Preclinical studies with non-standard and carrier-free radioisotopes from ISOLDE-CERN

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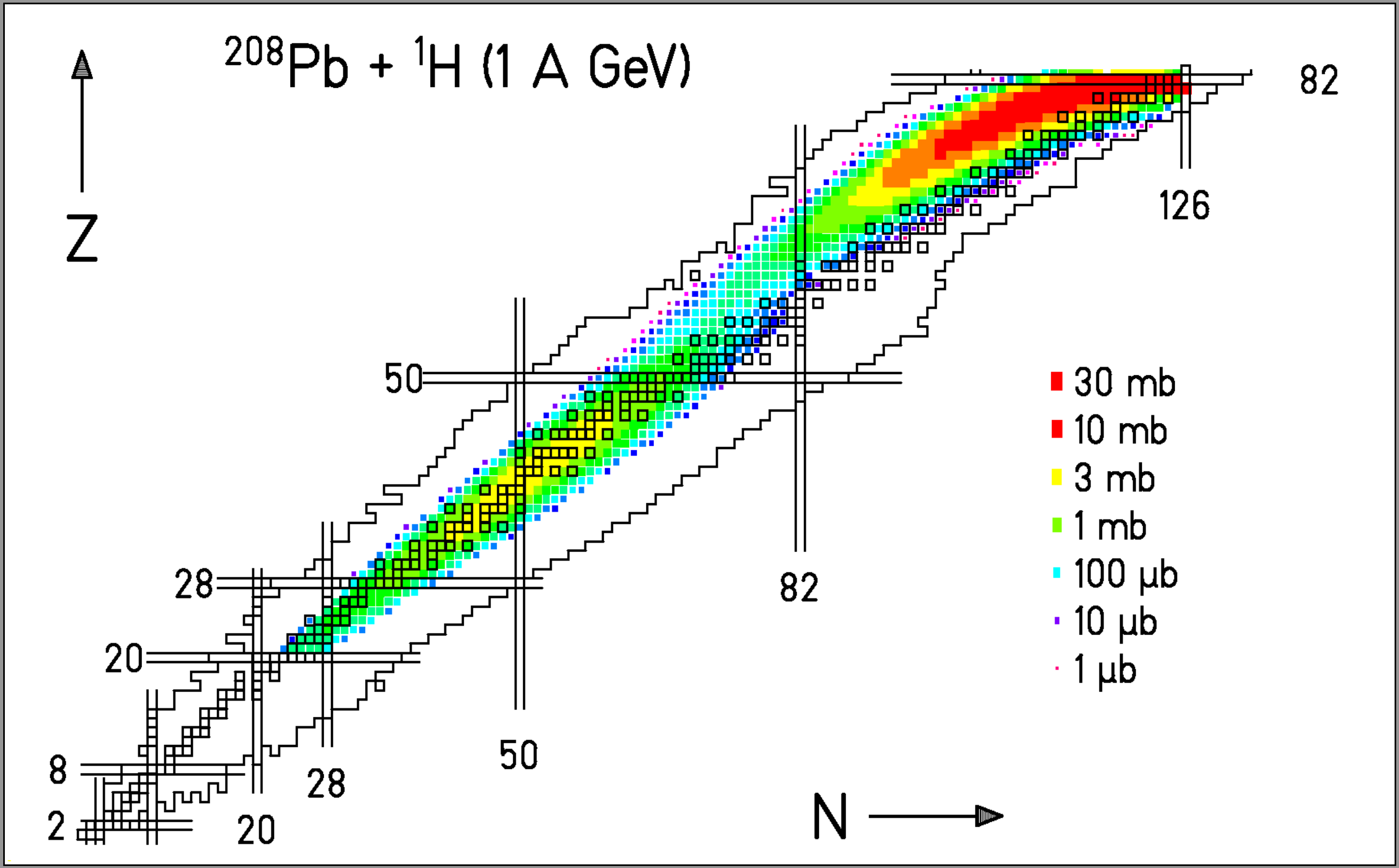
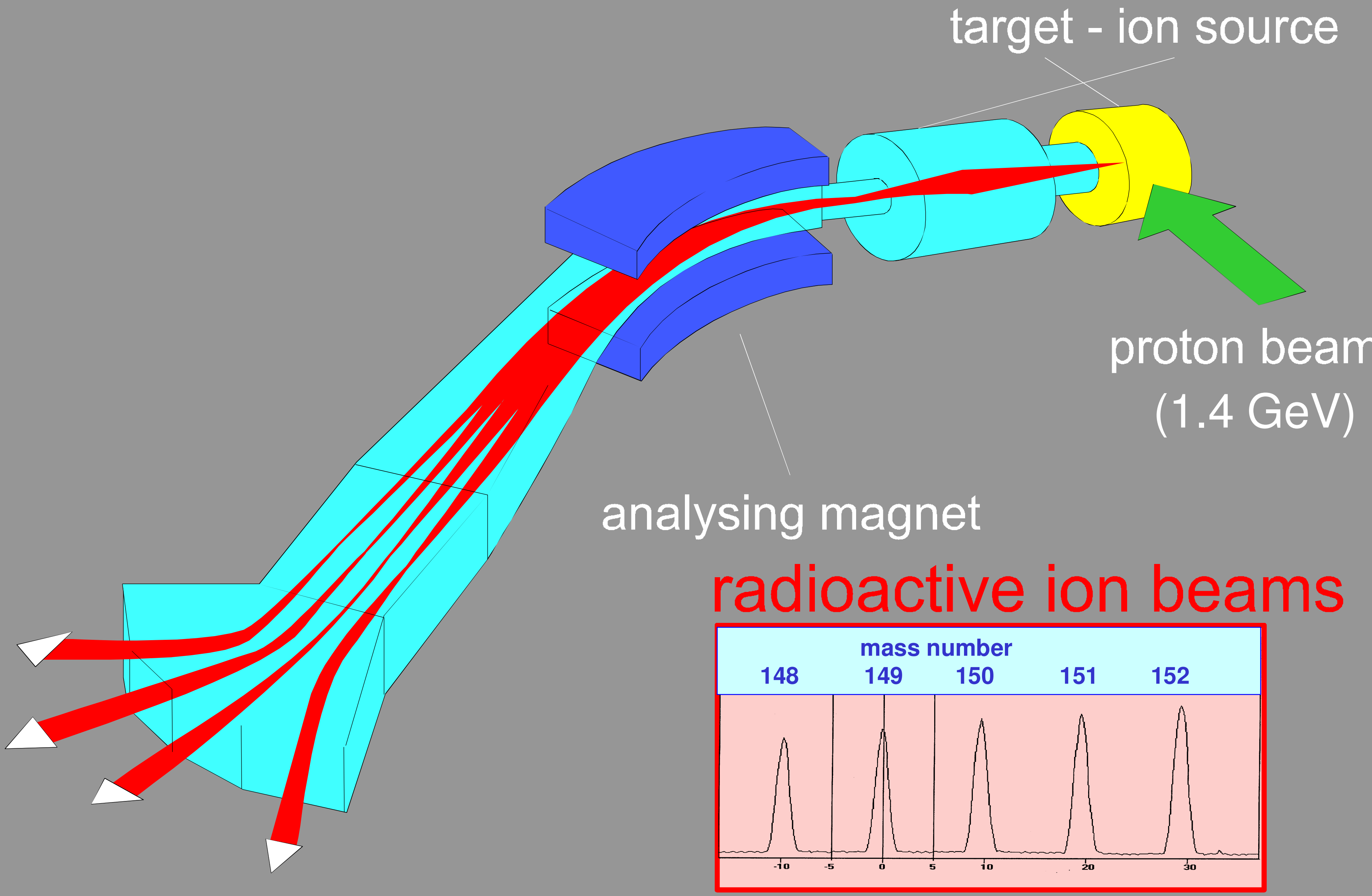
PHYSICS FOR HEALTH IN EUROPE WORKSHOP
2-4 February 2010

High-energy proton induced reactions

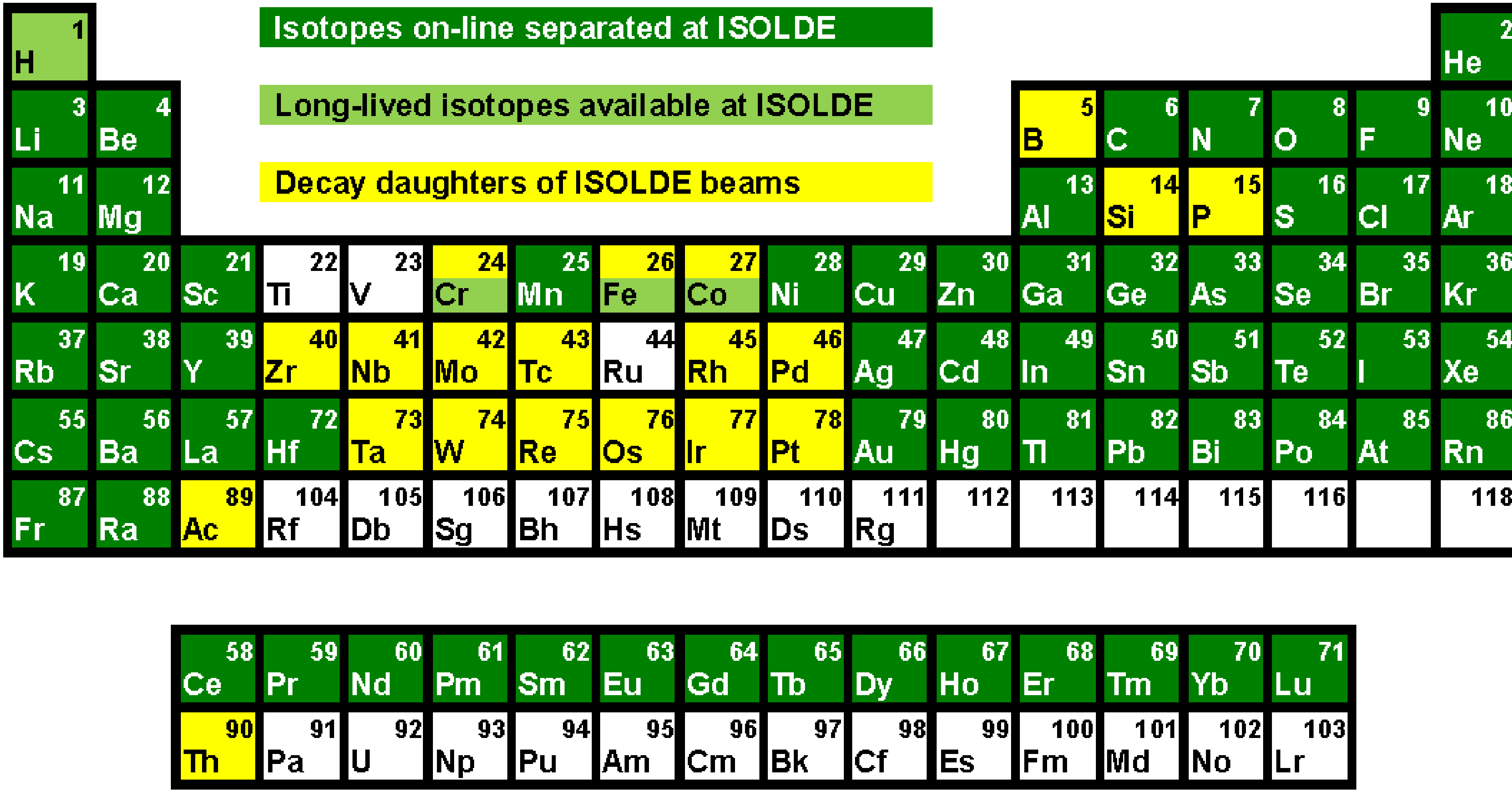


High-energy proton induced reactions can produce most of the isotopes of the chart of nuclides.

Isotope Separation On-Line



Radioisotopes available at ISOLDE-CERN



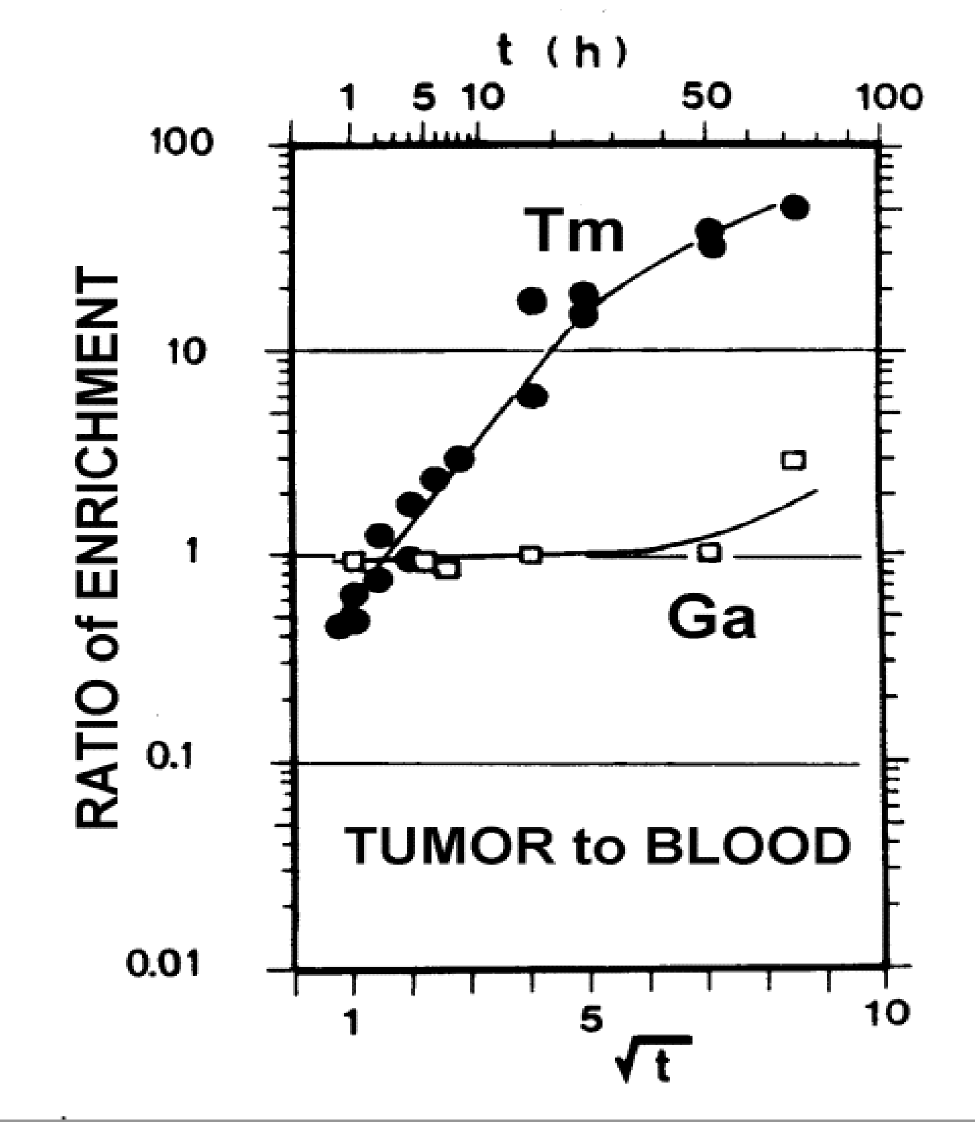
Currently available: more than 1000 different radioisotopes

Saturation activities of longer-lived radioisotopes: GBq and more

Content:

- Bio-Medical research performed at ISOLDE
  illustrating potential and possibilities
- Identify questions that require access
  to non-standard research isotopes
- Future possibilities at CERN

Main Focus: Endoradionuclide Therapy



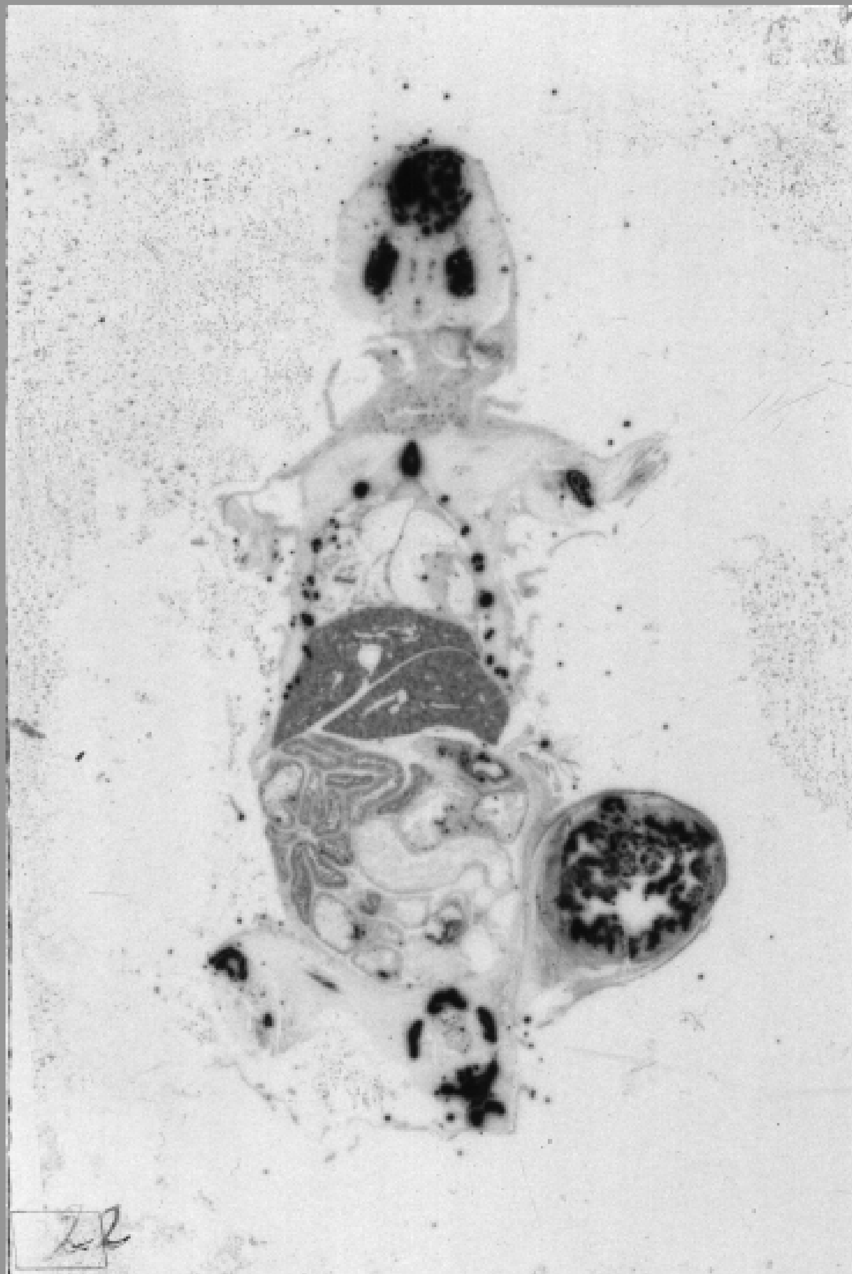
Direct comparison

^{67}Ga-Citrate
and
^{167}Tm-Citrate

in
tumor bearing mice

Lanthanides show much faster blood clearance compared to Ga

G.J.Beyer, W.G.Franke, K.Hennig et al.
Intern.J.Appl.Rad.Isot. 29, 673 (1978)



Autoradiogram

of a whole body sagittal slice of a tumor bearing mouse 24 hours after injection of 0.4 MBq of ^{167}Tm-Citrate

Lanthanides are unspecific tumor seeking tracers

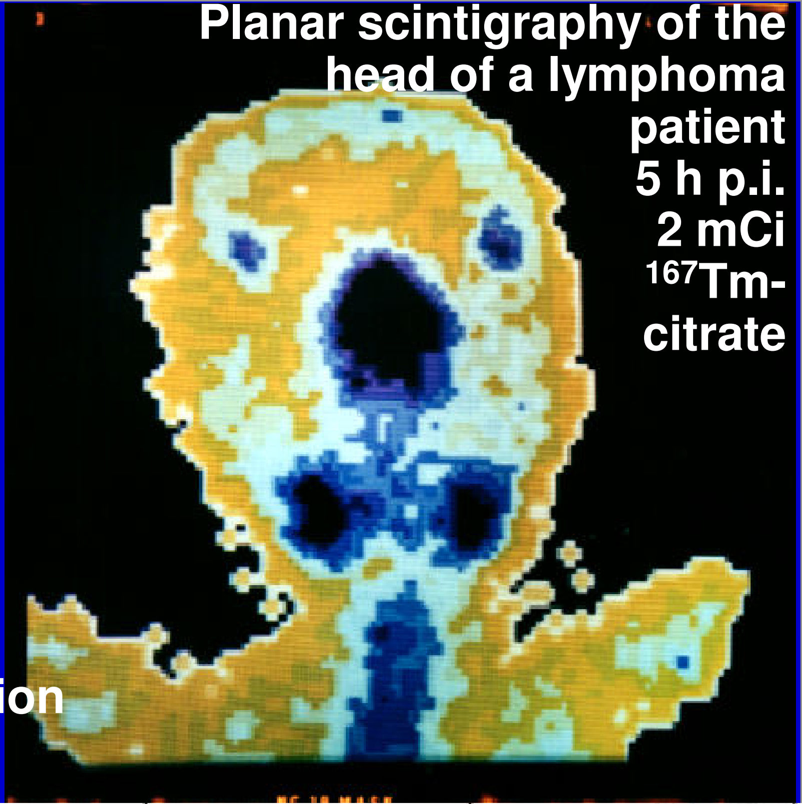
G.J.Beyer, R.Münze et al., in: "Medical Radionuclide Imaging 1980" IAEA Vienna, (1981)Vol.1 p.587

1980

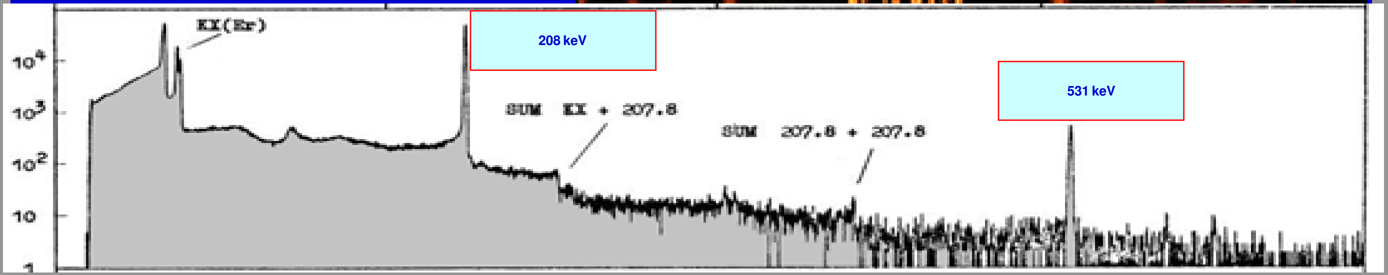
^{167}Tm-citrate

$T_{1/2}$ = 9.25 d
EC = 100 %
γ: 208 keV, 41.7 %
γ: 531 kev, 1.6 %

Production route:
- Ta (p,spallation)
- CERN – ISOLDE
- on-line mass separation
- cation exchange



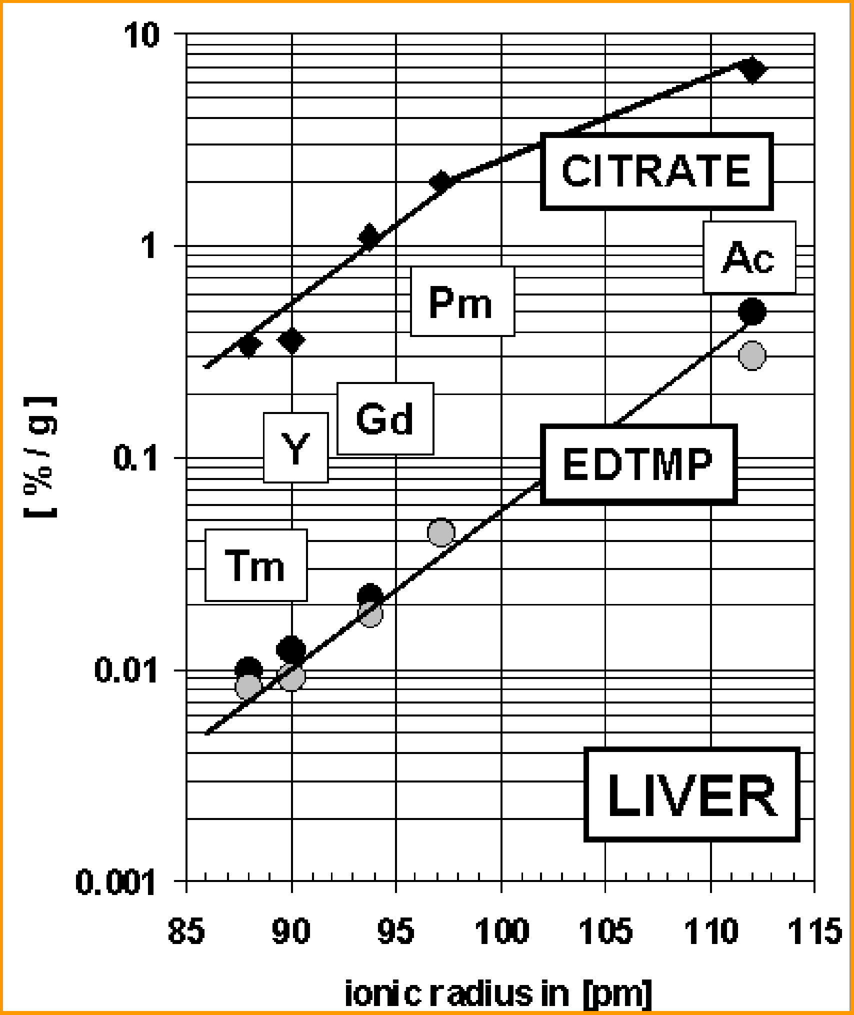
Planar scintigraphy of the head of a lymphoma patient
5 h p.i.
2 mCi
^{167}Tm-citrate



First scintigraphic examination in humans
using mass-separated lanthanides produced at CERN ISOLDE

G.J.Beyer et al., Medical Radionuclide Imaging 1980, IAEA Vienna (1981) 587

Simultanous injection of an isotope cocktail of rare earth isotopes

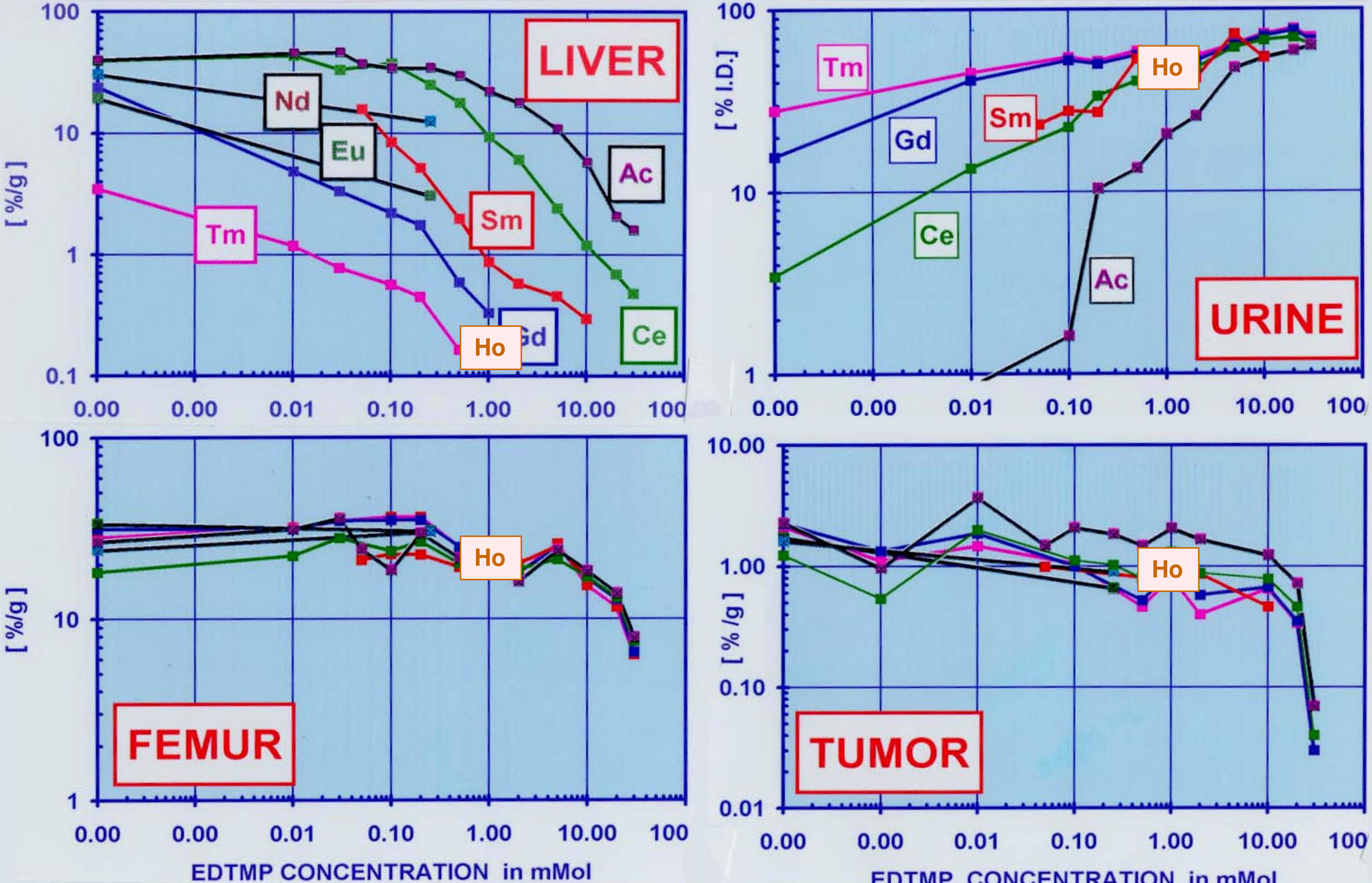


Liver uptake of ^{225}Ac and a mixture of carrier-free radio-yttrium and

radio-lanthanides (^{167}Tm, ^{88}Y, ^{153}Gd, ^{143}Pm and ^{225}Ac, injected in citrate and EDTMP containing solution) in tumor bearing rats (mamma carcinoma) 5 hours after injection. The injected volume was 0.5 ml, the ligand concentration was 20 mMol at pH=7

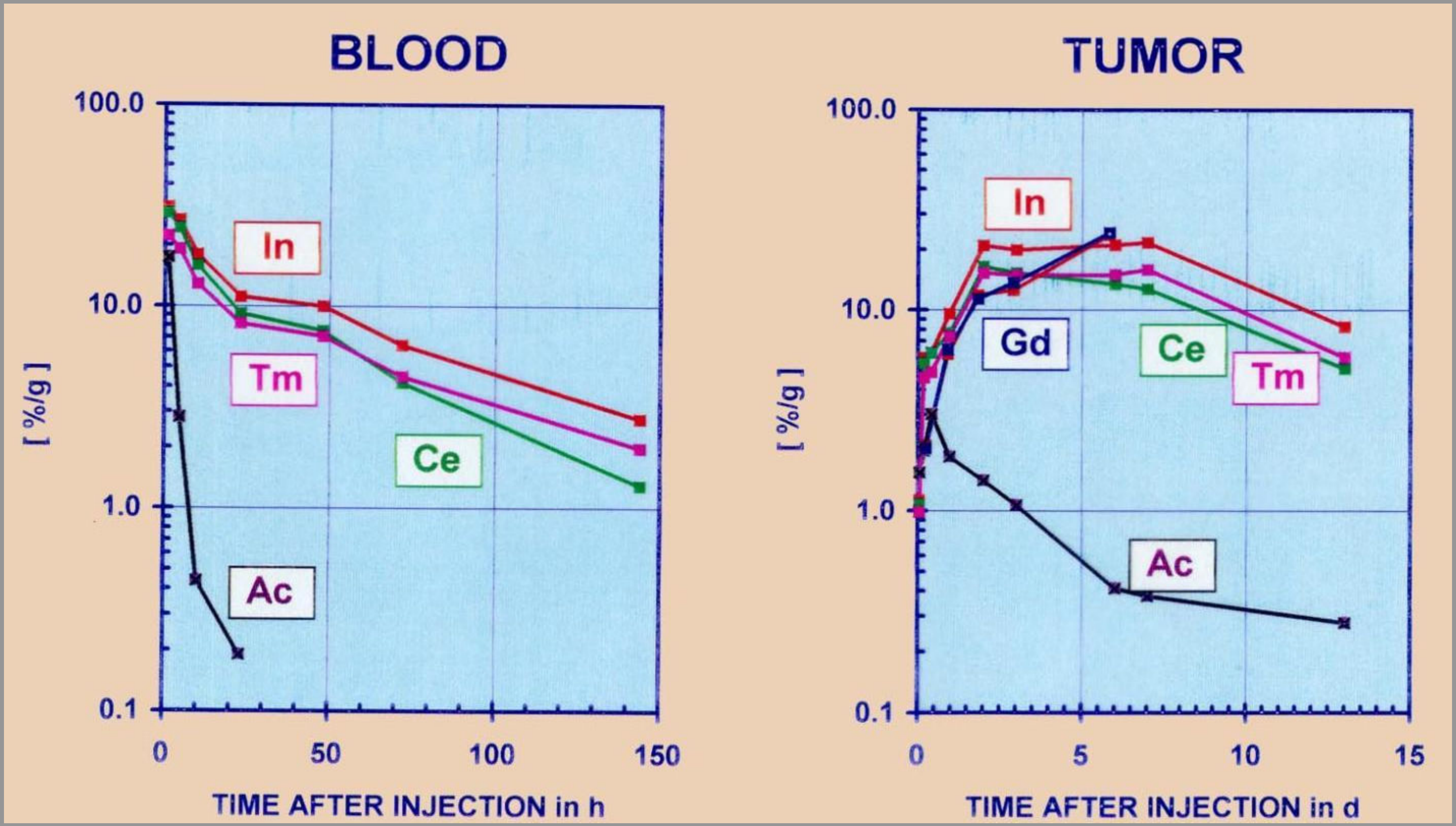
G.J.Beyer, R.Bergmann et al., Isotopenpraxis **26**,111 (1990)

LOW MOLECULAR WEIGHT CHELATORS: EDTMP BIODISTRIBUTION

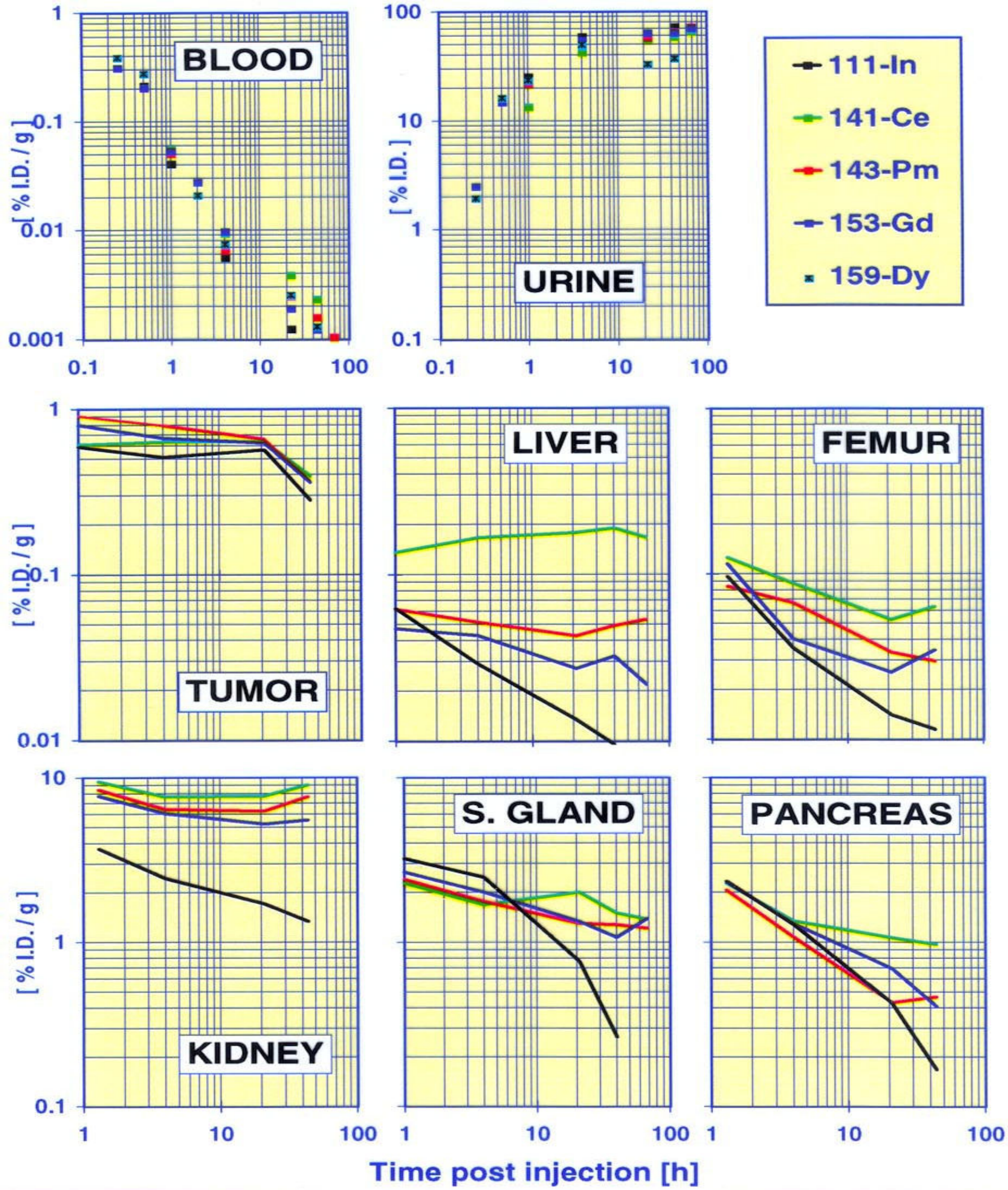


G.J.Beyer, R.Offord, G.Künzi et al. Nuclear Medicine and Biology **24** : 367-372, (1997)

Aminobencyl-DTPA-anti CEA-mab: Comparison of ^{111}In with radiolanthanides



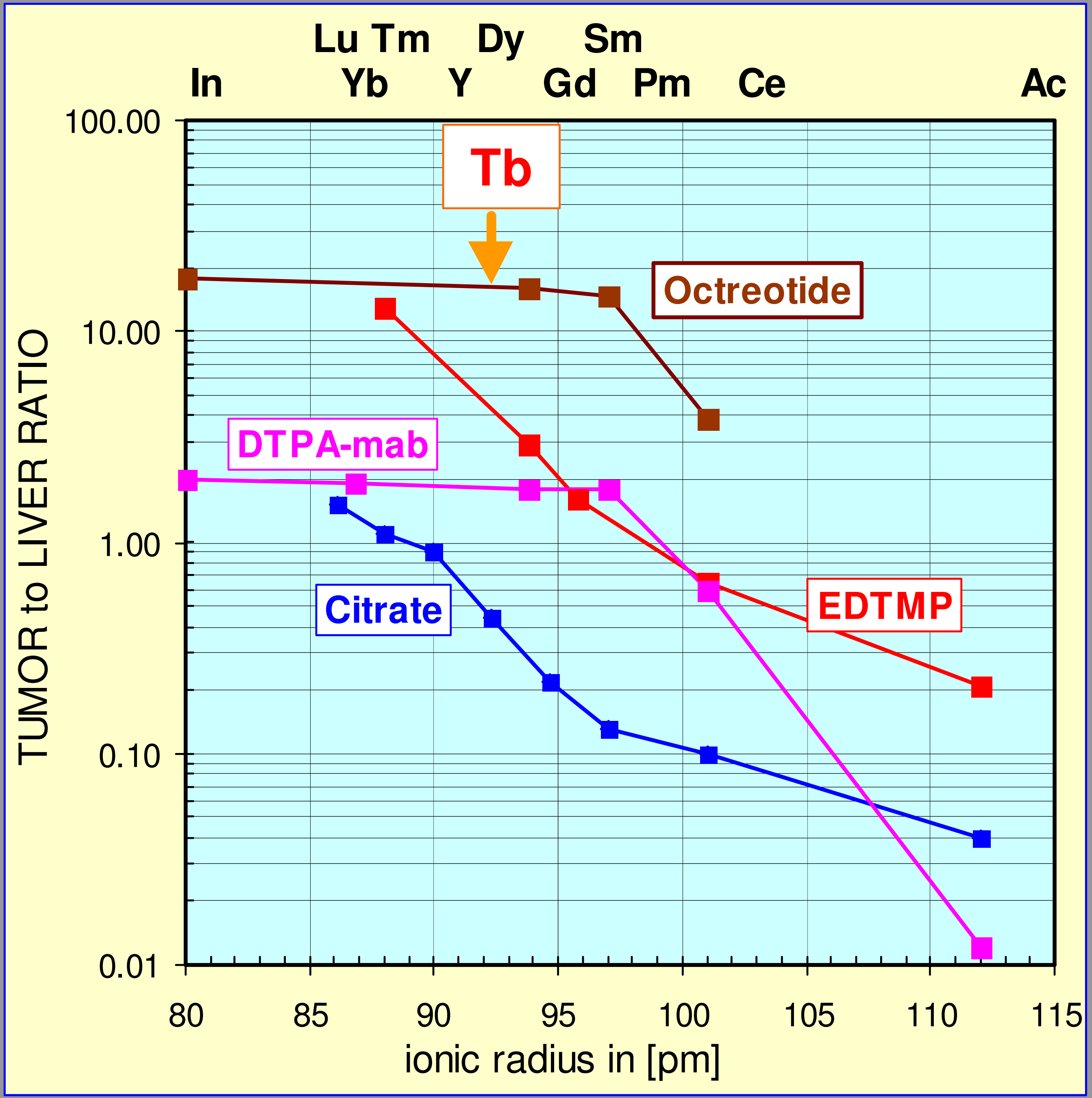
G.J.Beyer, R.E.Offord, G.Künzi et al. Journal of Labelled Compounds and Radiopharmaceuticals, **XXXVII**, 292, (1995)



Octreotide-aminobencyl-DTPA:

Comparison ^{111}In with lanthanides

G.J.Beyer, R.E.Offord, R.Werlen et al.
Europ.J.Nuclear Medicine **23** , 1132, (1996)



Comparison of the **bio-distribution** of different **tumor seeking tracers** labeled with **radio-lanthanides, ^{225}Ac and ^{111}In**

free chelates:
Citrate
EDTMP
specific tracers:
Octreotide
and
Mab
Linker:
Aminobenzyl-DTPA

G.J.Beyer, Hyperfine Interactions **129** 529 (2000)

Questions to be answered:

1. **Relationship between particle–energy and therapeutic response, depending on tumor size**

   Variation of radionuclides with different particle-energy:

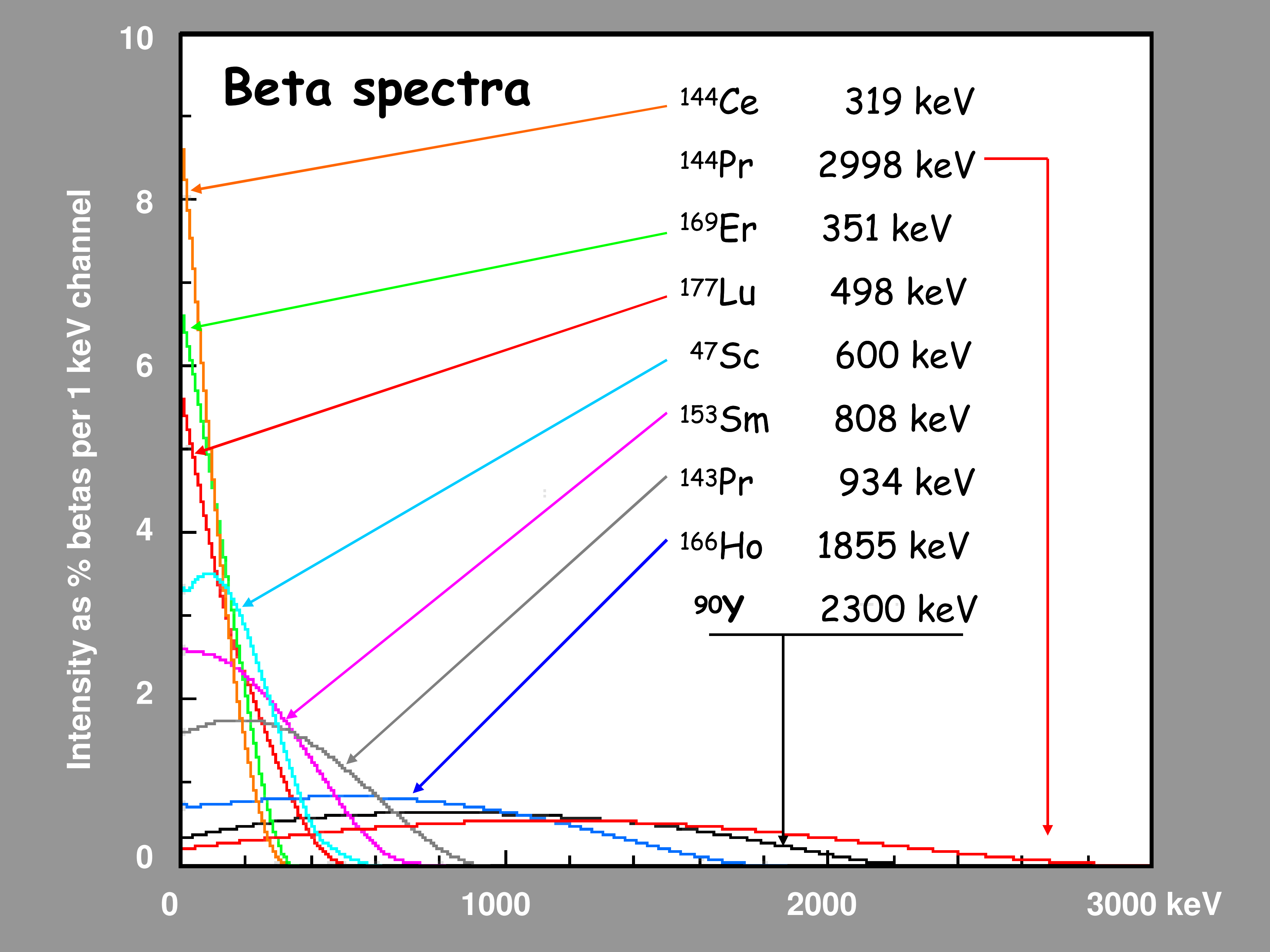
   → need for metallic ß$^{-}$ -emitters with very different energy

   → need for alpha emitting nuclides

2. **Relationship between radiation dose delivered to a lesion and the therapeutic response**

   Individual in-vivo dosimetry by quantitative PET imaging:

   → need for ß$^{+}$-emitting metallic radionuclides



Beta spectra
144Ce 319 keV
144Pr 2998 keV
169Er 351 keV
177Lu 498 keV
47Sc 600 keV
153Sm 808 keV
143Pr 934 keV
166Ho 1855 keV
90Y 2300 keV
Intensity as % betas per 1 keV channel
0
2
4
6
8
10
0
1000
2000
3000 keV

Selected radionuclides of the Rare Earth Elements with therapeutic potential

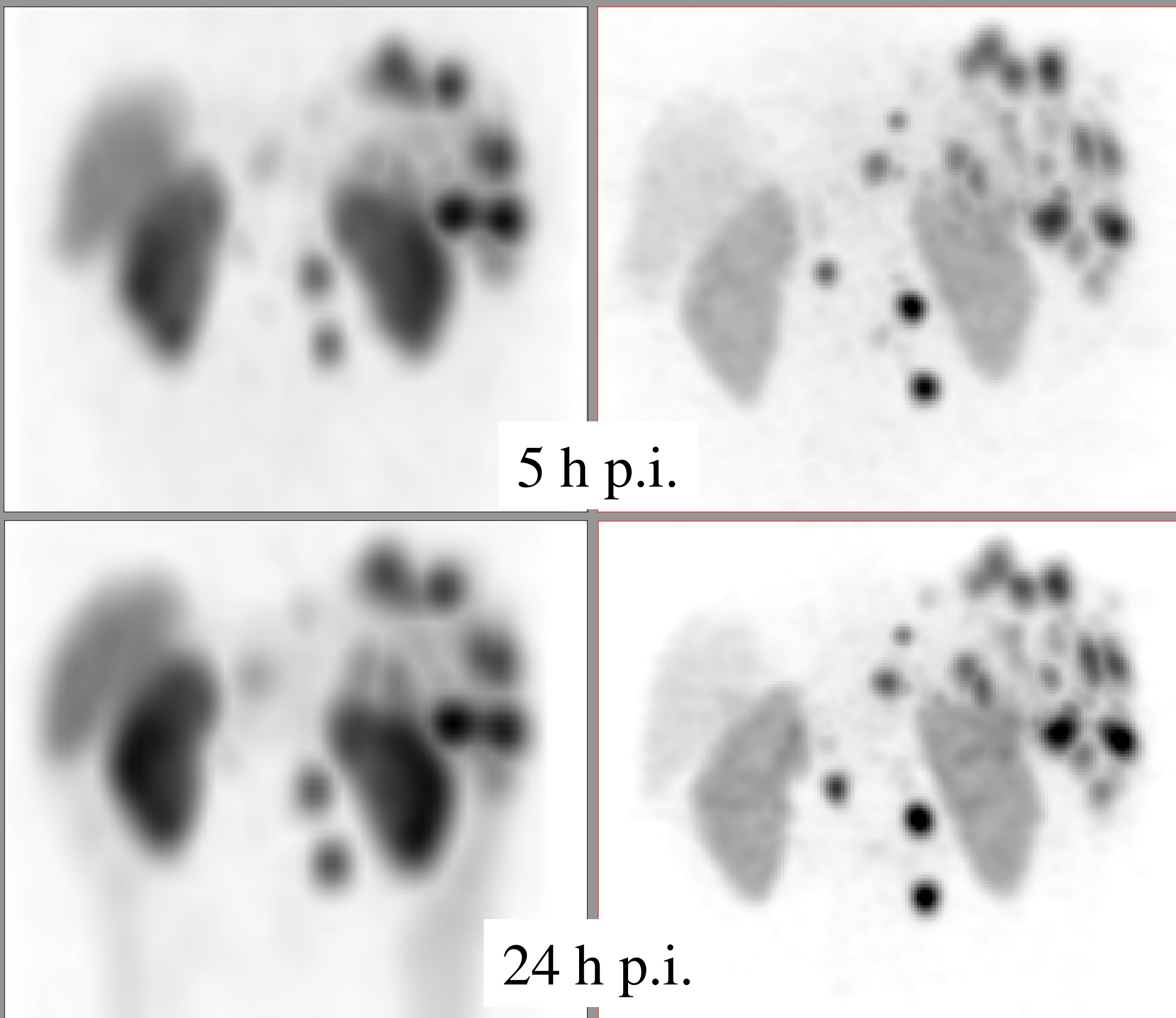
NUCLIDE	T1/2	Radiation	Emax [MeV]	E(mean) [MeV]	range [µm]	volume factor	Eγ [keV]	Iγ (*) [%]	production route
149-Tb	4.1 h	α	3967.0	3.97	28	1	s.Tab.1		see Tab.1
47-Sc	3.3 d	β , γ	0.6	0.161	300	1 200	159	70	47-Ca --ß--> 47-Sc generator
90-Y	64.1 h	β	2.3	0.934	4 200	3 400 000	no		90-Sr --ß ---> 90-Y generator
137m-Ce	34.4 h	e	0.2	0.203	500	5 700	254	11	136-Ce (n,γ) 137m-Ce reactor
141-Ce	32.5 d	β,γ	0.6	0.171	400	2 900	145	48.4	235-U (n,f) fis.prod. reactor
									141-Pr (p,n) 141-Ce cyclotron
142-Pr	19.1 h	β,γ	2.2	0.809	3 500	2 000 000	1576	3.7	142-Pr(n,γ)143-Ce --ß--> 143-Pr reactor
143-Pr	13.6 d	β	0.9	0.315	900	33 000	no		142-Ce(n,γ)143-Ce --ß-->143-Pr reactor
147-Nd	11 d	β,γ	0.9	0.27	700	16 000	91	28	235-U (n,f) fis.prod. reactor
							531	13	146-Nd (n,γ) 147-Nd reactor
149-Pm	53.1 h	β	1.1	0.366	1 100	61 000	weak		148-Nd(n,γ)149-Nd--ß-->149-Pm reactor
153-Sm	46.7 h	β,γ	0.8	0.269	1 000	57 000	103	28.3	152-Sm (n,γ) 153-Sm reactor
159-Gd	18.6 h	β,γ	1.0	0.312	800	23 000	364	10.8	158-Gd (n,γ) 159-Gd reactor
161-Tb	6.9 d	β,γ	0.6	0.195	800	26 000	75	9.8	160-Gd(n,γ)161-Gd--ß-->161-Tb reactor
166-Ho	26.8 h	β,γ	1.9	0.694	3 400	2 200 000	80.6	6.2	164-Dy(2n,γ)166-Dy--ß-->166-Ho reactor
169-Er	9.4 d	β	0.3	0.103	200	360	no		168-Er (n,γ) 169-Er reactor
175-Yb	4.2 d	β,γ	0.5	0.13	250	700	396	6.5	174-Yb (n,γ) 175-Yb reactor
177-Lu	6.7 d	β,γ	0.5	0.147	300	1 200	208	11	176-Yb(n,γ)177-Yb--ß-->177-Lu reactor

See presentation by M. Miederer for alpha-emitting ^{149}Tb.

β^+ emitters for in vivo dosimetry

$[^{111}In]$DTPA-octreotide SPECT

$[^{86}Y]$DOTA-DPhe^{1}-Tyr^{3}-octreotide PET



Scintigraphic abdominal images 5 & 24 h p.i. affected by carcinoid with extensive hepatic and paraaortal metastases.

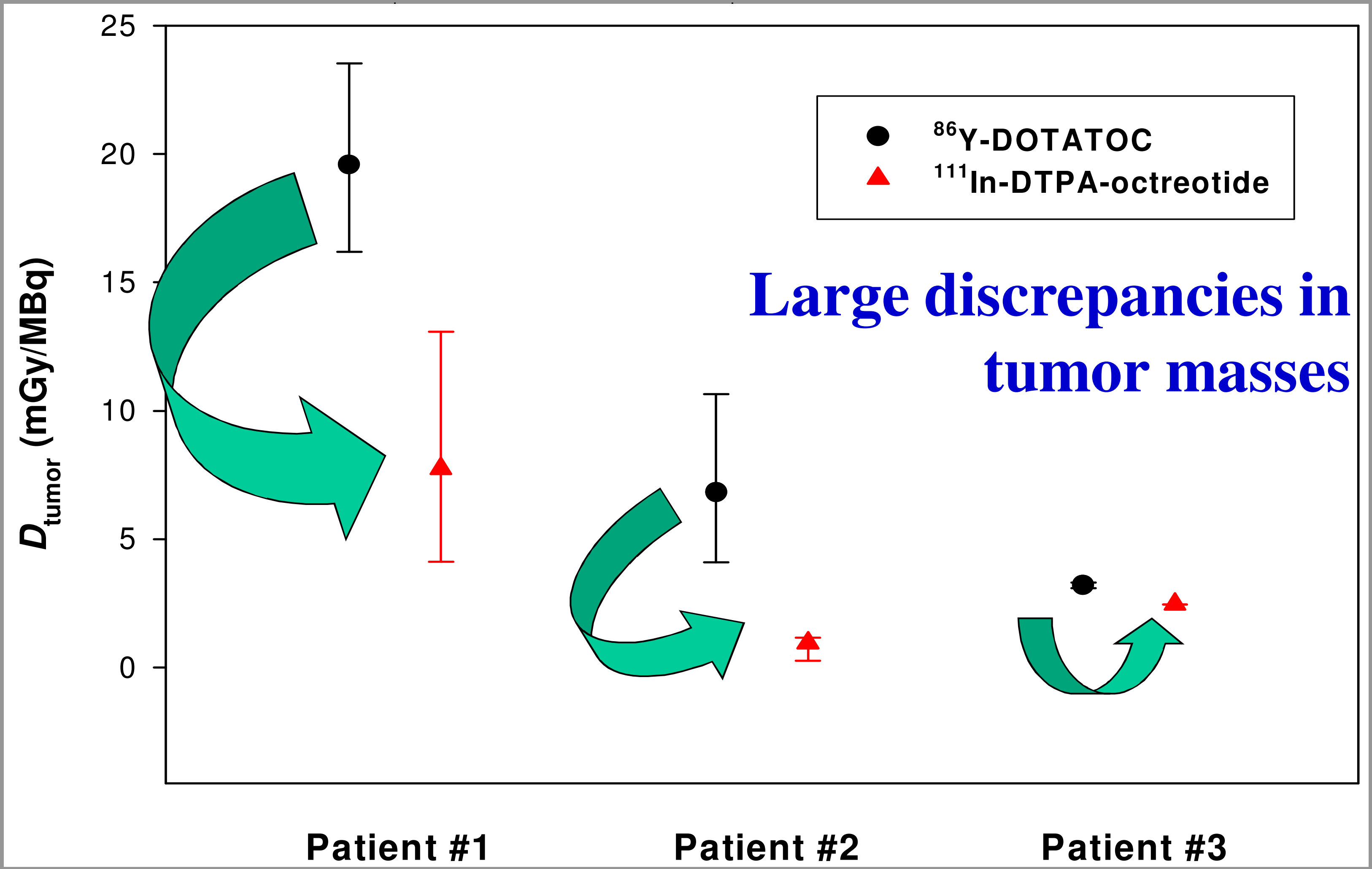
Patients:

- 3 patients with metastases of carcinoid tumor (histologically confirmed)
- No therapy with unlabeled somatostatin > 4 weeks
- Age: 46 – 67 years, male
- All were candidates for a possible ^{90}Y-DOTATOC therapy

F.Rösch et.al.

Radiation doses for [^{90}Y]DOTATOC therapy

(based on [^{86}Y]DOTATOC-PET)



universität mainz

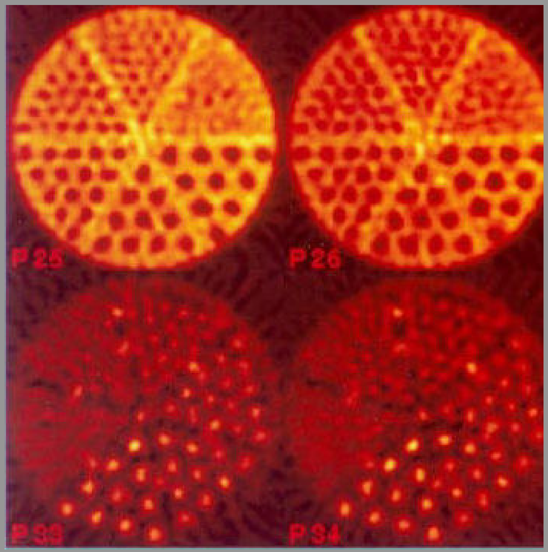
F.Rösch et.al.

H.Wagner Jr: A diagnostic dosimetric imaging procedure will be unavoidably a part of the protocol for the radioimmuno therapy (individual in vivo dosimetry).

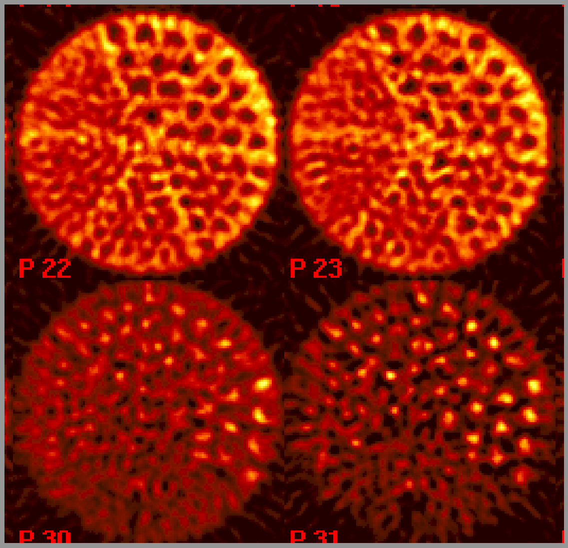
Rare Earth Elements - Positron Emitters

Nuclide	T ½	% β^+	MeV	MeV γ / %	Production Route
^{43}Sc	3.9 h	88	1.2		^{43}Ca (p,n) ^{43}Sc, ^{44}Ca (p,2n) ^{43}Sc
^{44}Sc	3.9 h	94	1.5		^{44}Ti decay (generator), ^{45}Sc (p,2n) ^{44}Ti V, Ti (p,spall)
^{85m}Y	4.9 h	67	2.3	238 34	^{86}Sr (p,2n) ^{85m}Y, ISOLDE
^{86}Y	14.7 h	32	1.2	637 33 1077 83	^{86}Sr (p,n) ^{86}Y ISOLDE
^{134}Ce ^{134}Pr	75.9 h 6.7 m	EC 64	 2.7	No 605	Ta, Er, Gd (p,spall) ^{132}Ba (α,2n) ^{134}Ce
^{138}Nd ^{138}Pr	5.2 h 1.5 m	EC 76	 3.4	No 789 4	Ta, Er, Gd (p,spall) ^{136}Ce (α,2n) ^{138}Nd, ISOLDE
^{140}Nd ^{140}Pr	3.4 d 3.4 m	EC 50	2.4	No No	Ta, Er, Gd (p,spall), ISOLDE ^{141}Pr (p,2n) ^{140}Nd,
^{142}Sm ^{142}Pm	72.4 m 40.5 s	6 78	1.5 3.9	No No	Ta, Er, Gd (p,spall), ISOLDE ^{142}Nd (α,4n)^{142}Sm
^{152}Tb	17.5 h	20	2.8	Div	Ta (p,spall) ISOLDE ^{152}Gd (p,4n) ^{149}Tb, ^{142}Nd(^{12}C,5n)^{149}Dy

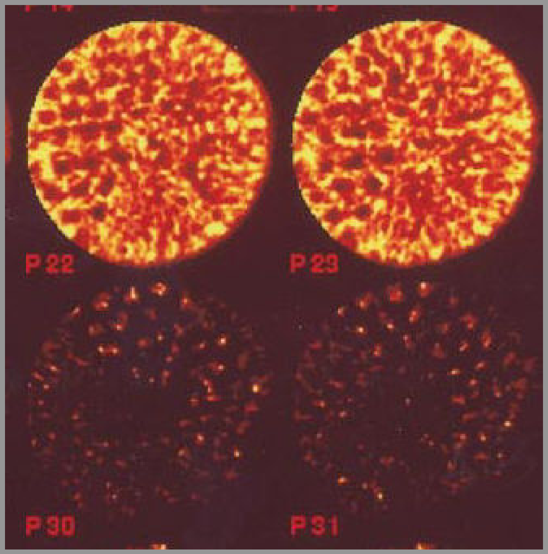
^{134}Ce/La



^{140}Nd/Pr



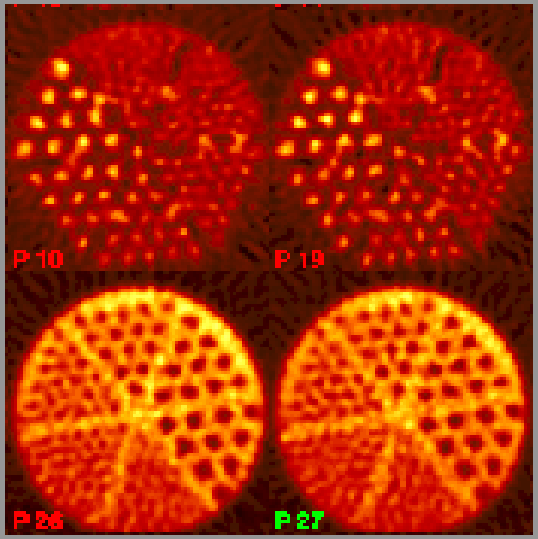
^{149}Tb



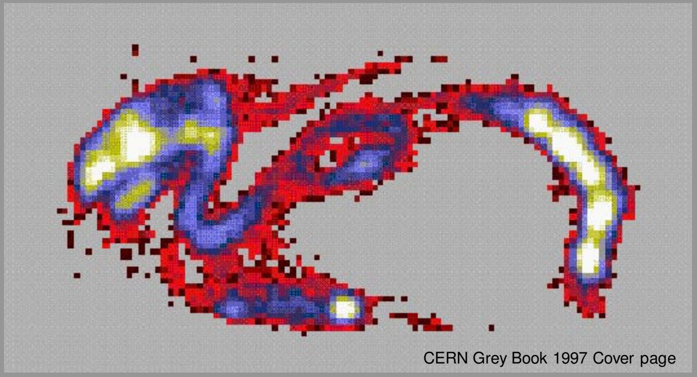
Positron emitting radiolanthanides

PET phantom studies

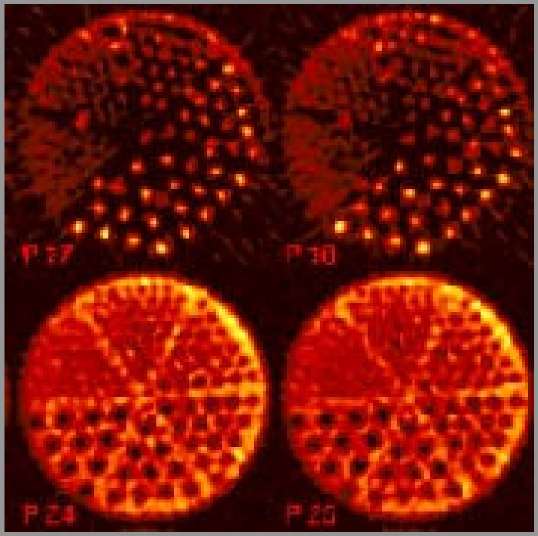
^{142}SmEDTMP in vivo study



^{138}Nd/Pr



^{142}Sm/Pm



^{152}Tb

α-emitters for therapy

Summary

- High-energy proton induced reactions can produce essentially all isotopes of medical interest
- High energy protons in combination with mass separation (on-line or off-line) provide a universal production method for R&D isotopes.
- These radioisotopes are practically carrier-free and of high purity.
- The universality of ISOLDE enables systematic biokinetic studies, simultaneously with different isotopes and different tracers.
- Already today ISOLDE can supply quantities of metallic PET-isotopes and α-emitters for preclinical and clinical "phase 0" studies in RIT.

ELSEVIER

Applied Radiation and Isotopes 63 (2005) 157–178

www.elsevier.com/locate/apradiso

The US national isotope program: Current status and strategy for future success

Mark J. Rivard[a,*], Leo M. Bobek[b], Ralph A. Butler[c], Marc A. Garland[d], David J. Hill[e,1], Jeanne K. Krieger[f], James B. Muckerheide[g], Brad D. Patton[e], Edward B. Silberstein[h]

The most demanding isotope supply challenge concerns the isotopes used in R&D, an area in which quantities are small, production techniques are not well established, and costs are high. Isotopes for R&D use without proven markets and profitability are not being adequately supplied.

Future of ISOLDE Isotopes for Nuclear Medicine

What should be done at CERN:

- **Launch a new European collaboration for bio-medical and nuclear medicine studies with carrier-free radioisotopes from ISOLDE and other sources.**
- **Rebuild a radiochemical laboratory at ISOLDE for on-site chemical purification of radioisotopes.**
- **Prepare technological solutions for larger-scale isotope production with coming accelerator upgrades (LINAC4, SPL).**

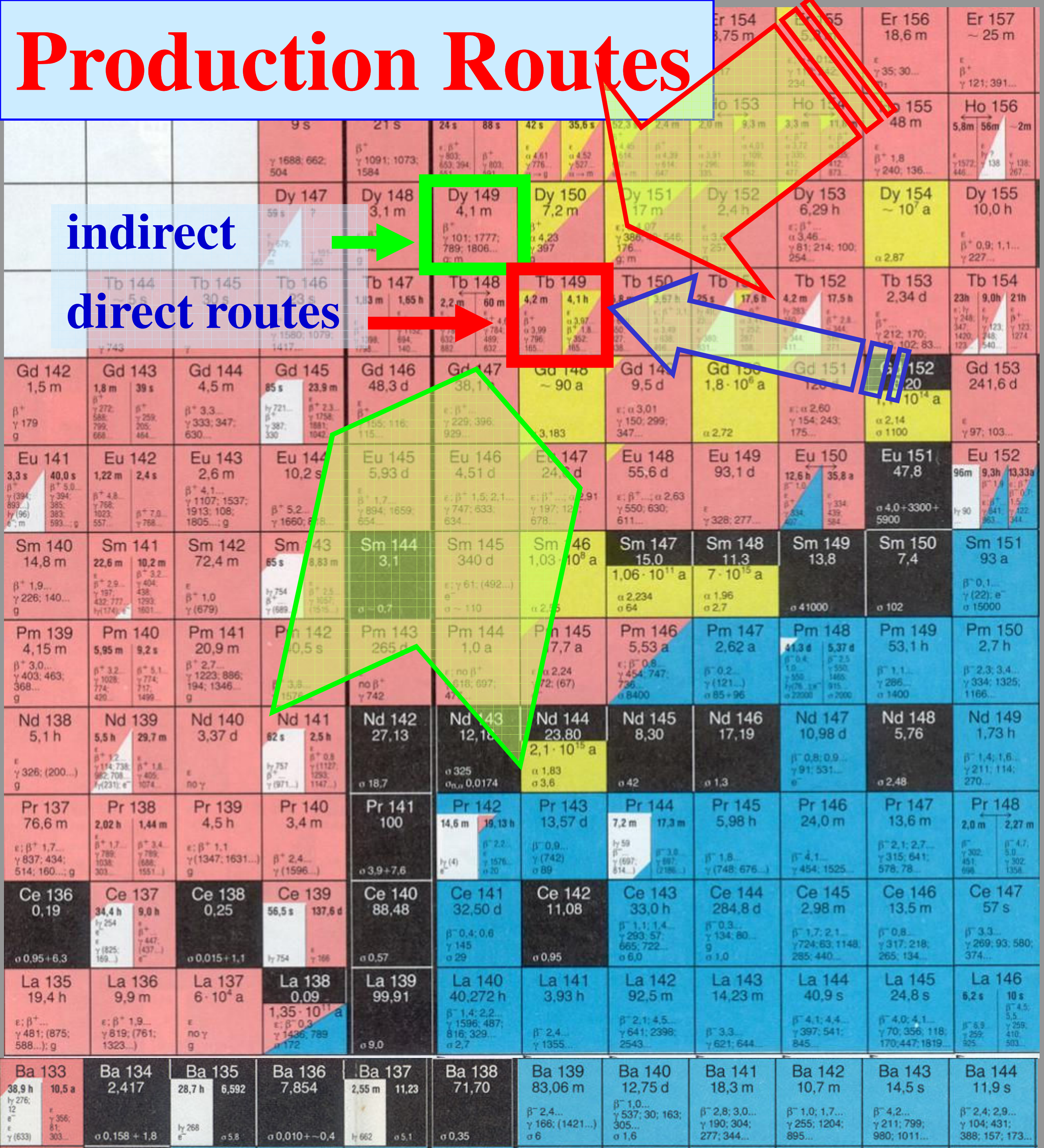
Possible longterm future: MW protons on Hg target

Radio-isotope	Half-life $T_{1/2}$	X-section (mb)	Production rate (per s)	Alternative production processes		Applications
192-Ir	74 d	2.58E+00	**1.0E+14**	(n,γ)	reactor	Sealed sources for industry and cancer therapy
188-W/Re	69 d	6.90E-02	**2.7E+12**	(2n,γ)	HFR	Radio-immuno-therapy with 188-Re
178-W/Ta	22 d	8.08E+00	**3.1E+14**	(p,4n)	accelerator	Generator with potential in PET
177-Lu	6.7 d	6.31E-02	**2.4E+12**	(n,γ)	reactor	Therapy with labelled antibodies and peptides
166-Ho	25.8 h	5.30E-03	**2.0E+11**	(n,γ)	reactor	Therapy with labelled antibodies and peptides
149-Tb	4.12 h	9.21E-01	**3.5E+13**			Targeted Alpha Therapy, single cancer cell targeting
148-Gd	74.6a	5.31E-01	**2.1E+13**	spallation	accelerator	Low-energy alpha sources
153-Sm	46.75 h	1.41E-03	**0.6E+11**	(n,γ)	reactor	Therapy of bone metastases
127-Xe	76.4 d	9.22E-02	**3.5E+12**	(p,x...)	accelerator	SPECT, lung ventilation and brain perfusion
117m-Sn	13.6 d	1.78E-01	**0.7E+13**	(n,γ)	HFR	Systemic radionuclide therapy
99-Mo/99m-Tc	66 h	2.78E-01	**0.6E+13**	(n,f)	reactor	Most important radionuclide for nuclear medical imaging
89-Sr	50.5 d	5.39E-01	**2.1E+13**	(n,γ), (n,p)	reactor	Palliative therapy of bone metastases
82-Sr/Rb	25.5 d	1.36E-01	**0.5E+13**	(p,4n)	accelerator	Generator, PET, myocardial perfusion
68-Ge/Ga	288 d	9.38E-02	**3.6E+12**	(p,2n), spall.	accelerator	Different PET imaging procedures, calibration of PET
67-Cu	61.9 h	3.83E-01	**1.5E+13**	(p,γ)	accelerator	Therapy with labelled antibodies and peptides
44-Ti/Sc	47.3 y	1.77E-03	**0.7E+11**	spallation	accelerator	Generator, great potential for PET
32-Si	101 y	3.03E-02	**1.2E+12**			Important isotope for R&D and technical application
26-Al	7.16e5 y	6.05E-03	**2.3E+11**	(p,n)	cyclotron	Important isotope for R&D and technical application
28-Mg	20.9 h	1.45E-02	**0.6E+12**			Important isotope for R&D

See poster ID120


Thank you
for your kind attention
Gerd Beyer

Production Routes



3 p-spallation ~1 GeV p / Ta

2 Light particle induced reactions

1 HI induced reactions

G.J.Beyer, J.Comor et al.
Radiochimica Acta 90, 247-252 (2002)