U}(\text{n}_{\text{fast}}, \text{f})$

$^{238}\text{U}(\gamma, \text{f})$

$^{238}\text{U}(\text{p}, \text{f})$

$^{98}\text{Mo}(\text{n}, \gamma)$

$\text{nat Mo}(\text{n}, \gamma)$

$^{100}\text{Mo}(\text{d}, \text{p})$

$^{100}\text{Mo}(\text{n}, 2\text{n})$

$^{100}\text{Mo}(\text{p}, \text{np})$

$^{96}\text{Zr}(\alpha, \text{n})$

$^{102}\text{Ru}(\text{n}, \alpha)$

Ru 98 1.87 $\sigma < 8$	Ru 99 12.76 $\sigma 4$	Ru 100 12.60 $\sigma 5.8$	Ru 101 17.06 $\sigma 5$	Ru 102 31.55 $\sigma 1.2$
Tc 97 92.2 d $\text{I}_{\gamma}(97)$ e^- $\text{no } \gamma$ $4.0 \cdot 10^5 \text{ a}$	Tc 98 4.2 $\cdot 10^6$ a $\beta^- 0.4$ $\gamma 745; 652$ $\sigma 0.9$	Tc 99 h $\beta^- 2.1 \cdot 10^5 \text{ a}$ $\text{I}_{\gamma}(90)$ $\text{d} 23$	Tc 100 15.8 s $\beta^- 3.4 \dots$ $\text{I}_{\gamma}(740; 591 \dots)$	Tc 101 14.2 m $\beta^- 1.3 \dots$ $\gamma 307; 545 \dots$
Mo 96 16.68 $\sigma 0.5$	Mo 97 9.56 $\sigma 2.5$ $\sigma_{\text{n}, \alpha} 4E-7$	Mo 98 4.19 $\sigma 0.14$	Mo 99 66.0 $\beta^- 1.1 \cdot 10^{19} \text{ a}$ $\gamma 400; 770 \dots$ m; g	Mo 100 9.67 $\beta^- 2.8 \cdot 10^{-19} \text{ a}$ $\gamma 787; 723; 1169 \dots$
Nb 95 86.6 h $\text{I}_{\gamma} 236$ $\text{e}^- 0.2$ $\beta^- 1.0 \dots$ $\gamma 204$ $\sigma < 7$	Nb 96 23.4 h $\beta^- 0.7 \dots$ $\gamma 778; 569; 1091 \dots$	Nb 97 53 s $\text{I}_{\gamma} 743$ $\beta^- 1.3 \dots$ $\gamma 658$	Nb 98 1 m $\beta^- 2.0 \dots$ $\gamma 787; 723; 1169 \dots$ $\text{I}_{\gamma} 1024 \dots$	Nb 99 2.6 s $\beta^- 3.2 \dots$ $\gamma 98; 254; 2642; 2854 \dots$ $\text{I}_{\gamma} 365 ?$ 15 s
Zr 94 17.38 $\sigma 0.049$	Zr 95 64.0 d $\beta^- 0.4; 1.1 \dots$ $\gamma 757; 724 \dots$ g	Zr 96 2.80 $3.9 \cdot 10^{19} \text{ a}$ $2\beta^-$ $\sigma 0.020$	Zr 97 16.8 h $\beta^- 1.9 \dots$ $\gamma 508; 1148; 355 \dots$ m	Zr 98 30.7 s $\beta^- 2.3$ $\text{no } \gamma$ g

direct ^{99m}Tc production

$^{100}\text{Mo}(\text{p}, 2\text{n})$

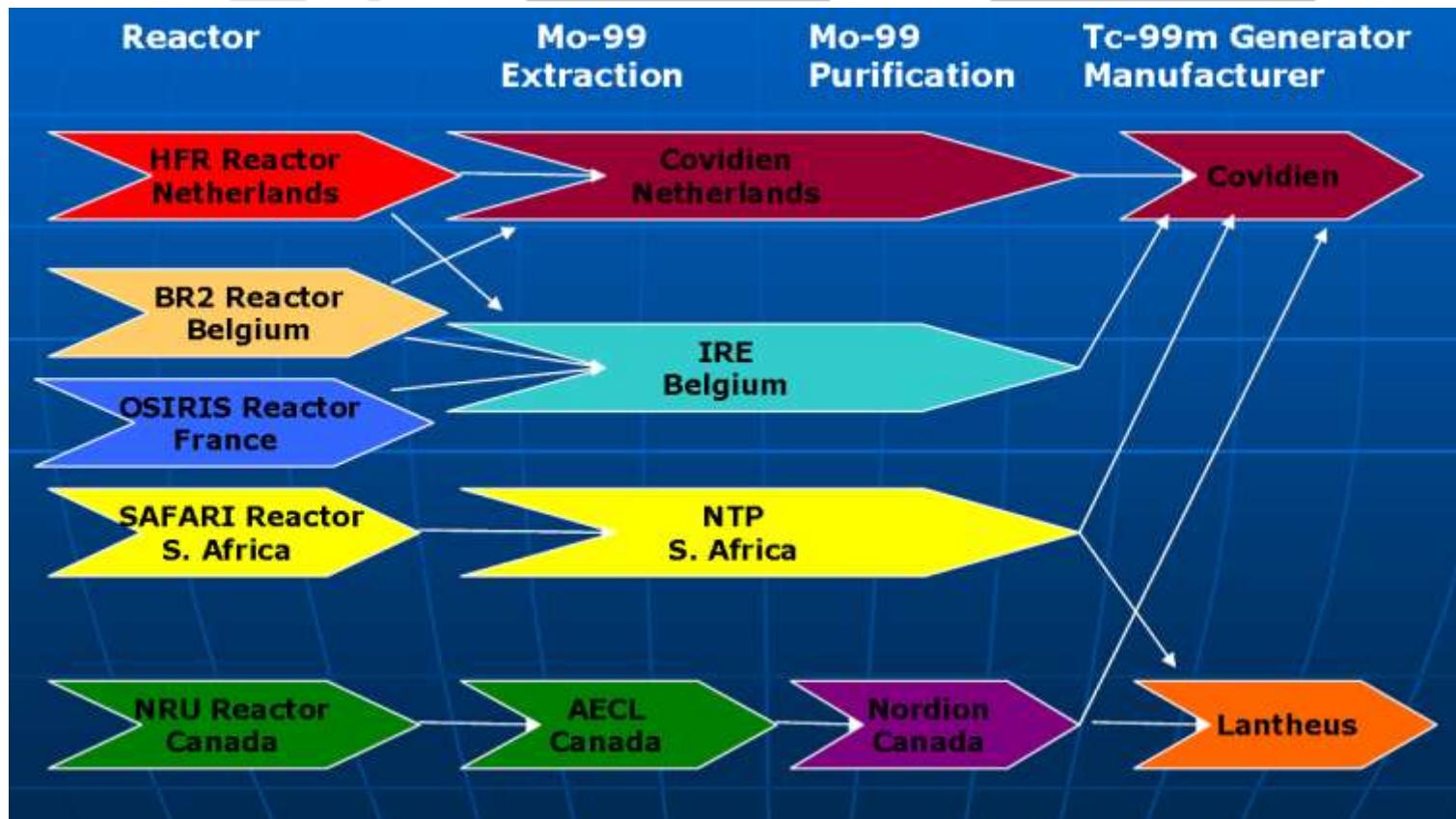
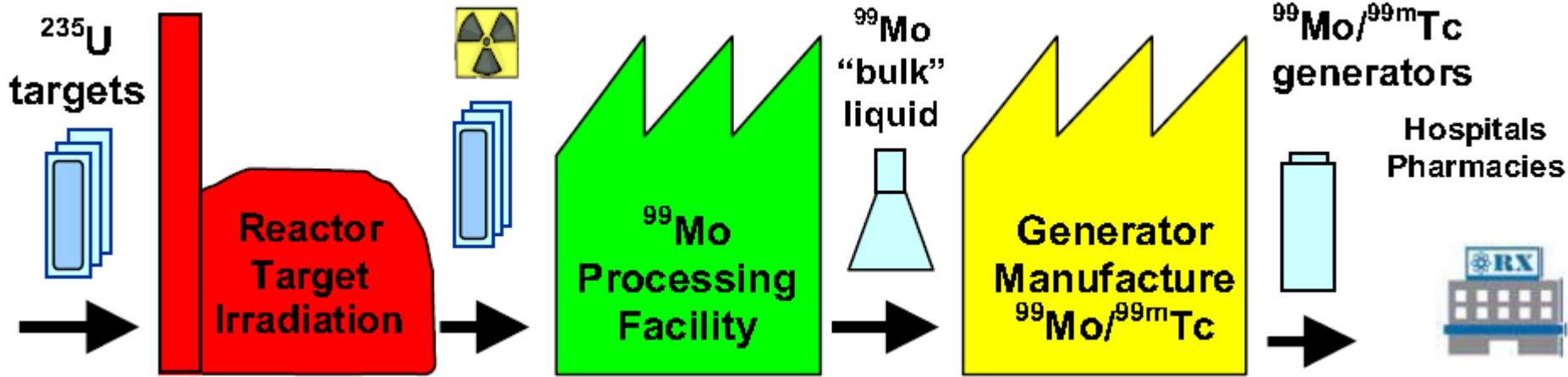
$\text{nat Mo}(\alpha, \text{x})$

$^{98}\text{Mo}(\text{d}, \text{n})$

$^{99}\text{Ru}(\text{n}, \text{p})$

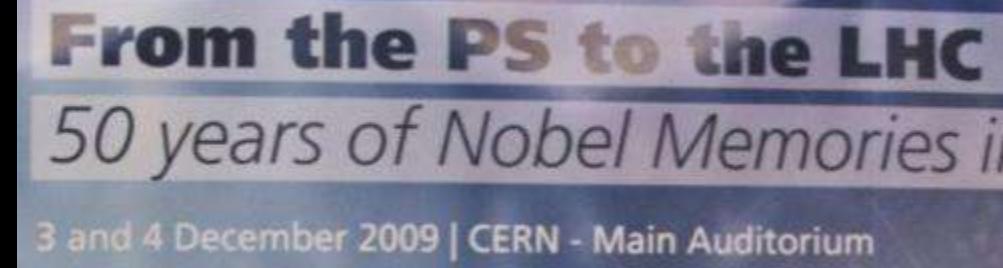
^{99m}Tc production is not a physics problem!

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



Main reactors used for ^{99}Mo production

Reactor	Location	Country	Power (MW)	Fuel	Operation (days per year)	Age (years)	Typical ^{99}Mo world market share
NRU	Chalk River	Canada	135	LEU	315	57	40%
HFR	Petten	Netherlands	45	LEU	280	53	30%
BR2	Mol	Belgium	100	HEU	140	53	10%
OSIRIS	Saclay	France	70	LEU	180	48	3%
SAFARI	Pelindaba	South Africa	20	HEU	315	49	10%



>50 years old accelerators (CERN-PS, BNL-AGS, etc.)
are celebrated, not retired!

New research reactors

FRM2 2004



OPAL 2006



CARR 2010



RJH 2017

New/additional reactors for ^{99}Mo production

Reactor	Location	Country	Power (MW)	Fuel	Operation (days per year)	Operation (Age)	Potential ^{99}Mo world market share
LVR-15	Rez	Czech Republic	10	LEU	200	57	10%
MARIA	Warsaw	Poland	20-30	LEU	180	40	5%
FRM2	Garching	Bavaria	20	HEU	240	10	20%
OPAL	Lucas Heights	Australia	20	LEU	290	8	25%
RJH	Cadarache	France	100	LEU	220	-3	25%
RA-10	Ipero	Brazil	10	LEU	290	-4	20%
AR-10	Argentina		10	LEU	290	-?	20%

Research reactors are multi-use facilities

Neutron scattering

Neutron radiography

Nuclear physics

Neutron physics

Fuel testing

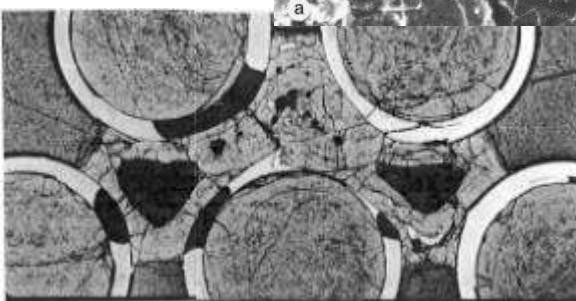
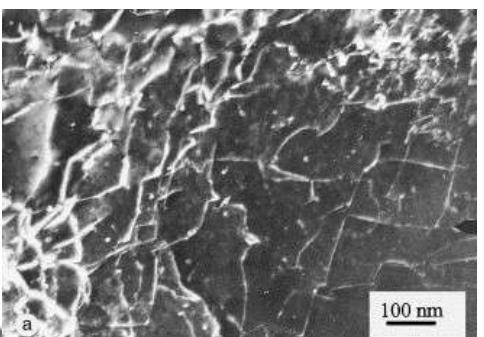
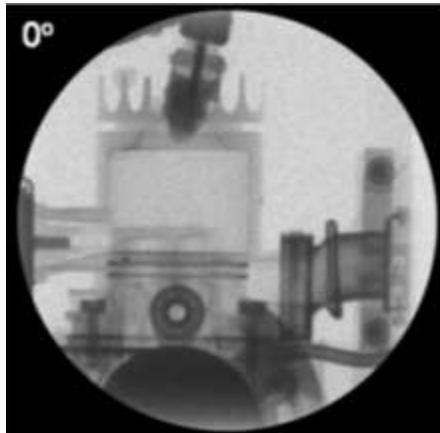
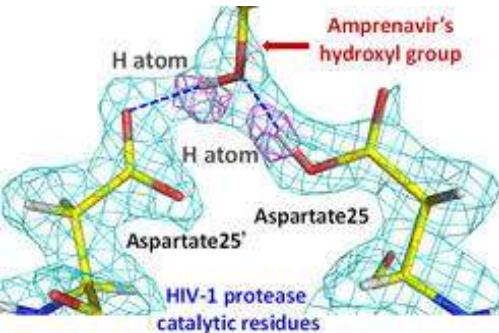
Materials irradiation

NTD silicon

Neutron activation analysis

Radioisotope production

etc.



**Research reactors are not like power reactors.
They do NOT have a technical retirement age.**

**In the long run there will be no shortage of
reactors for radioisotope production.**

**It is simply a question of market price how
many of these want to produce ^{99}Mo .**

The economy of the aviation industry and of nuclear medicine



19% “Fuel” sourcing
Reactor **0.11% (0.26€)**



5% “Fuel” refinement
Mo processing **0.67% (1.64€)**
Generator **0.14% (0.34€)**



Transport
Radiopharmacy **3.51% (8.62€)**



17% Equipment
(amortization,
maintenance,
leasing, chartering)



31% Personal costs

Total 245.61€
OECD-NEA, 2008



Recent voices on $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ supply

Atcher has doubts about both NorthStar and SHINE. "In a nutshell, both of these companies are start-up companies," he says, adding, "2016 is not that far away and they are scrambling to get their programmes going."

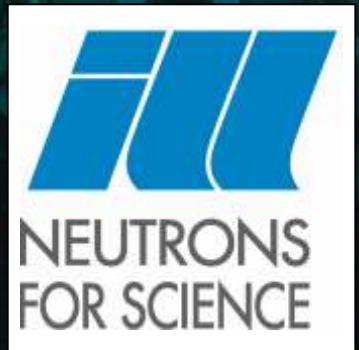
reactor approach. "Obviously, each of these competitors has a secret recipe where they think they can beat the odds," says Meyer. But the uncertainty in the economics scared away larger companies such as General Electric and Babcock and Wilcox, both of which initially showed an interest in developing medical-isotope schemes but backed out last year.

more diverse future. "The long-term scenario will really be driven by the market," says Schaffer. "I equate it to the electricity market, where we have nuclear, wind, hydroelectric, solar and so on. And the price of that source of electricity pretty much defines its share of the market. I

All the uncertainty about the technologies is leaving doctors such as Verzijlbergen concerned. "There is a lot of optimism but we need proof," he says. "Even though there is a lot of potential, there is also a lot of risk."

Should a research facility engage in production ?

Institut Laue-Langevin



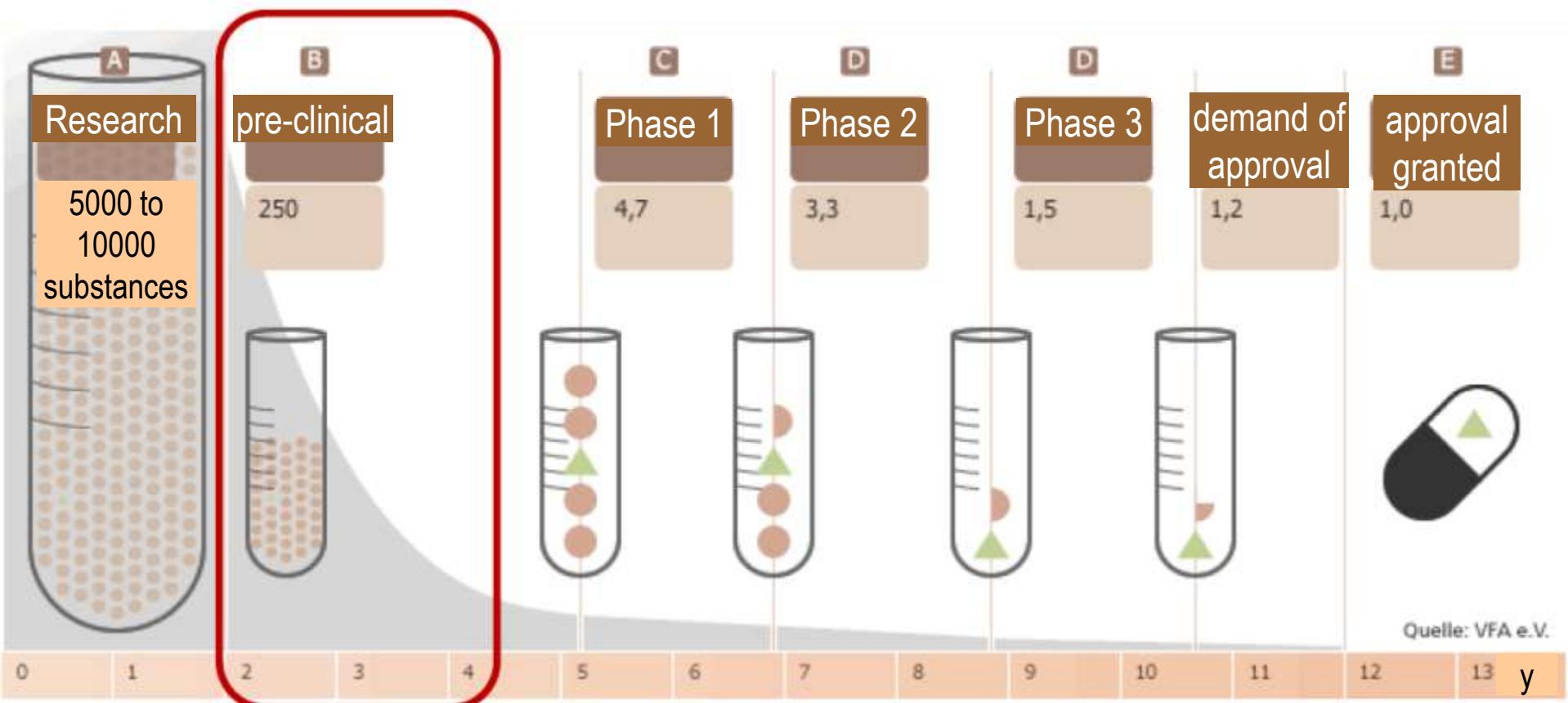
$^{188}\text{W}/^{188}\text{Re}$ generator

Os 188 13.24	Os 189 6 h β^- (31) e^-	Os 189 16.15 β^- (40) e^- $\alpha < 1\text{E-}5$	Os 190 9.9 m β^- 503; 617; 361; 187... $\alpha 9 + 4$ $\sigma_{\text{n}, \alpha} < 2\text{E-}5$
Re 187 62.60 $5 \cdot 10^{10} \text{ a}$ β^- 0.0026 no γ $\sigma 2 + 72$	Re 188 18.9 m β^- 64; 106... e^- 633...	Re 188 16.98 h β^- 1.0... γ 217; 219; 245... g; m	Re 189 24.3 h β^- 1.0... γ 217; 219; 245... g; m
W 186 28.43 $\sigma 37$	W 187 23.72 h β^- 0.6; 1.3... γ 686; 480; 72... $\sigma 70$	W 188 69 d β^- 0.5... γ (291; 227...) g $\sigma 12$	



^{188}W production requires high-flux reactor:
HFIR (Oak Ridge), SM3 (Dimitrovgrad), BR2 (Mol)
ILL (Grenoble)

Development of pharmaceuticals



Screening

in vitro tests
animal exp.

tests with humans

toxicity wanted effect
side effects

comparison
with standard

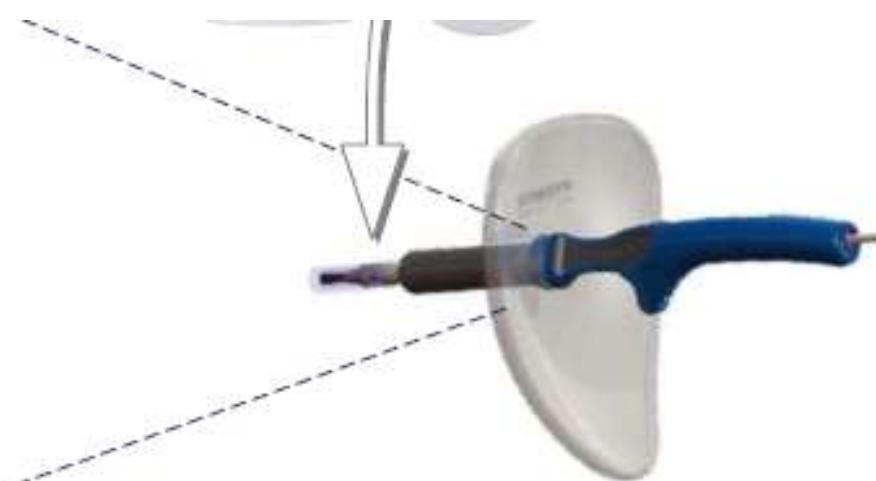
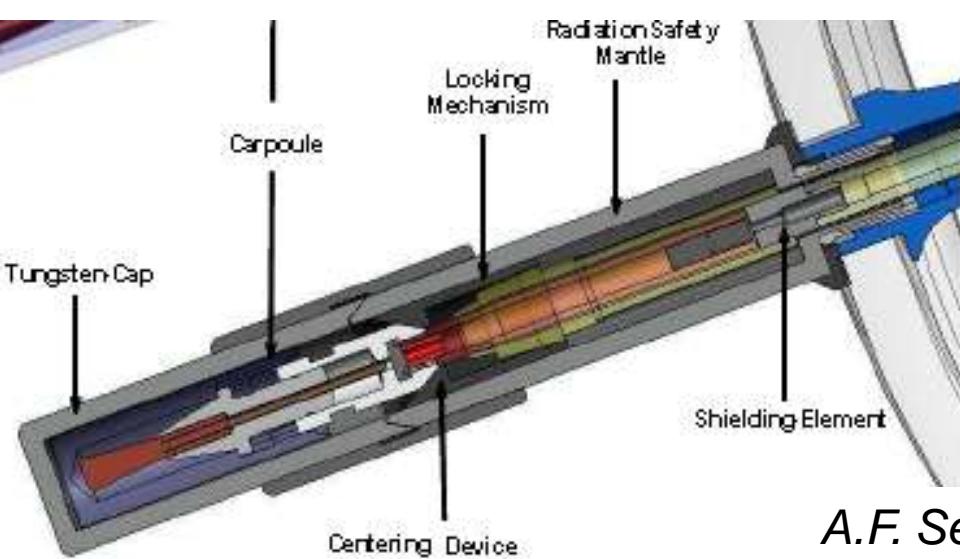
20-80 healthy volunteers 100-300 patients x00-x000 patients

Rhenium skin cancer therapy

non-melanoma skin cancer

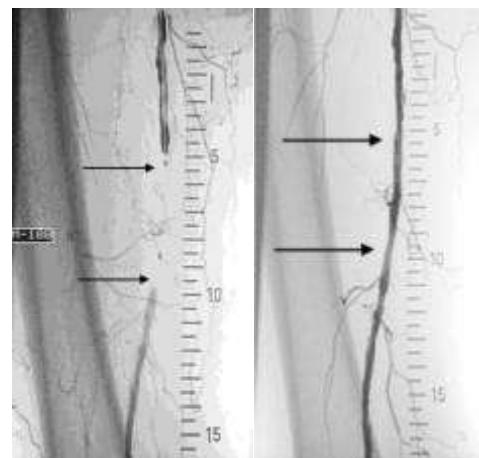
(basal cell carcinoma and squamous cell carcinoma):

in the Alps 20-30% lifetime risk to develop skin cancer



Rhenium-PTA

- frequent restenosis within few months due to deposition of vascular smooth muscle cells in intima (NIHA)
- repeated restenosis may lead to amputation of extremity: 60000 amputations/year in Germany (70% due to diabetes)
- alternative: Re-PTA (percutaneous transluminal angioplasty), i.e. irradiation of cells after balloon dilatation prevents restenosis \Rightarrow ideal isotope ^{188}Re with high concentration



- clinical study in Augsburg: **13% restenosis in 16 months** versus **usually 50-75% in 6 months**

W.A. Wohlgemuth et al., J Cardiovascular Surgery 2010;51:573.

^{188}Re -SSS-Lipiodol: SIRT of HCC and liver metastases

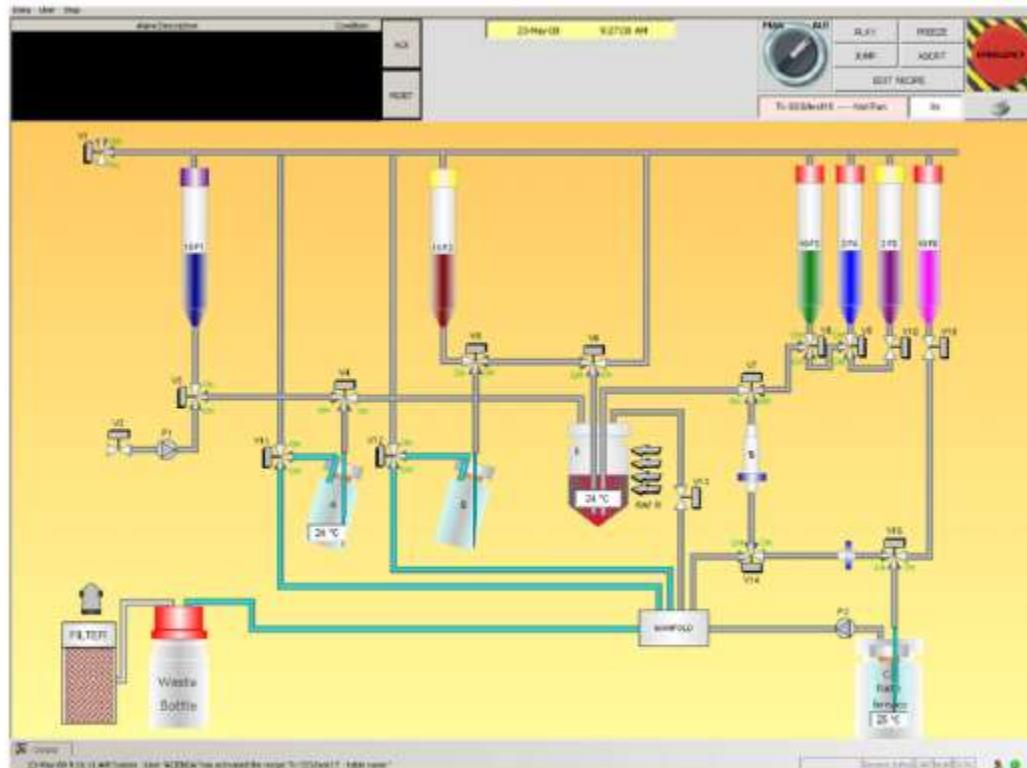
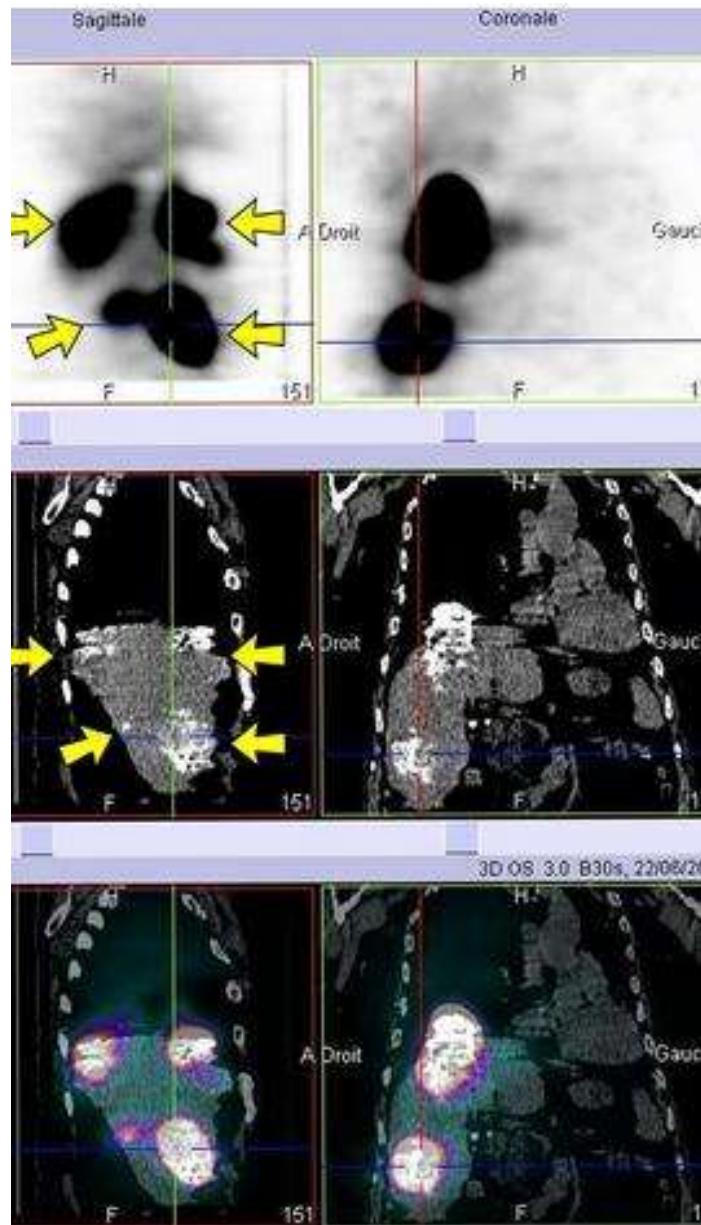
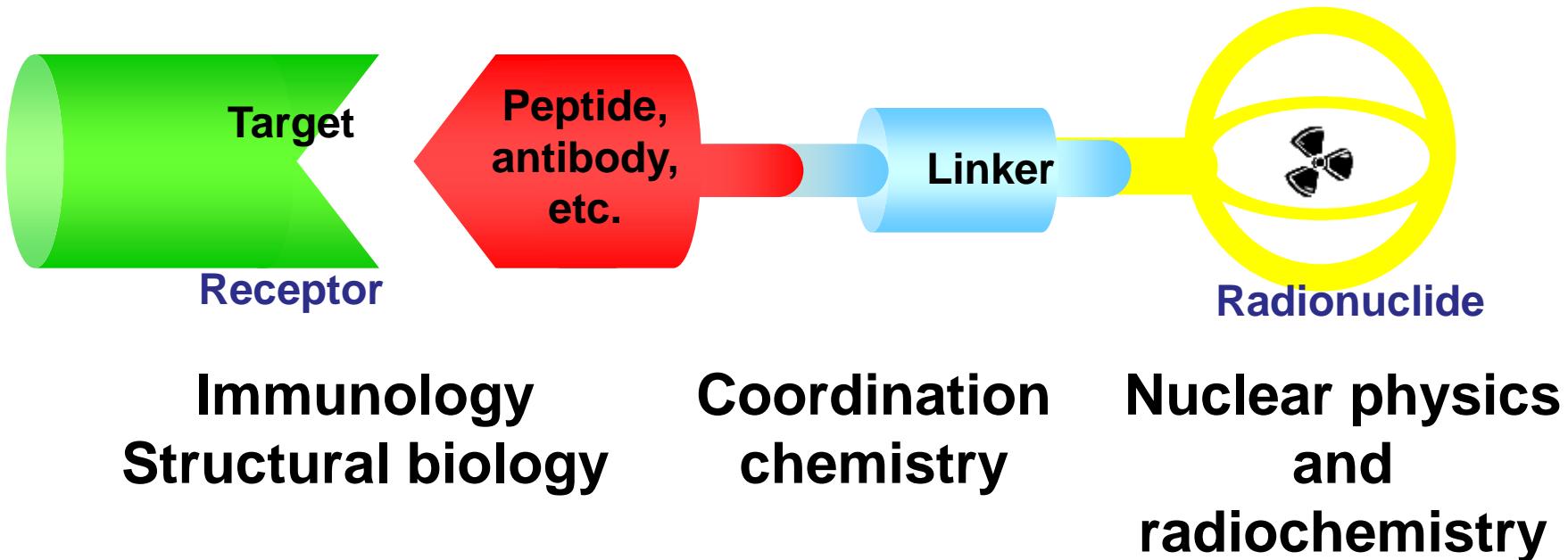


Fig. 3. Flowchart of the module for the preparation of ^{188}Re -SSS/Lipiodol.



Receptor Targeted Therapies



Lymphoma therapy: RITUXIMAB+¹⁷⁷Lu

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

¹⁸FDG PET



1.9.2002

¹⁷⁷Lu-Scan



13.9.2002

¹⁸FDG PET



15.11.2002

Still
in
CR

15.9.2009

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

Cost effectiveness ?

11th Int. Conf. on Malignant Lymphoma
Lugano, Switzerland, June 2011



2010 TARMED prices:

650 mg rituximab 3939 CHF

1x Zevalin 24330 CHF
(⁹⁰Y-anti-CD20-ibritumomab)

6.2x more expensive

16x rituximab 63024 CHF

1x Zevalin is 2.6x cheaper!

"A single infusion of ZEVALIN matched roughly 16 infusions of rituximab in terms of achieving the same increase in progression free survival. I leave it up to the audience to draw conclusions about cost effectiveness. Thus, in conclusion, RIT represents the most effective single drug in the treatment of follicular NHL."

Dr. Anton Hagenbeek, the Academic Medical Center, Amsterdam, NL,
on "Controversies in Follicular Lymphomas"

Saturation of selective receptors per cell



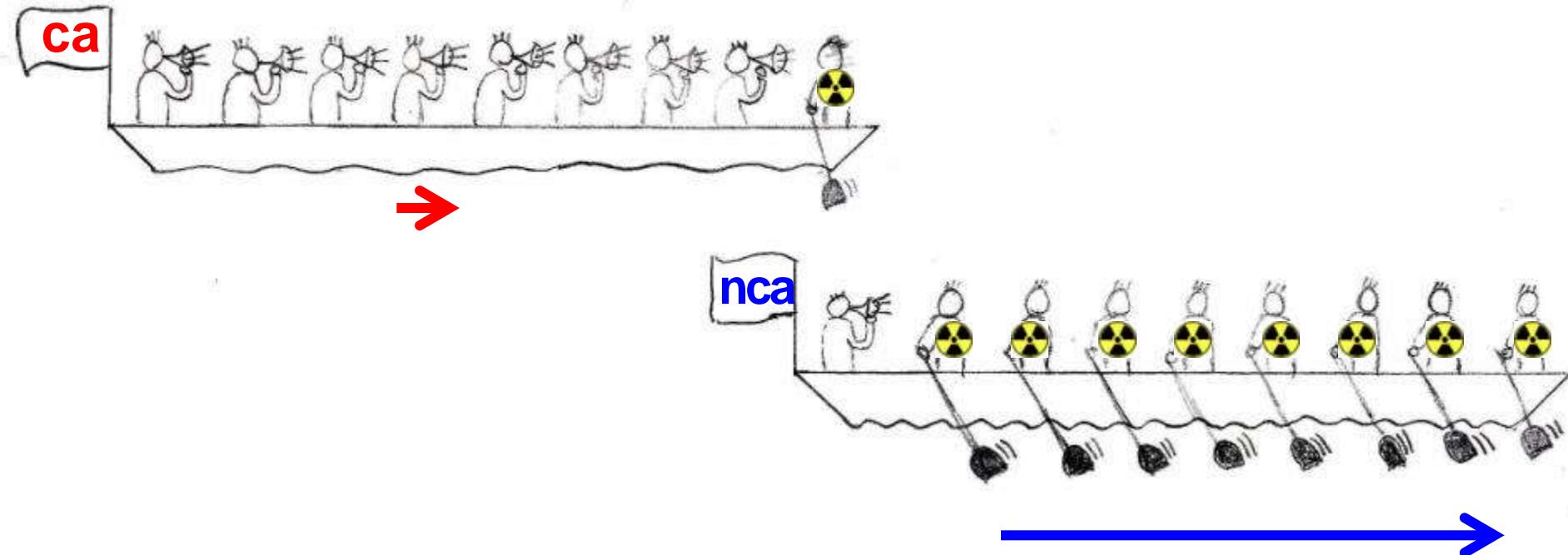
Specific activity

**Physical quantity describing
the activity per mass
(GBq/mg, Ci/mg),**

**basically the ratio of
radioactive atoms to all atoms
(including stable ones).**



Carrier added vs. non-carrier added



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)

Bone metastases:

Metastron® ($^{90}\text{SrCl}_2$)

Quadramet® ($^{153}\text{Sm-EDTMP}$)

Zofigo® ($^{223}\text{RaCl}_2$)

Neuroblastoma:

^{131}I -MIBG

Neuroendocrine

(GEP-NET):

^{177}Lu -peptides (III)

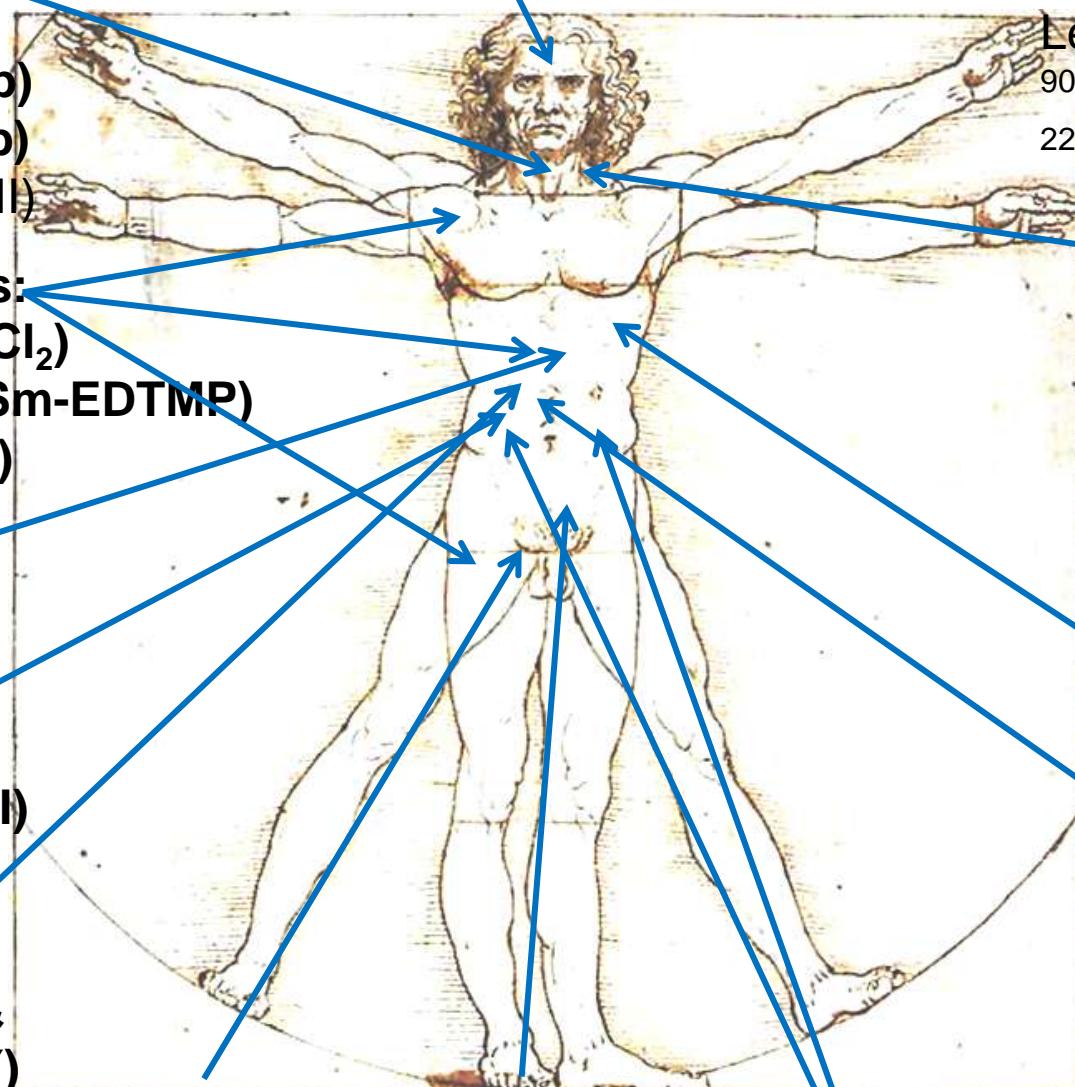
^{90}Y -peptides

Liver (HCC):

Theraspheres® &
SIRspheres® (^{90}Y)

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

^{166}Ho -microspheres



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

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

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

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

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

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

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

^{177}Lu -mab (II)

^{90}Y , ^{177}Lu -mab (I)

The rising star for therapy



“Clean” production route to ^{177}Lu

Ta 175 10.5 h	Ta 176 8.1 h	Ta 177 56.6 h	Ta 178 9.25 m $\xleftarrow{2.45\text{ h}}$	Ta 179 665 d	Ta 180 0.012	Ta 181 99.988
ϵ γ 207; 349; 267; 82; 126; 1793...	ϵ β^+ ... γ 1159; 88; 1225...	ϵ β^+ γ 113; 208... g	ϵ β^+ 0.9 γ 93; 1351; 1341... g	ϵ no γ g σ 930	$> 10^{15}$ a ϵ β^- 0.7... γ 93; 104; g	σ 0.012 + 20 $\sigma_{n,\alpha} < 10^{-6}$
Hf 174 0.16 $2.0 \cdot 10^{15}$ a	Hf 175 70.0 d	Hf 176 5.26	Hf 177 51 m 1.1 s 18.60	Hf 178 31 a 4.0 s 27.28	Hf 179 25 d 18.7 s 13.62	Hf 180 5.5 h 35.08
α 2.50 σ 600	ϵ γ 343...	σ 23	γ 277; 295; 327... 379...	γ 574; 495; 217... σ 45	γ 426; 326; 213; 89... σ 32	γ 454; 363; 123; 146... σ 46
Lu 173 1.37 a	Lu 174 142 d 3.31 a	Lu 175 97.41	Lu 176 2.59	Lu 177 160.1 d 6.71 d	Lu 178 22.7 m 28.4 m	Lu 179 4.6 h
ϵ γ 272; 79; 101... e^-	ϵ β^+ ... γ (992; 273...) 76...	σ 16 + 8	β^- 1.2; 1.3...; ϵ γ 88... e^-	β^- 0.2... γ 414; 319; 122... m_i σ 3.2	β^- 0.5... γ 208; 113... g σ 1000	β^- 2.0... γ 93; 1341; 1310; 1269...; g
Yb 172 21.83	Yb 173 16.13	Yb 174 31.83	Yb 175 4.2 d	Yb 176 12 s 12.76	Yb 177 6.5 s 1.9 h	Yb 178 74 m
$\sigma \sim 1.3$ $\sigma_{n,\alpha} < 1E-6$	σ 16 $\sigma_{n,\alpha} < 1E-6$	σ 63 $\sigma_{n,\alpha} < 0.00002$	β^- 0.5... γ 396; 283; 114...	γ 293 390; 190; 96... σ 3.1	γ 104; 228 e^- g	β^- 0.6... γ 391; 348;... g
Tm 171 1.92 a	Tm 172 63.6 h	β	γ			Tm 177 85 s
β^- 0.1... γ (67); e^- $\sigma \sim 160$	β^- 1.8; 1.9... γ 79; 1094; 1387; 1530; 1466; 1609...					β^- γ 105; 518... g; m

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

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

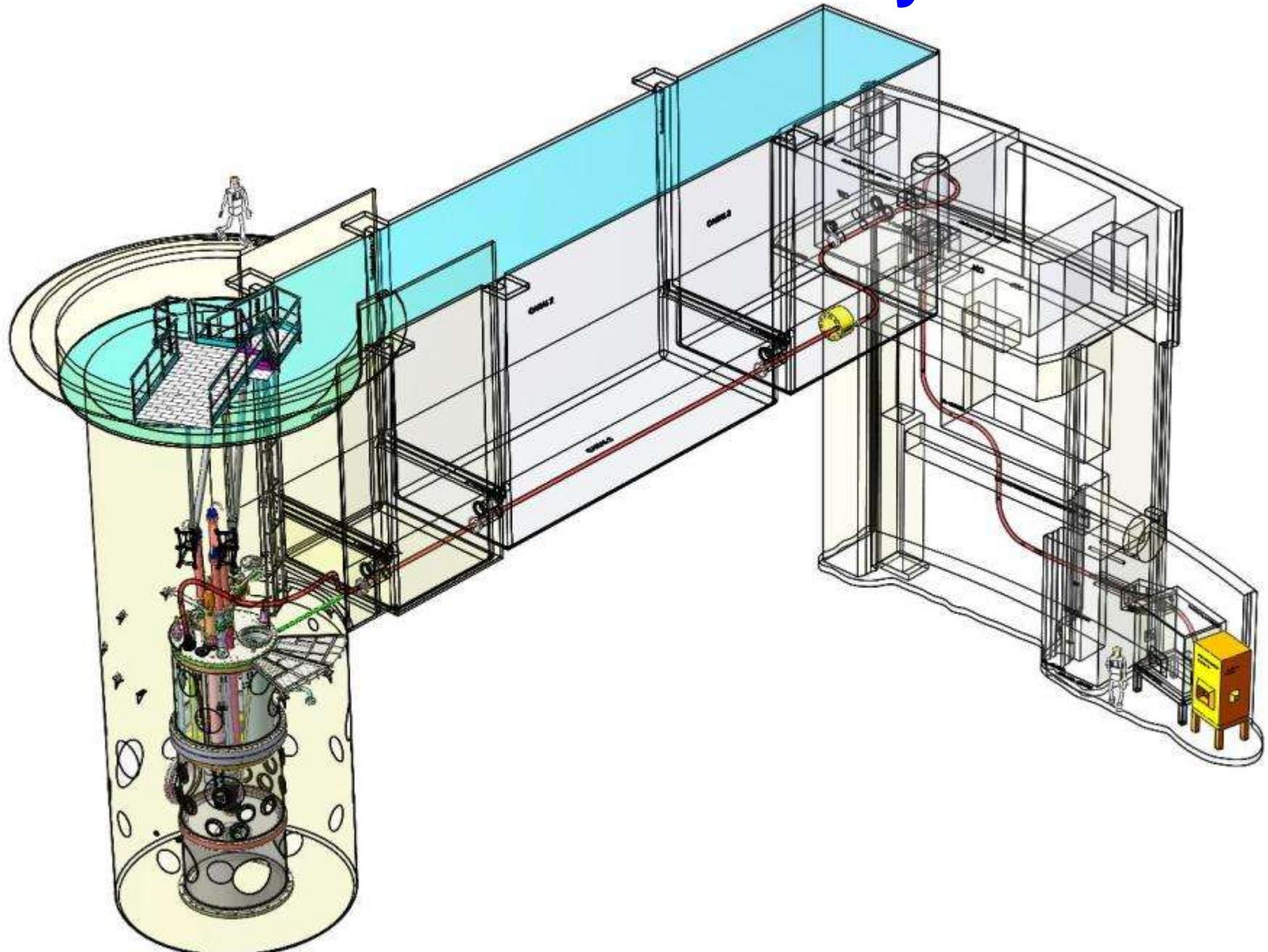
Charles James

**1995- Large-scale separation of Lu
for production of LSO/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**



New automated irradiation system for V4



Neutrons for Science AND Neutrons for Health

Radioisotope production is outside of ILL's normal sphere of activity, but we have a moral imperative to do this work. It's a great example of how a publicly funded facility can have a totally unexpected and unpredictable payoff for society.

Prof. Andrew Harrison (ILL Director)



An example for other research facilities!

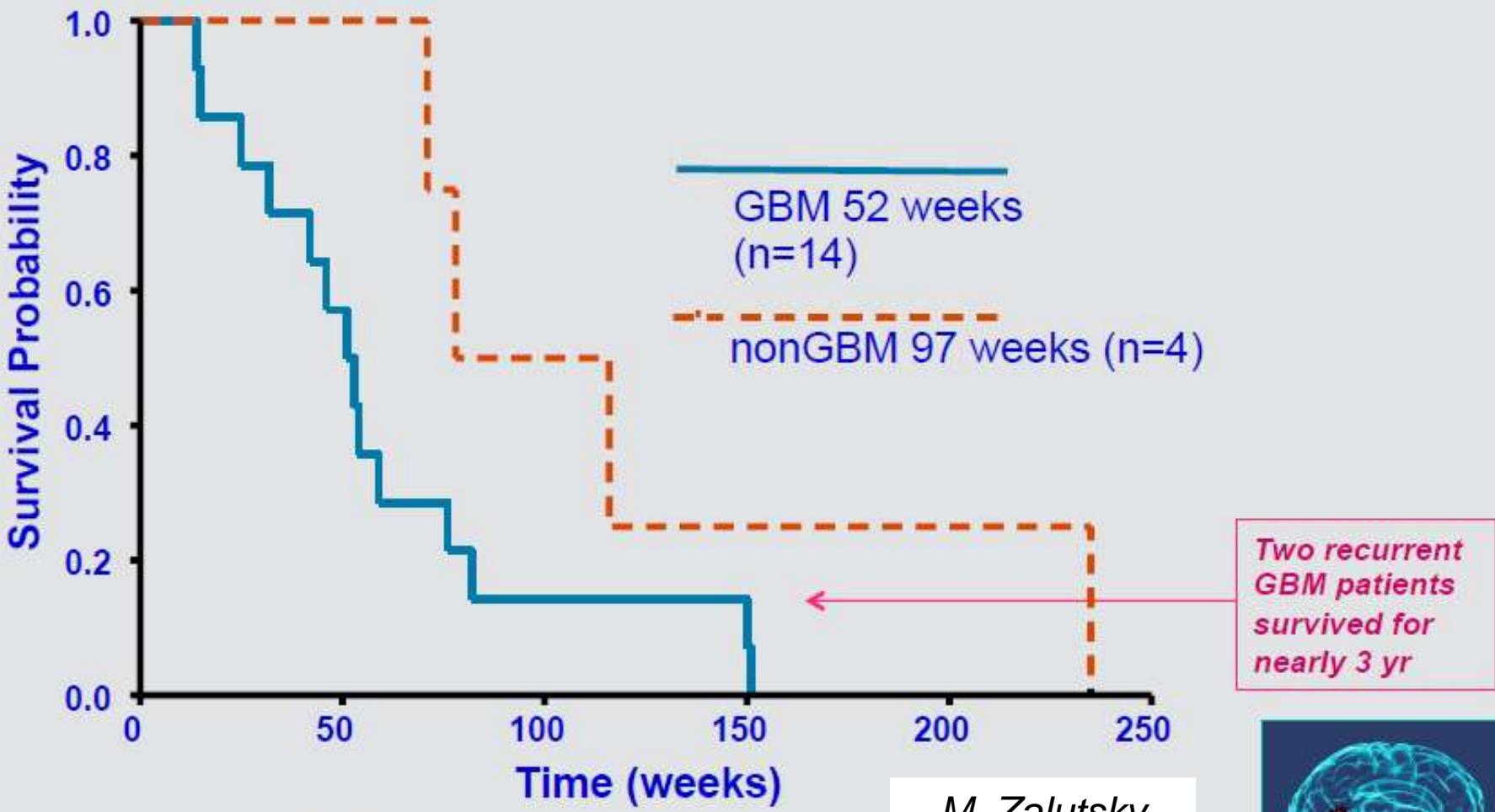
Alpha emitter for targeted therapy

single α emission

decay chains

Radio-nuclide	Half-life	Daughters	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
<hr/>						
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
Th-227	18.7 d	Ra-223 Rn-219 Po-215 Pb-211 Bi-211	11.4 d 4 s 1.8 ms 0.6 h 130 s	5	6.45	>50
U-230	20.8 d	Th-226 Ra-222 Rn-218 Po-214	0.51 h 38 s 35 ms 0.16 ms	5	6.71	>50

Phase 1 ^{211}At -Labeled Chimeric 81C6 in Recurrent Brain Tumor Patients: Outcome



Historical Control: GBM 31 weeks
Brem et al. 1995

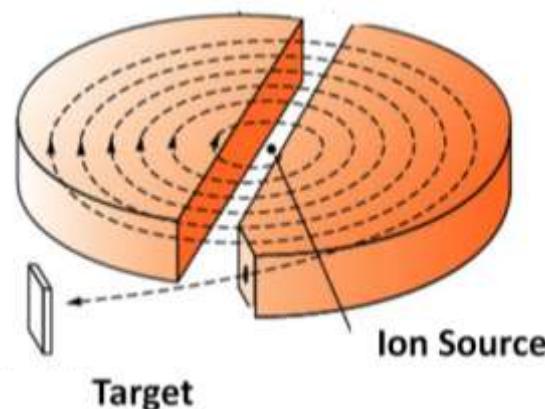
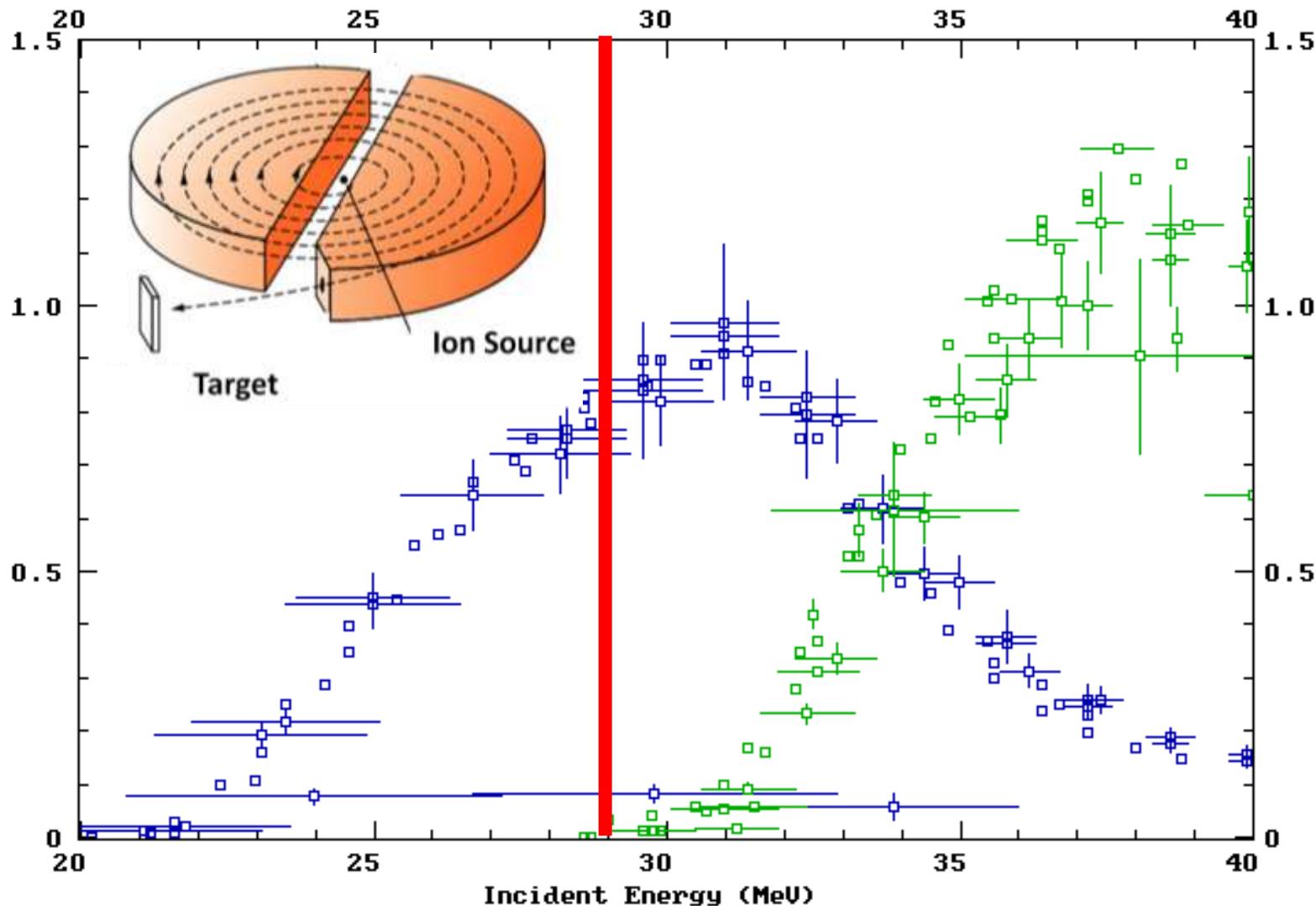


$^{209}\text{Bi}(\alpha, xn)$

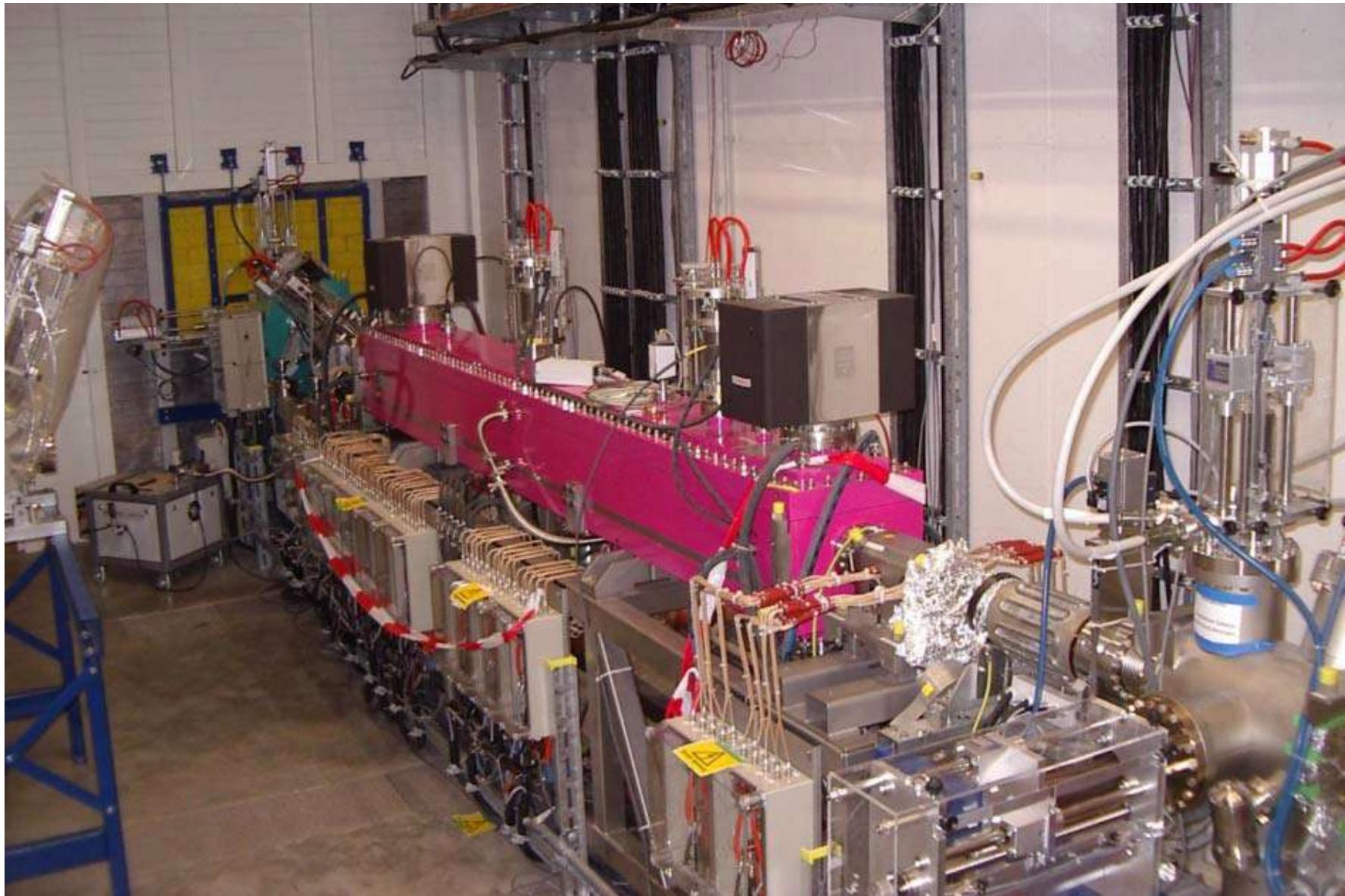
$^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$

$^{209}\text{Bi}(\alpha, 3n)^{210}\text{At} > ^{210}\text{Po}$

Cross Section (chans)



7.2 MeV/u light ion LINAC A/q=3



Shared use ?



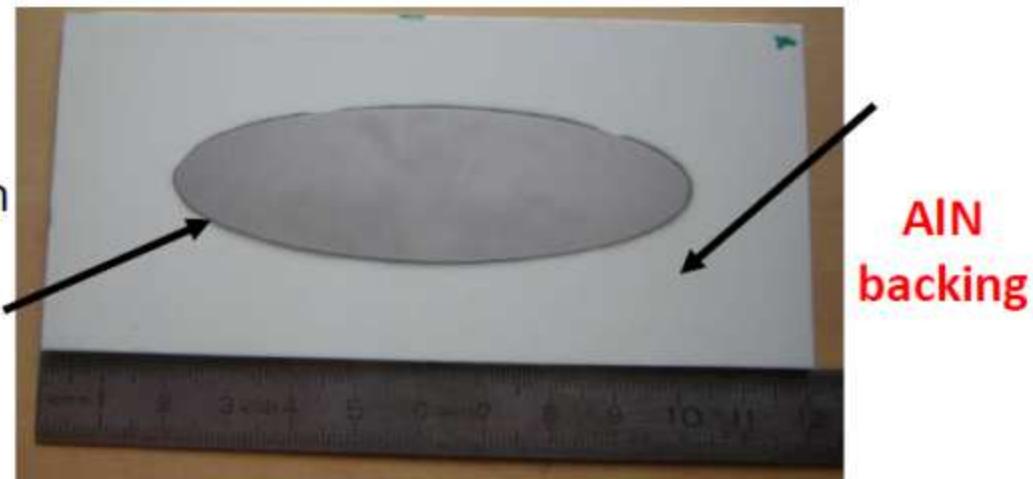
22:00 – 06:00
06:00 – 22:00

^{211}At production
Hadrontherapy

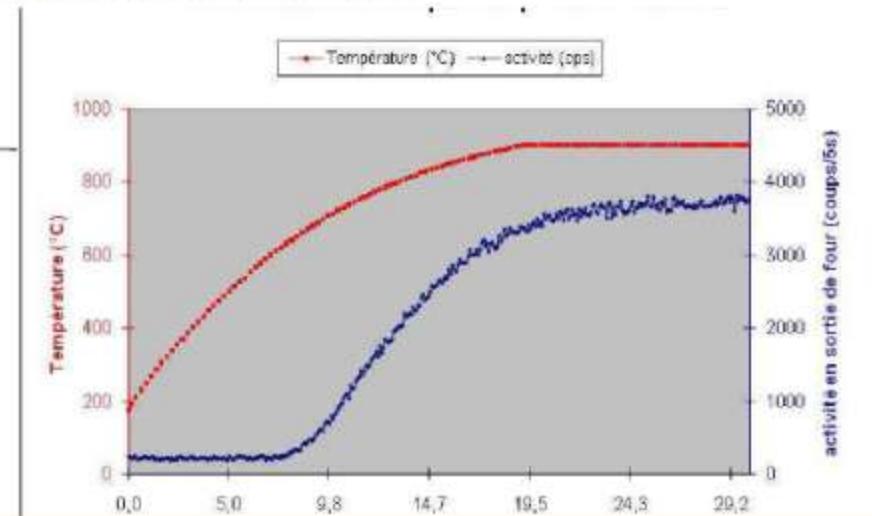
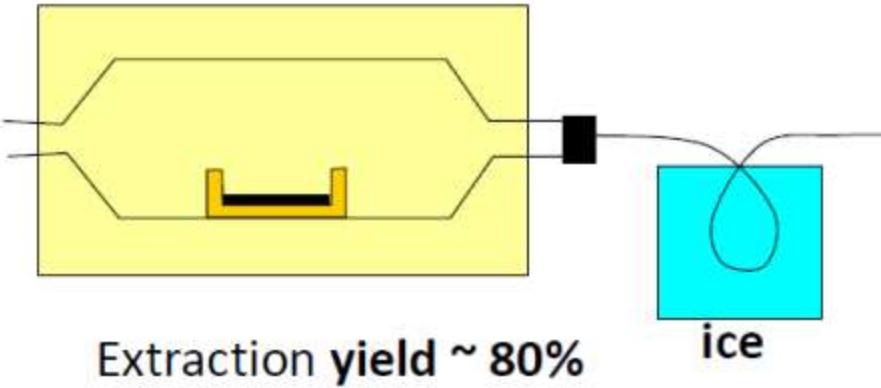
Too low duty cycle!

Present target and separation technology

Bismuth targets are made by deposition under vacuum on AlN backing:

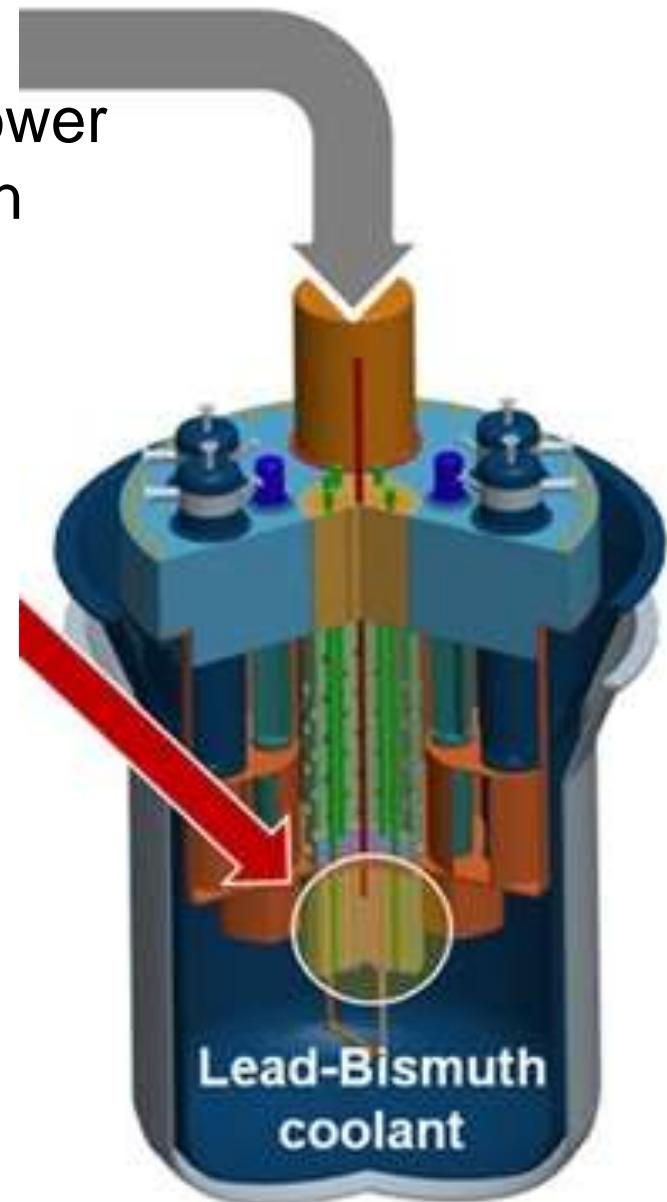
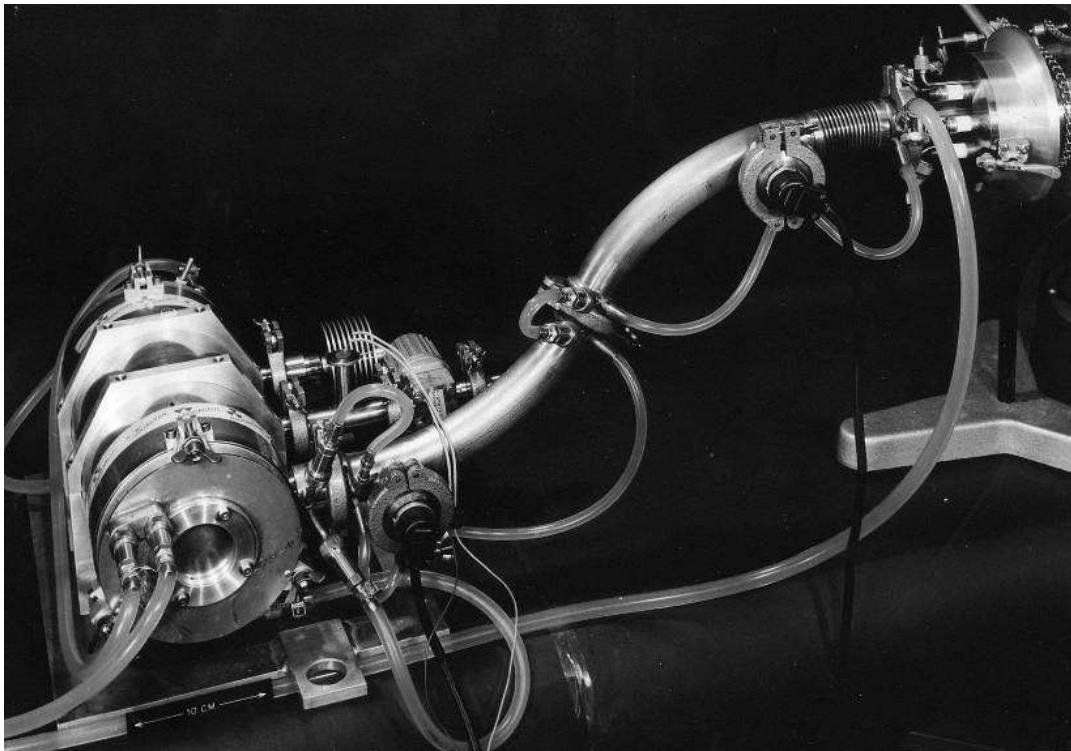


Dry distillation: tests made with small target irradiated at cemhti

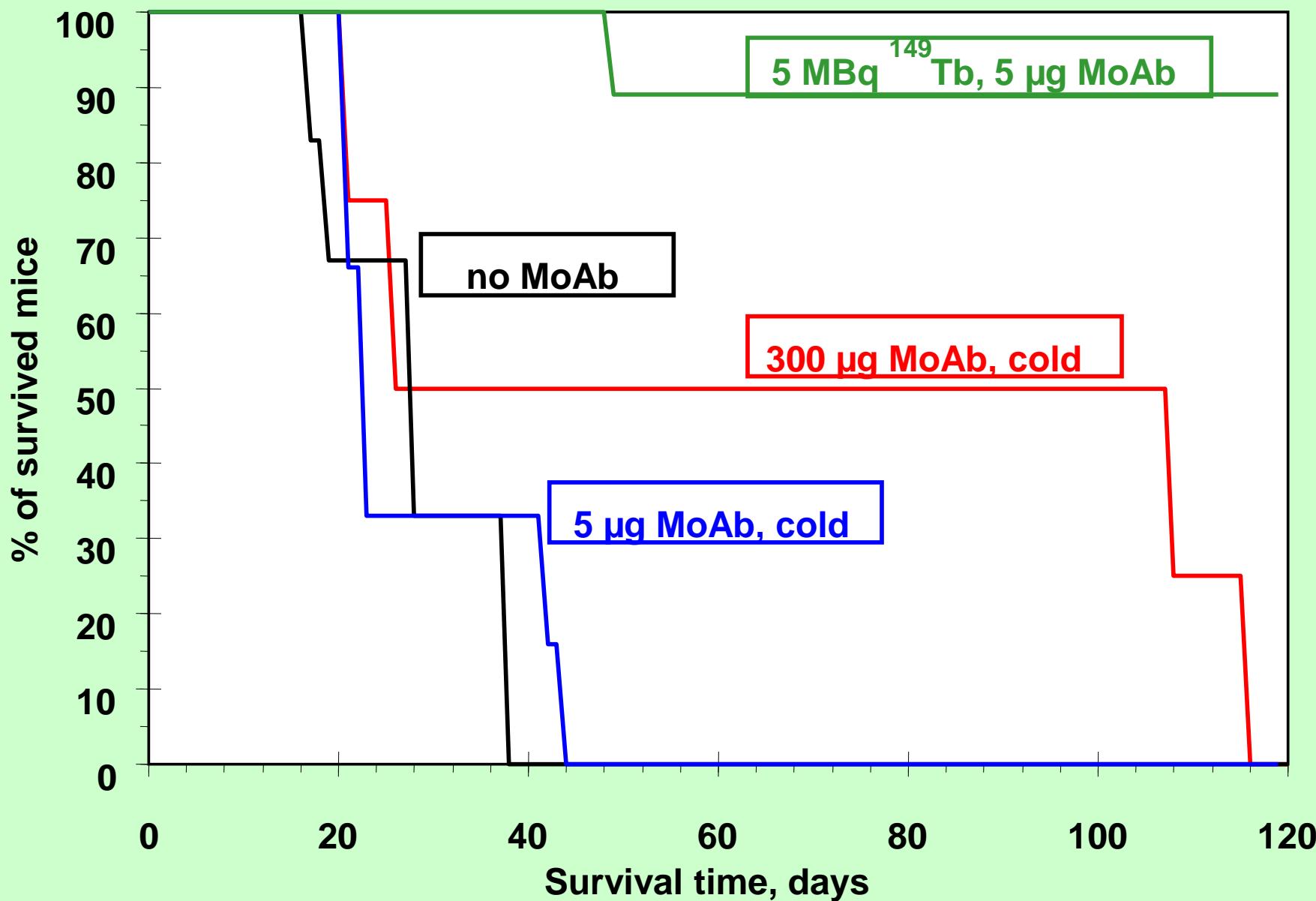


Midterm option: molten bismuth target

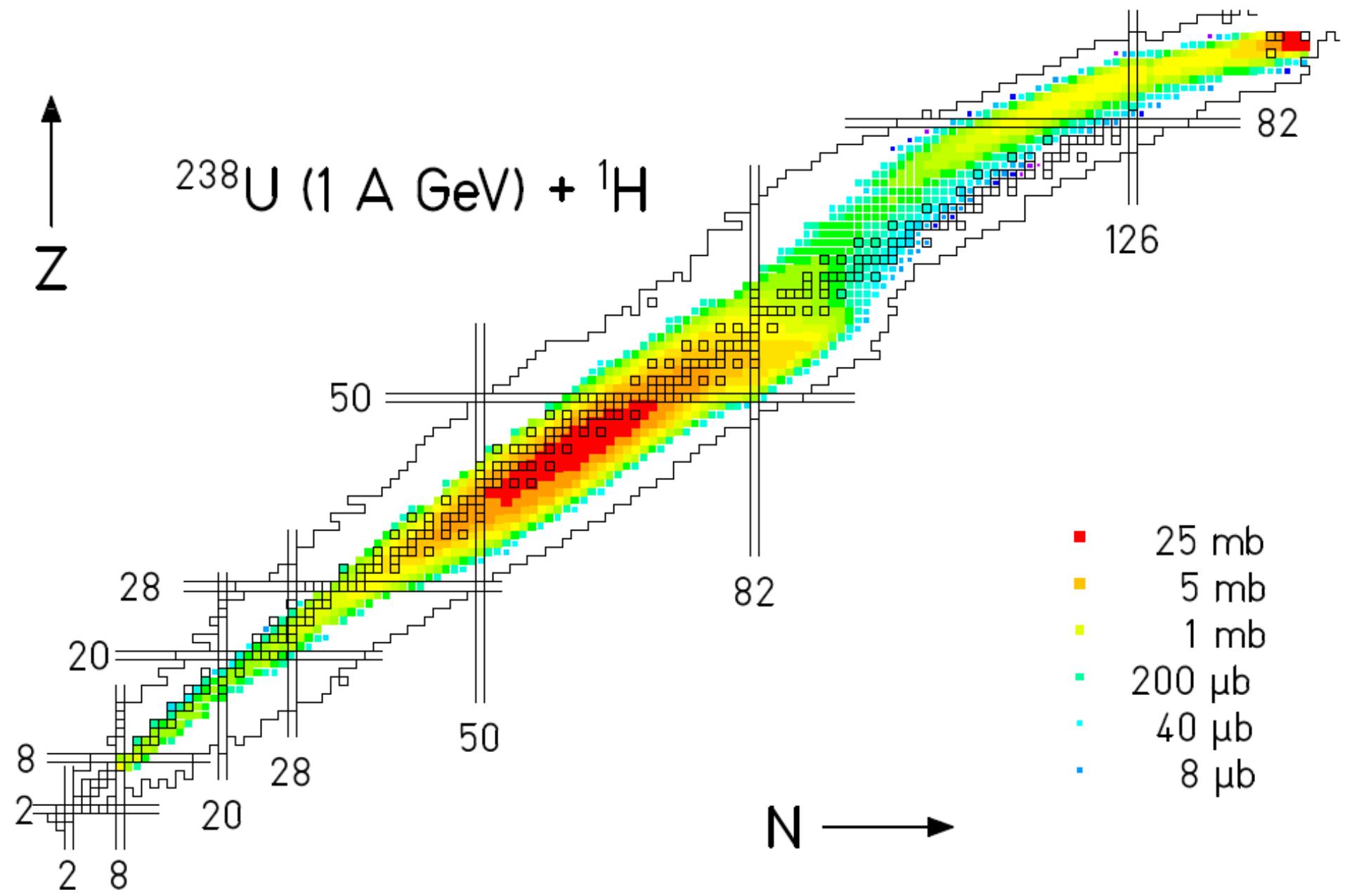
- Better heat dissipation > higher beam power
- Continuous operation + on-line extraction
- Synergies with ISOLDE and MYRRHA molten metal targets



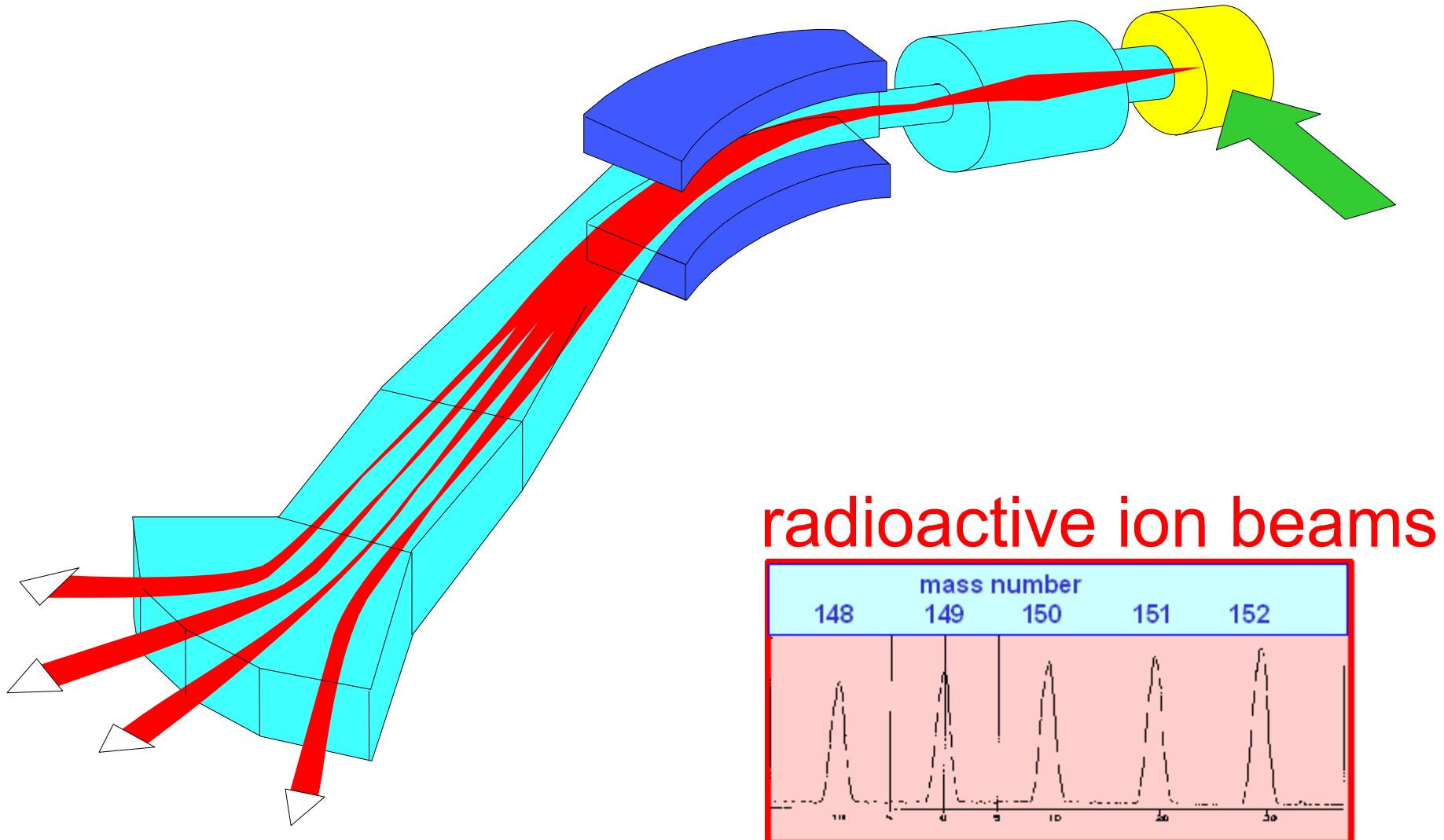
Preclinical study with lymphoma SCID mouse model



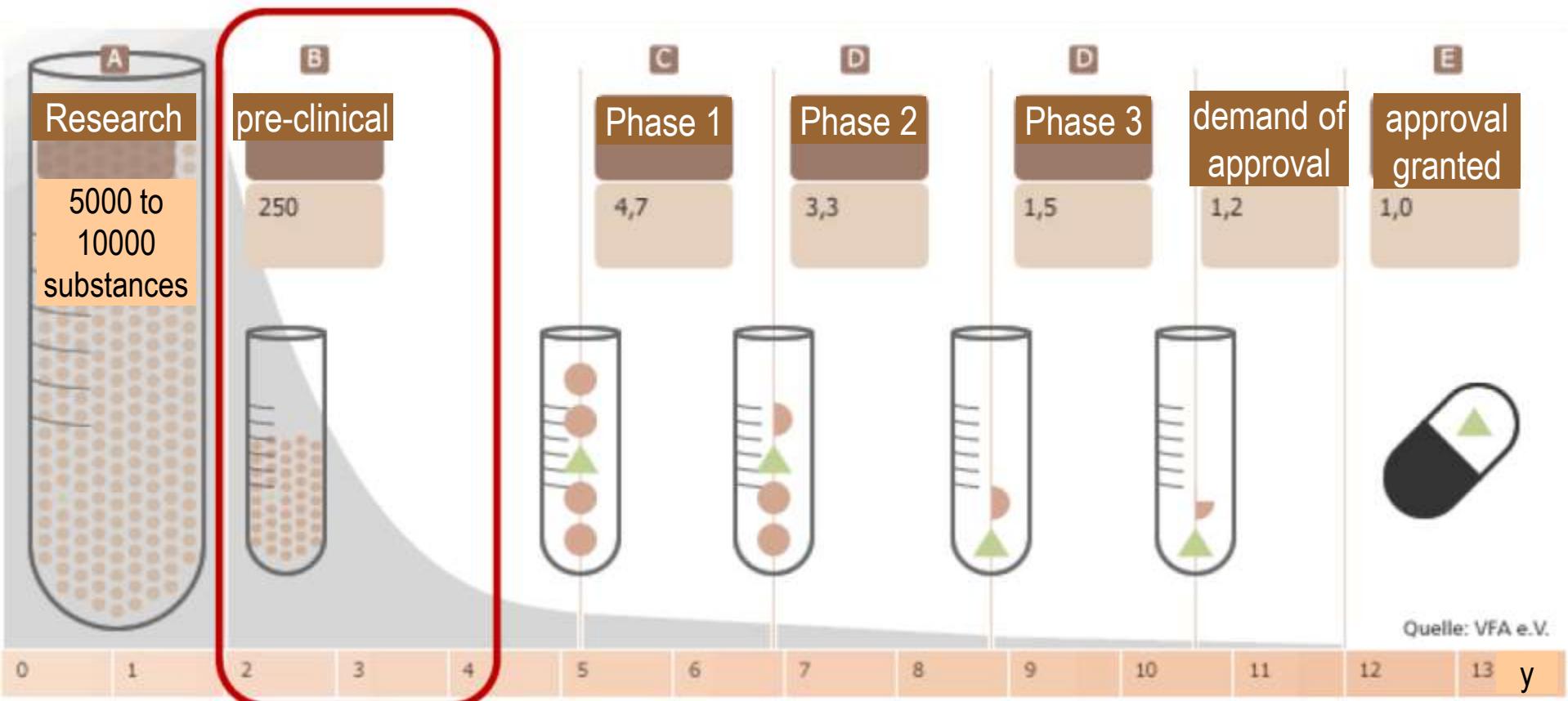
High energy proton induced reactions



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



Development of pharmaceuticals



Screening

in vitro tests
animal exp.

ISOLDE ⇒

tests with humans

toxicity wanted effect

MEDICIS ⇒

comparison

EURISOL

20-80 healthy 100-300 µ
volu

ESS
ISOL@MYRRHA

Commercial viability ?

Isotope	T _{1/2}	MBq	Yield*Decay	atoms
99mTc	6 h	700		2.2E+13
201Tl	73 h	150	0.72	7.9E+13
18F	1.8 h	370	0.38	9.4E+12
131I	8 d	3700	0.69	5.3E+15
177Lu	6.7 d	7000	0.59	9.9E+15
211At	7.2 h	350	0.37	3.5E+13
149Tb	4.1 h	1000	0.48	4.4E+13

Radionuclides for RIT and PRRT

Radio-nuclide	Half-life	E mean (keV)	E γ (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

Established isotopes

Emerging isotopes

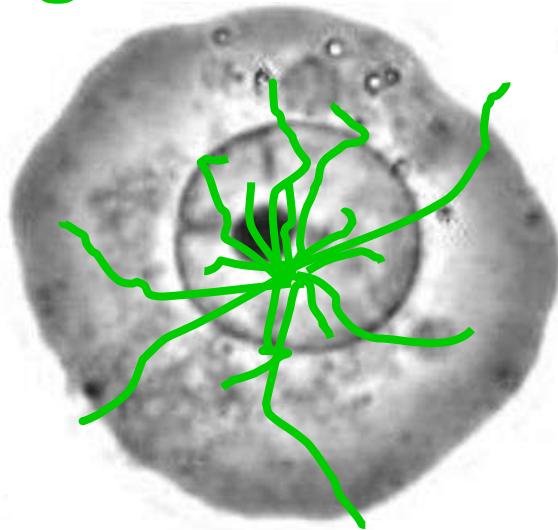
R&D isotopes:
supply-limited!

localized

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

Multiple Auger electrons

Auger-e⁻



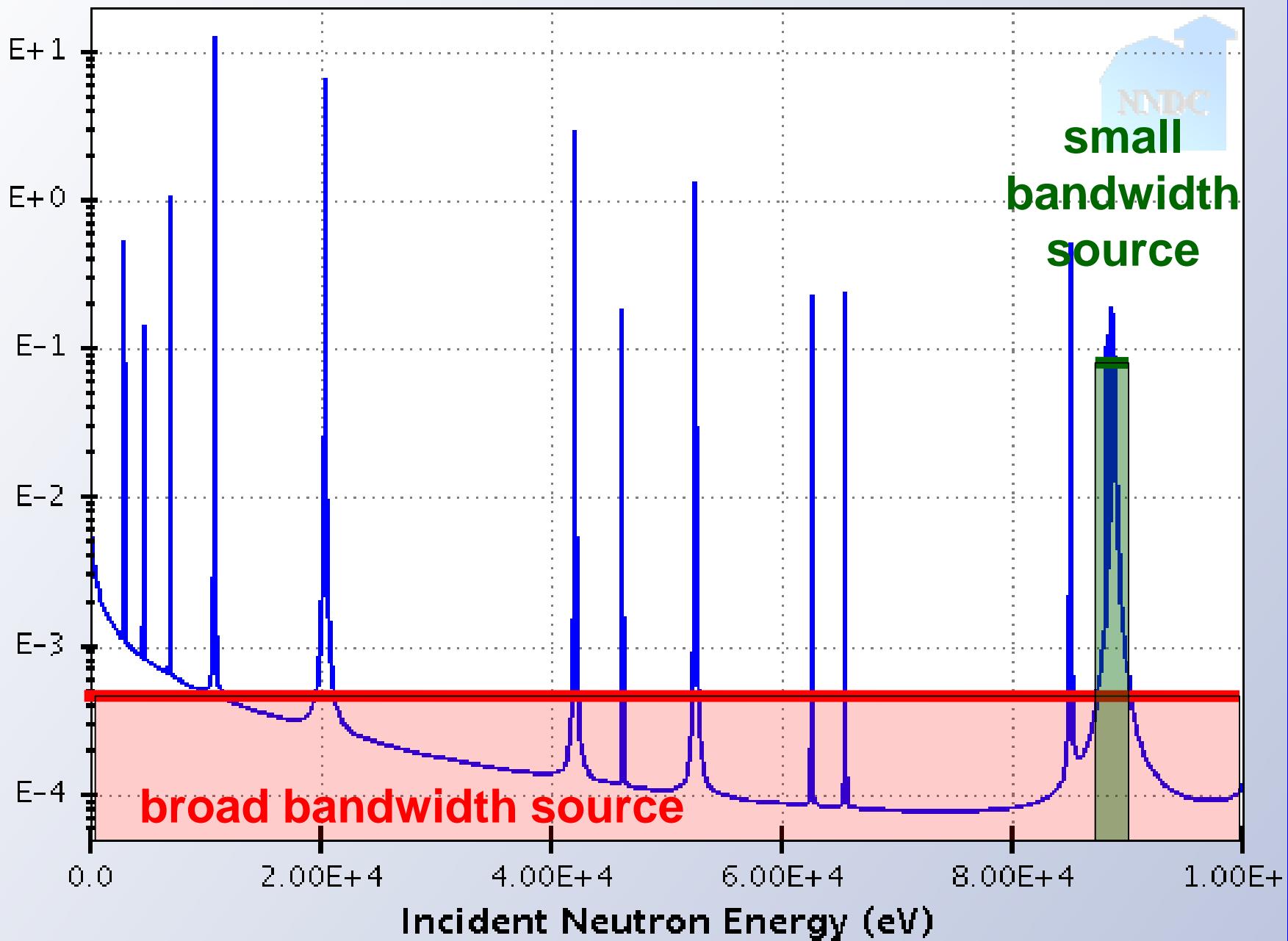
Pt 192 0.782	Pt 193 4.33 d -50 a	Pt 194 32.86	Pt 195 4.02 d 33.78	Pt 196 25.21
$\sigma = 2.0 + 6$ $\sigma_{n,\alpha} < 0.0002$	$\text{ly } (136...) \text{ e}^-$ $\text{no } \gamma \text{ g}$	$\sigma = 0.1 + 1.1$ $\sigma_{n,\alpha} < 5E-6$	$\text{ly } 99$ $130... \text{ e}^-$	$\sigma = 28$ $\sigma_{n,\alpha} < 5E-6$
Ir 191 4.94 s $\text{ly } 129... \text{ e}^-$ $\sigma = 0.14 + 660 + 260$	Ir 192 37.3 $\text{ly } (155) \text{ e}^-$ $\beta^- \text{ g}$ $\gamma (317) \sigma = 1588$	Ir 193 1.4 m $\text{ly } (58) \text{ e}^-$ $\beta^- \text{ g}$ $\gamma (317) \sigma = 317$ $\text{ly } (455) \text{ e}^-$ $\beta^- \text{ g}$ $\gamma (317) \sigma = 1588$	Ir 194 73.82 d $\text{ly } (80) \text{ e}^-$ $\sigma = 0.04 + 111$	Ir 195 62.7 $\beta^- 2.2$ $\gamma 328$ $\gamma 294$ $\gamma 328 \sigma = 1600$ $\text{ly, g, m } \sigma = 9$
Os 190 9.9 m $\text{ly } 503$ $617, 361$ $187... \sigma = 9 + 4$ $\sigma_{n,\alpha} < 2E-5$	Os 191 26.26 $\text{ly } (74) \text{ e}^-$	Os 192 13.10 h $\beta^- 0.1$ $\text{m } \sigma = 380$	Os 193 15.4 d $\text{ly } 569$ $206, 453$ $302, 485... \sigma = 3$ $\sigma_{n,\alpha} < 1E-5$	Os 194 40.78 $\beta^- 1.1...$ $\gamma 139, 460, 73...$ $\text{g } \sigma = 250$ $\beta^- 0.1...$ $\gamma 43, \text{e}^- \text{ g}$
Os 193 30.11 h $\beta^- 1.1...$ $\gamma 139, 460, 73...$ $\text{g } \sigma = 250$	Os 194 6.0 a $\beta^- 0.1...$ $\gamma 43, \text{e}^- \text{ g}$			

^{195m}Pt, ^{193m}Pt 30-36 Auger electrons per decay

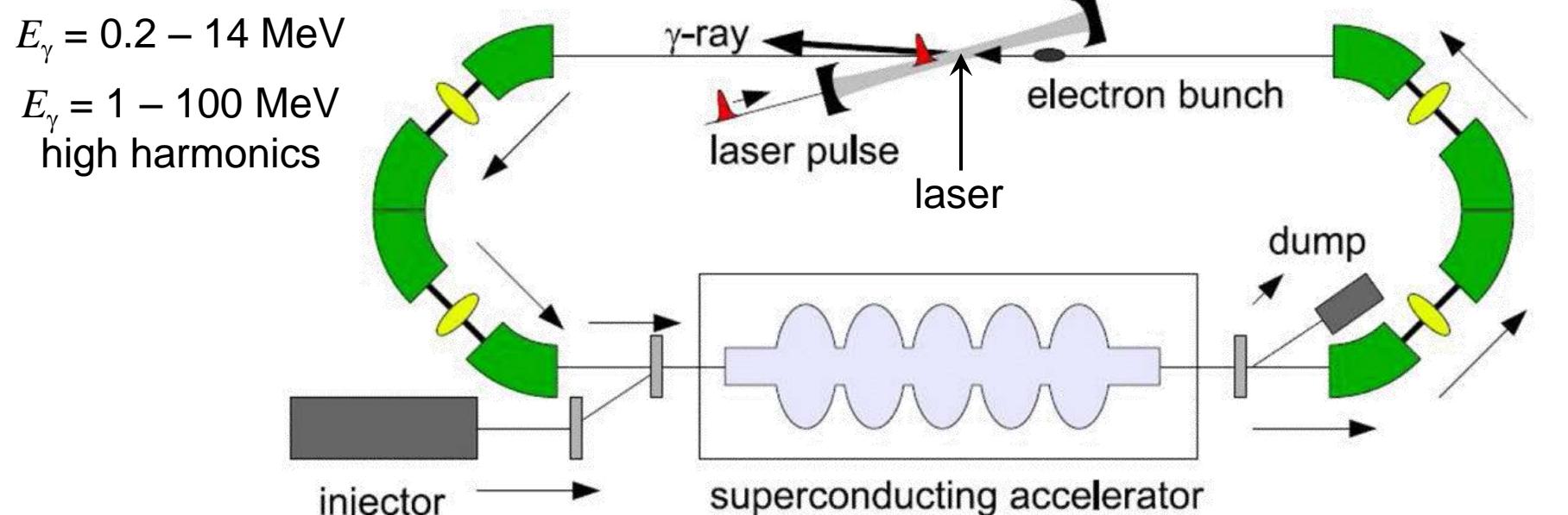
cisplatinum, carboplatinum, oxaliplatin target nucleus

20-Ca-40(n,gamma) ENDF /B-VII.0

Cross Section (b)



Energy recovery linac (ERL)



high flux mode high brilliance mode ultra-fast mode

80 pC, 130 MHz 8 pC, 1.3 GHz

100 fs

peak brilliance $8 \cdot 10^{21}$
 $(\text{s mm}^2 \text{ mrad}^2 0.1\% \text{BW})^{-1}$

flux $5 \cdot 10^{15} \text{ s}^{-1}$

spot 15 μm 10 μm 15 μm

20% energy spread accepted for recovery; $1 \text{ GeV} \cdot 0.1 \text{ A} = 100 \text{ MW}$

MEMORANDUM

Which radioisotopes will we need in 2030?

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."

Conclusions

1. Reactors and cyclotrons are complementary (meridian).
2. Research reactors will not die out.
3. H⁻/D⁻ cyclotrons are a mature, industrialized technology.
4. Serious lack of ⁴He beams.
5. No alternative to ^{99m}Tc in SPECT and ¹⁸F/¹¹C in PET.
6. Great future for generator isotopes: ⁶⁸Ga, ⁸²Rb, ⁴⁴Sc, etc.
7. n.c.a. ¹⁷⁷Lu and ⁹⁰Y are the gold standards for β⁻ therapy.
8. Possible complements: ¹⁶¹Tb, ¹⁶⁹Er, ¹⁵³Sm, ⁶⁷Cu, ⁴⁷Sc
9. Serious lack of alpha emitters: ¹⁴⁹Tb, ²¹¹At, ²²⁵Ac/ ²¹³Bi
10. Auger emitters (^{193m}Pt, ^{195m}Pt, ¹⁶⁵Er, ¹¹⁹Sb, ⁷¹Ge,...)
promising, but pending radiobiology and microdosimetry.
11. Easier access to new R&D isotopes needed.

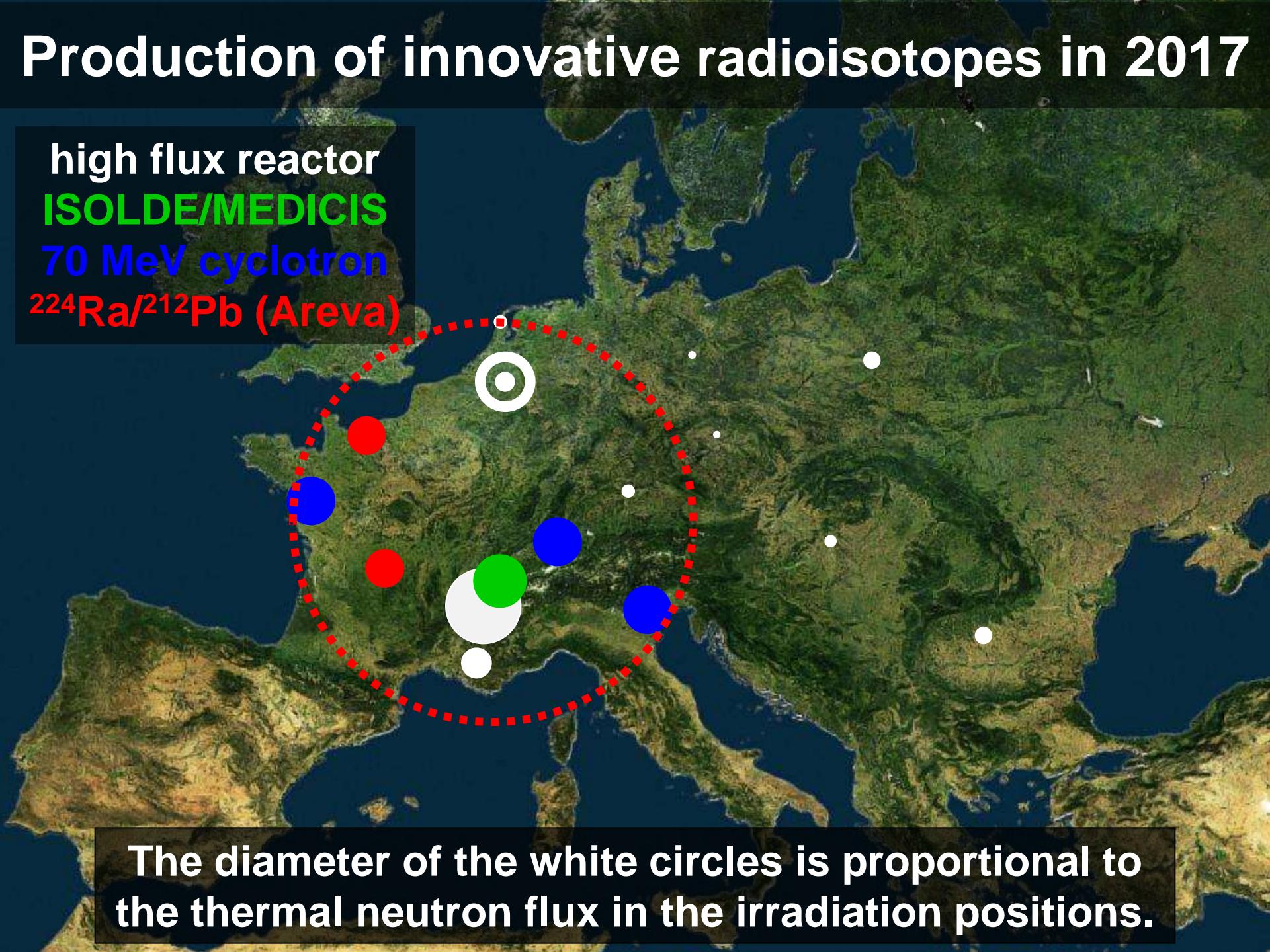
Production of innovative radioisotopes in 2017

high flux reactor

ISOLDE/MEDICIS

70 MeV cyclotron

$^{224}\text{Ra}/^{212}\text{Pb}$ (Areva)



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

Radioisotopes wish list for CERN

- ramp up ^{149}Tb supply: ISOLDE & MEDICIS (transp. container)
- spallation production of $^{225}\text{Ac}/^{213}\text{Bi}$ (ISOLDE/MEDICIS)
- provide long-term perspective by sharing technology with **ESS, ISOL@MYRRHA, TRIUMF, J-PARC, LANL, SNS,...**
- develop “cheap” 7.5 MeV/nucl. A/q=2 high current LINAC
- share ISOLDE liquid Bi target technology for ^{211}At production
- complementary $^{211}\text{Rn}/^{211}\text{At}$ development (ISOLDE/MEDICIS)
- organize/join European and French ^{211}At networks
- supply more R&D radioisotopes from ISOLDE & MEDICIS:
 ^{152}Tb , ^{155}Tb , ^{67}Cu , $^{117\text{m}}\text{Sn}$, etc.
- offline separation of reactor isotopes (^{169}Er , etc.) at MEDICIS

Radioisotopes wish list for CERN

- “earmark” supplementary ISOLDE shifts for medical applications
- foresee collimators & beamdumps made from Sc/Ti/V for long-term production of $^{44}\text{Ti}/^{44}\text{Sc}$ generators
- attract & train radiochemists, radiopharmacists and nuclear MD

Complementary technologies:

- push 3-photon camera development
- conceptual design of high current e^- ERL for future γ beam
- detailed design study for post-accelerated β^+ emitters
- real effort in simulation for micro-dosimetry of Auger emitters

Post-accelerated β^+ emitters for PET image guidance

O [15.99903; 15.99977] $\sigma_{n,p}$ 0.00029	O 12 580 keV $7.9 \cdot 10^{-21}$ s $\beta^+?$	O 13 8.58 ms $\beta^+ 16.7...$ $\beta p: 1.44, 6.44...$ $\gamma(4439^*, 3500...)$	O 14 70.59 s $\beta^+ 1.8, 4.1...$ $\gamma 2313...$	O 15 2.03 m $\beta^+ 1.7$ no γ	O 16 99.757 $\sigma_{n,p}$ 0.00019
N 10 2.3 MeV $200 \cdot 10^{-24}$ s $p?$	N 11 ~0.77 MeV? ~ $590 \cdot 10^{-24}$ s? p	N 12 11.0 ms $\beta^+ 16.4...$ $\gamma 4439...$ $\beta\alpha 0.2...$	N 13 9.96 m $\beta^+ 1.2$ no γ	N 14 99.636 $\sigma_{n,p}$ 0.080 0.2	N 15 0.364 $\sigma_{n,p}$ 2.4 E-5
C 9 126.5 ms $\beta^+ 15.5...$ $\beta p: 8.24, 10.92...$ $\beta\alpha$	C 10 19.308 s $\beta^+ 1.9...$ $\gamma 718, 1022$	C 11 20.38 m $\beta^+ 1.0$ no γ	C 12 98.93 $\sigma_{n,p}$ 0.0035	C 13 1.07 $\sigma_{n,p}$ 0.0014	C 14 5730 a $\beta^- 0.156$ no γ
B 8 770 ms $\beta^+ 14.1...$ $\beta 2\alpha -1.6, 8.3$	B 9 0.54 keV $800 \cdot 10^{-21}$ s p	B 10 19.9 $\sigma_{n,p}$ 0.3 $\sigma_{n,p}$ 3840 $\sigma_{n,p}$ 0.007	B 11 80.1 $\sigma_{n,p}$ 0.005	B 12 20.20 ms $\beta^- 13.4...$ $\gamma 4439...$ $\beta\alpha 0.2...$	B 13 17.33 ms $\beta^- 13.4...$ $\gamma 3684...$ $\beta n 3.6, 2.4...$
Be 7 53.22 d ϵ $\gamma 478$ $\sigma_{n,p}$ 38820	Be 8 5.57 eV $67 \cdot 10^{-18}$ s $\alpha 0.046$	Be 9 100 $\sigma_{n,p}$ 0.0078	Be 10 $1.387 \cdot 10^5$ a $\beta^- 0.6$ no γ $\alpha < 0.001$	Be 11 13.8 s $\beta^- 11.5...$ $\gamma 2125, 6791...$ $\beta\alpha 0.77, 0.29$	Be 12 21.50 ms $\beta^- 11.7...$ βn
Li 6 7.59 $\sigma_{n,p}$ 0.039 $\sigma_{n,p}$ 940	Li 7 92.41 $\sigma_{n,p}$ 0.045	Li 8 840.3 ms $\beta^- 12.5$ $\beta 2\alpha -1.6$	Li 9 178.3 ms $\beta^- 13.6...$ $\beta\alpha 0.7...$ $\beta\alpha$	Li 10 230 keV $2.0 \cdot 10^{-21}$ s n	Li 11 8.5 ms $\beta^- 18.0, 20.4...$ $\gamma 3368^*, 320...$ $\beta n, \beta 2n, \beta 3n$ $\beta\alpha, \beta t, \beta d$

	$T_{1/2}$ (s)	Range (mm)	
^{11}C	1222	1.3	
^{10}C	19	3.6	3 γ imaging
^{15}O	122	3.2	
^{14}O	71	3.4	3 γ imaging