Medical Application of Radioactive Ion Beams

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NuPAC
CERN
10-12 October 2005
CERN

NUCLEAR MEDICINE 2005

DIAGNOSIS

SPECT (SINGLE PHOTON EMISSION TOMOGRAPHY)

- increase of diagnostic value
- new radiopharmaceuticals
- dedicated instrumentation & quantification

PET AS RESEARCH TOOL

- Molecular in vivo biochemistry
- Gene expression
- Clinical research

Molecular Imaging

PET AS CLINICAL TOOL

- Oncology
- Reimbursement of FDG-studies
- Neurology
- Cardiology

Multi - modality Imaging

- combined SPECT -PET
  (image of the year at the 46.SNM)
- Function and morphology
  (PET – CT)

THERAPIE

NEW APPROACHES IN RADIONUCLIDE THERAPY

- bio-selective antibodies
  (mab = monoclonal antibodies)
- bio-specific peptides
  (Octreotides, others)
- gene therapy
- free chelators like EDTMP
- labelled particles (microspheres, colloids)
- labelled macromolecules

NEW RADIONUCLIDES for THERAPY

- β - emitters
- α-emitters

α-THERAPY & AUGER THERAPY

PET FOR IN VIVO DOSIMETRY

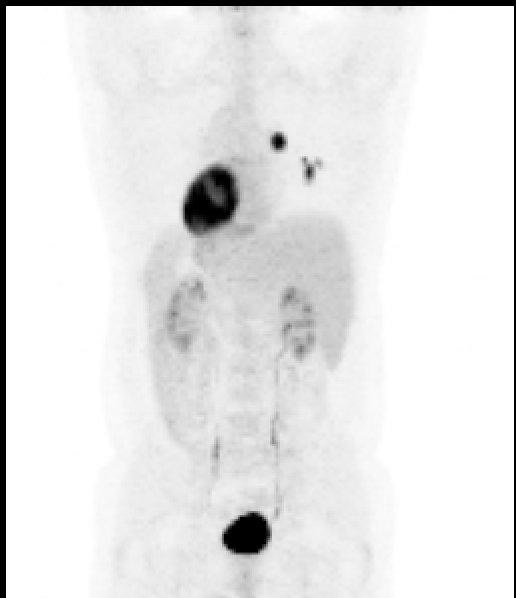
- metallic positron emitters
- labelled drugs
- dose localization

G.BEYER (HUG, Geneva, 2005)

3D whole-body PET

ECAT HR+

25 year-old male with Melanoma,
71 kg, 178 cm, 625 MBq FDG, 45 min p.i.

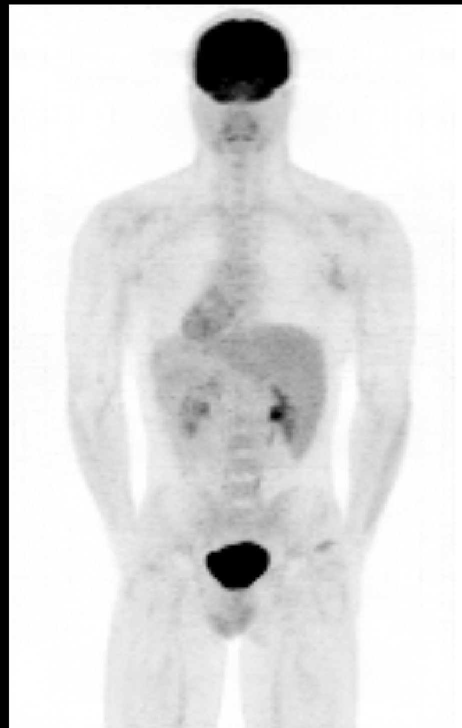


Emission scan time: 54 min
Transmission scan time: 18 min

Data courtesy of
Kettering Memorial Hospital, Kettering, USA

ECAT ACCEL

50 year-old male with colon CA
91 kg, 183 cm, 720 MBq FDG, 162 min p.i.



Emission scan time: 27 min
Transmission scan time: 18 min

Data courtesy of
NC PET Imaging Center, Sacramento, USA

Clinical PET/CT protocols

*The **biograph***

CPS INNOVATIONS™

Thomas Beyer, PhD

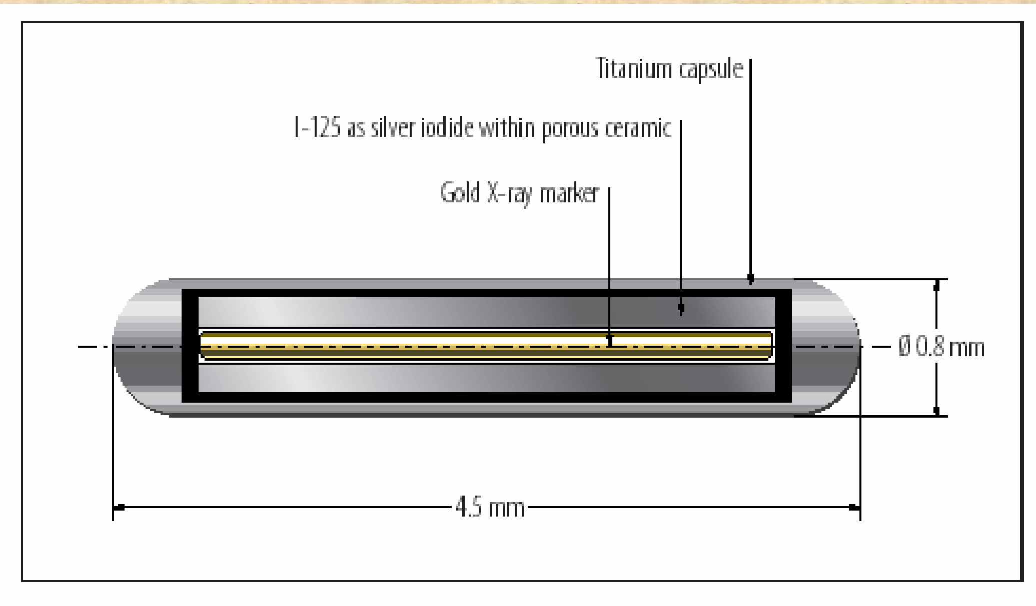
ISOTOPES in Therapy =

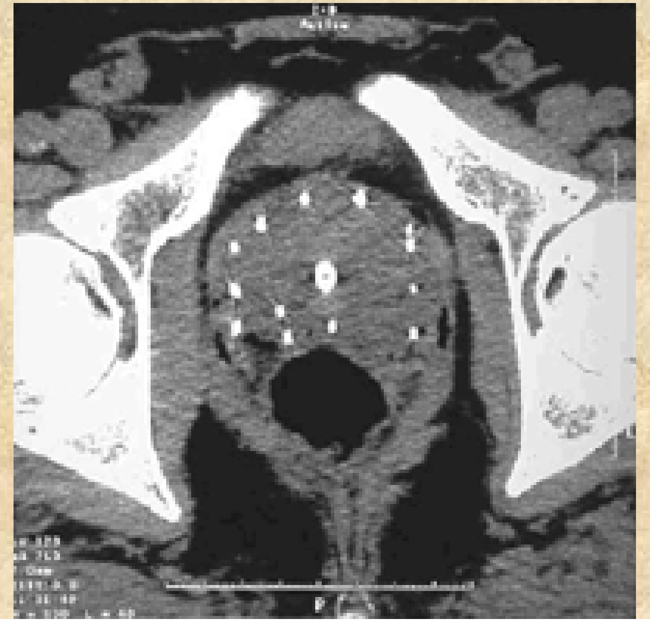
surgery with radiation

	Tissue surgery	Cell surgery	Molecular surgery
ISOTOPE	^{131}I, ^{90}Y, ^{153}Sm, ^{166}Ho, ^{177}Lu Others $E_ß$ 1 – 3 MeV	$^{212, 213}$ Bi, ^{211}At, ^{149}Tb, $^{223, 224}$Ra Eα 4–8 MeV	^{125}I ^{165}Er E_e few eV
Range	about 1 cm	30 - 80 μm	1 μm
	ß-Knife	α-Knife	Auger Knife

BEBIG
An Eckert & Ziegler Company

IsoSeed I-125

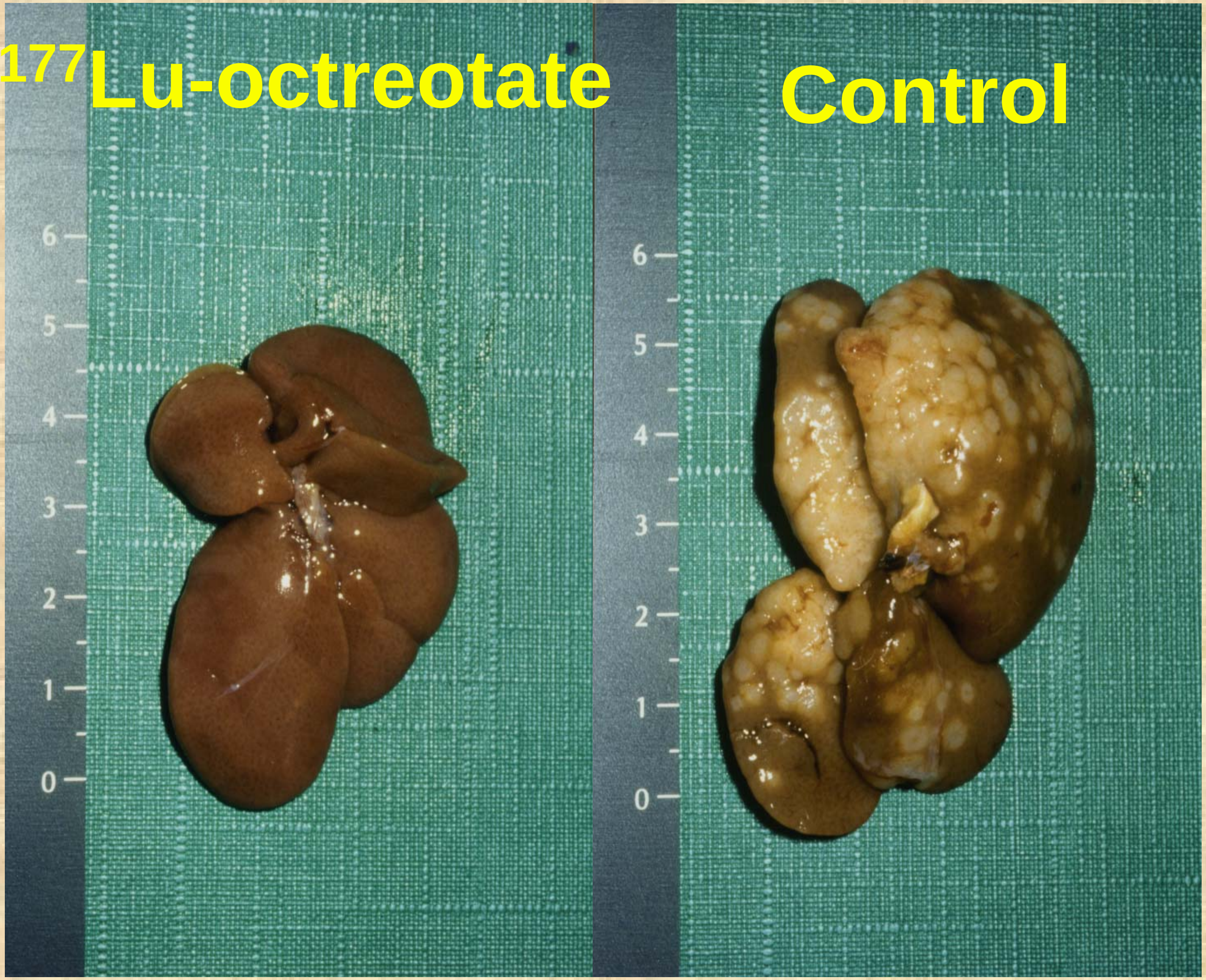




The IsoSeed is equipped with a high-density gold marker providing excellent CT visibility. The full-length marker allows easy and precise location of each seed and produces minimal artefacts. This enhances the precision of the post-implant quality control.

Rats with SSR-positive tumours in liver model mimics disseminated disease ⇒ PRRT

(PRRT = Peptide Receptor Radionuclide Therapy)



Wouter A.P. Breeman
Erasmus MC Rotterdam
The Netherlands

Int J of Cancer 2003

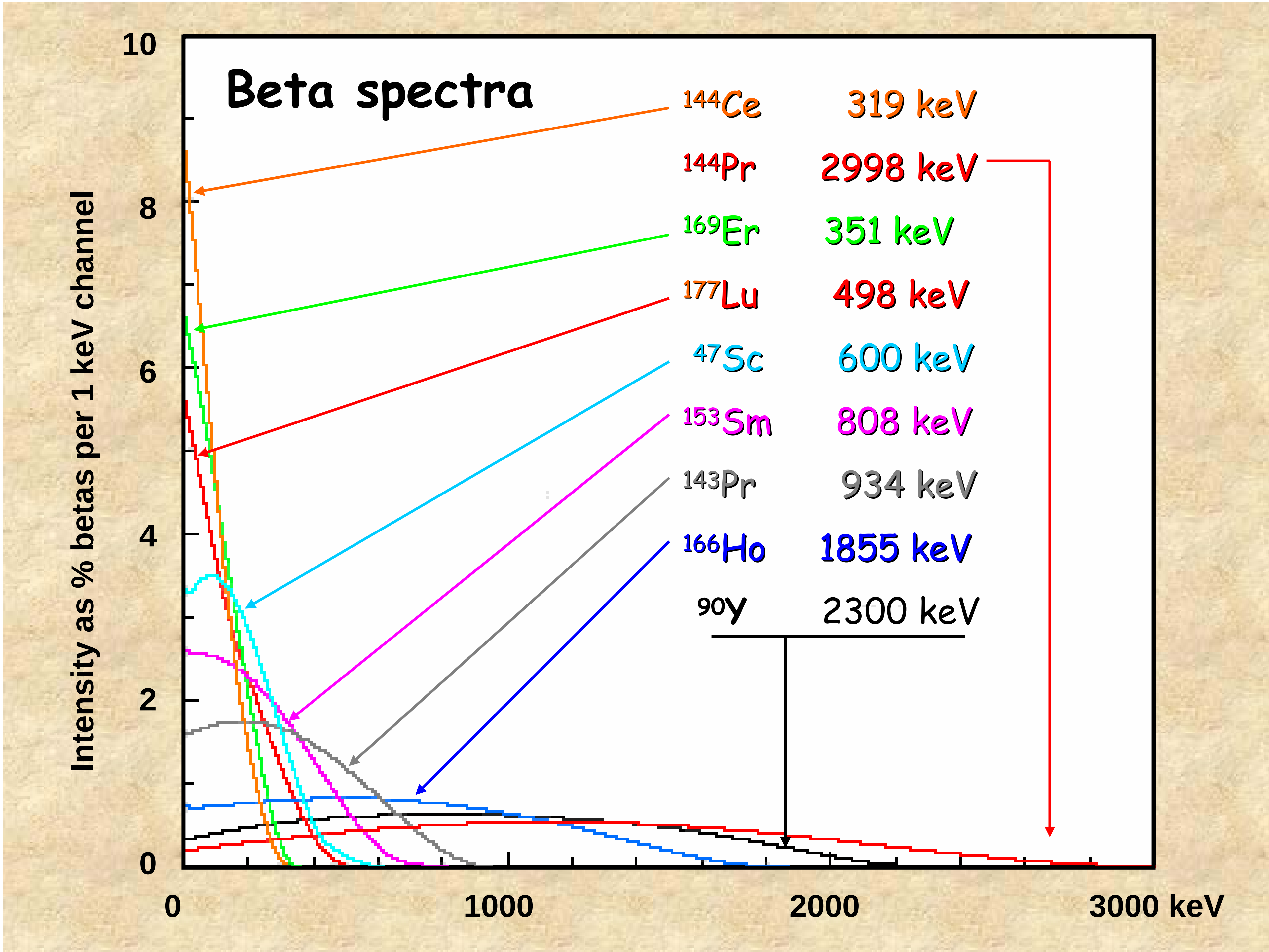
Questions to be answered:

- Realationship between radiation dose delivered to a leason and the therapeutic response

  In vivo dosimetry by quantitative PET imaging: need for $ß^+$-emitting metallic radionuclides

- Relationship between beta – energy and therapeutic response

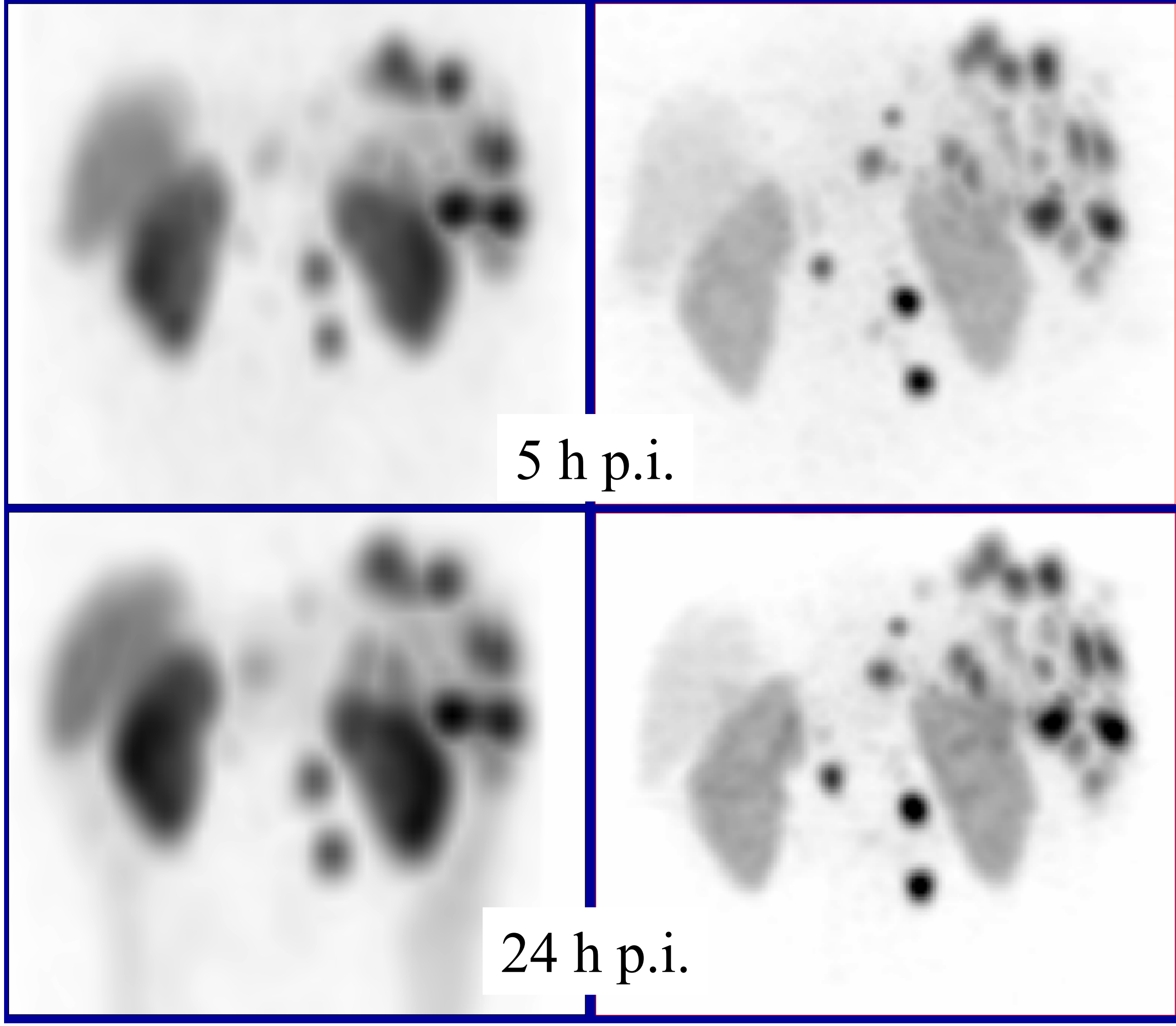
  Variation of radionuclides with different ß-energy: need for metallic $ß^-$ -emitters with very different energy


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
10
8
6
4
2
0
0
1000
2000
3000 keV

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.

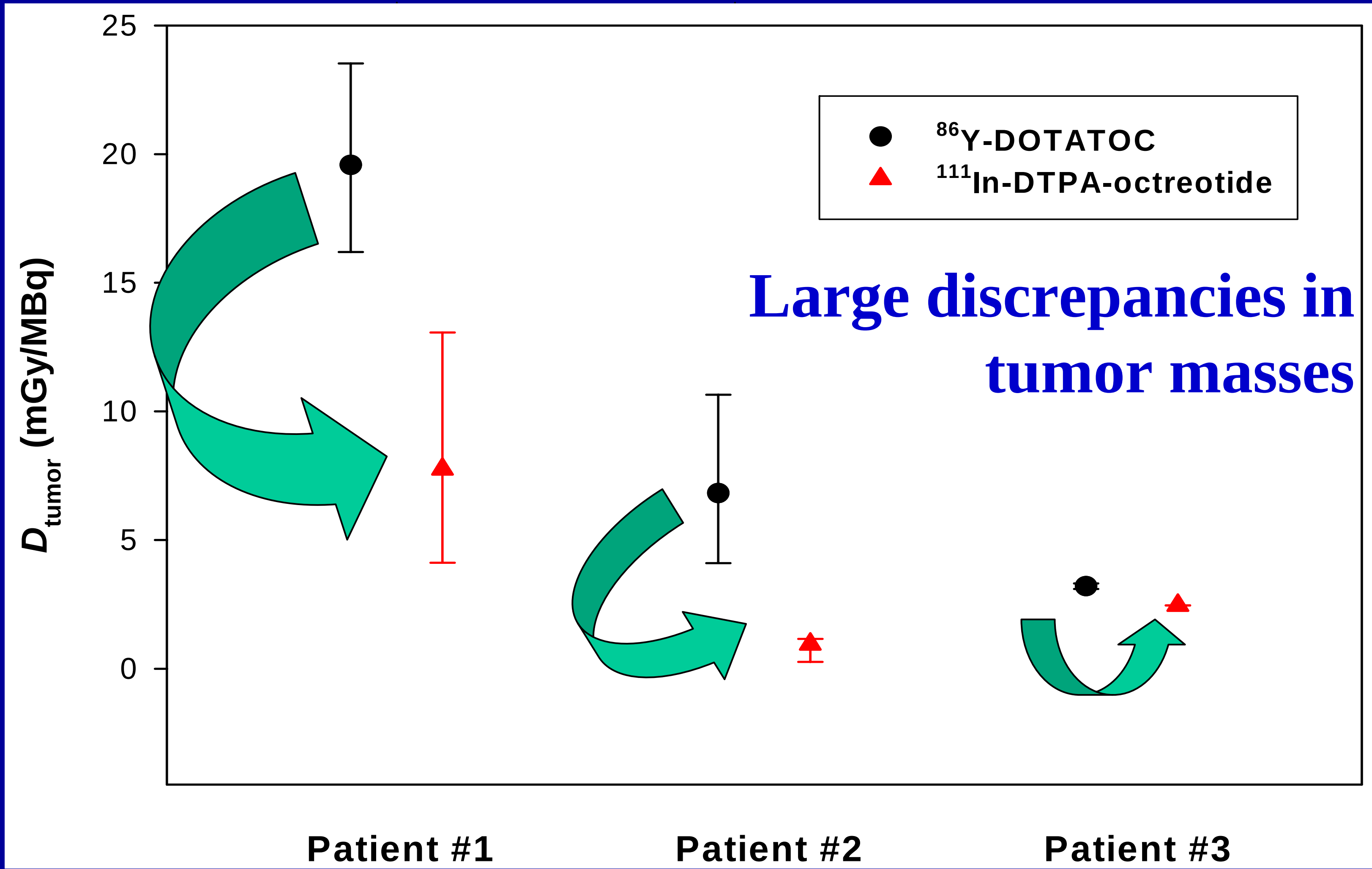
Patients:

- 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)



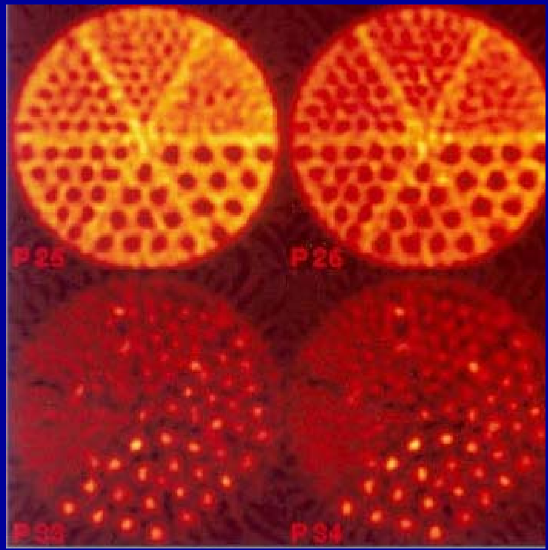
H.Wagner Jr: A diagnostic dosimetric imaging procedure will be unevoidable a part of the protocoll for the radioimmuno therapy (individual in vivo dosimetry).

F.Rösch et.al.

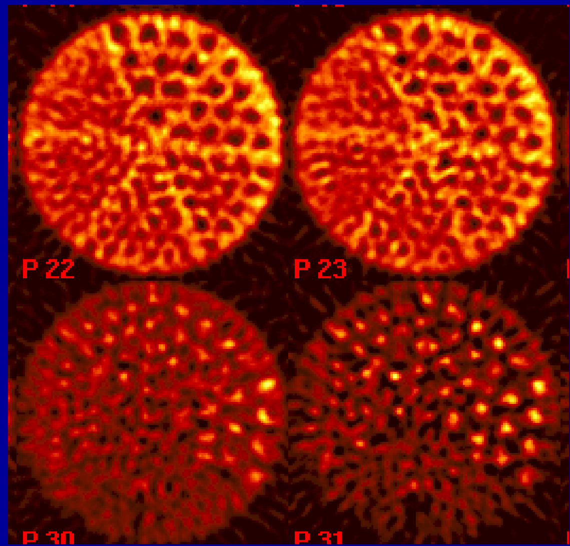
Rare Earth Elements - Positron Emitters

Nuclide	T ½	% ß+	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

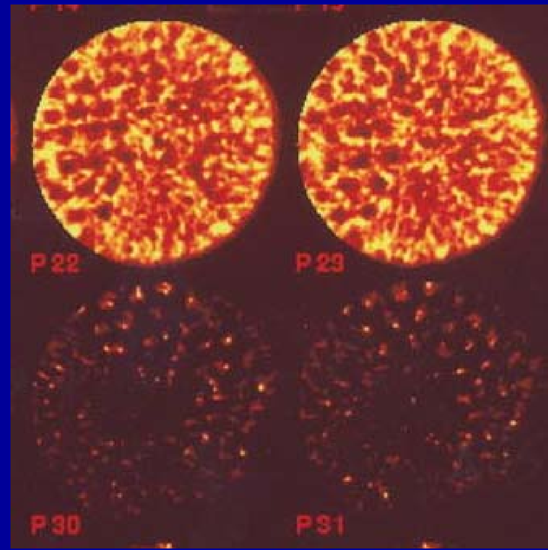
^{134}Ce/La



^{140}Nd/Pr



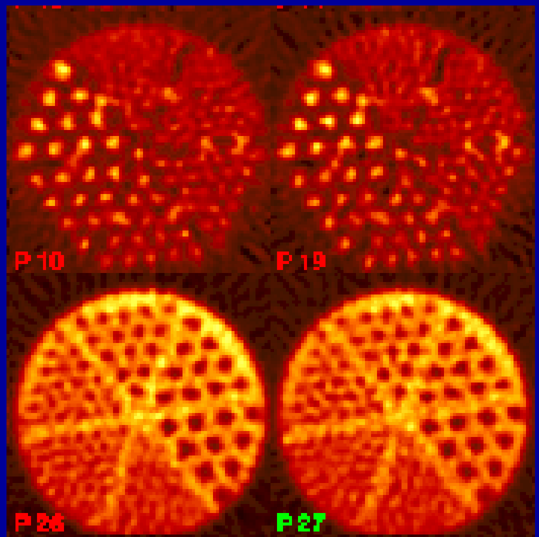
^{149}Tb



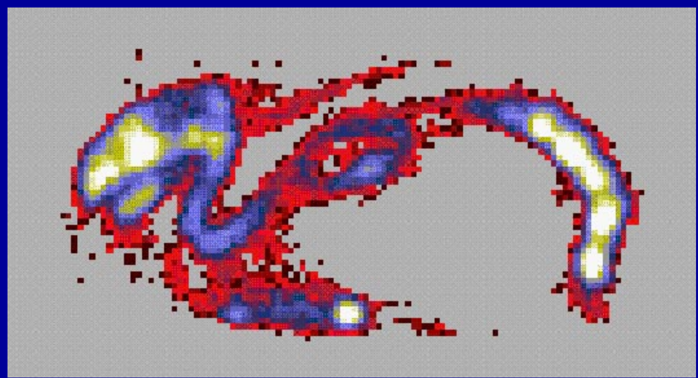
Positron emitting radiolanthanides

PET phantom studies

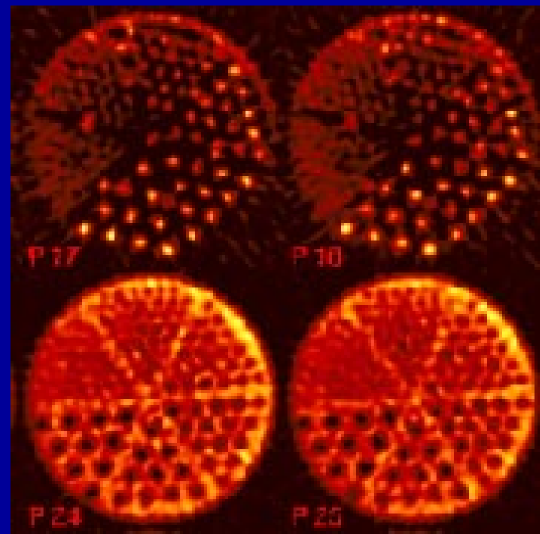
^{142}SmEDTMP in vivo study



^{138}Nd/Pr

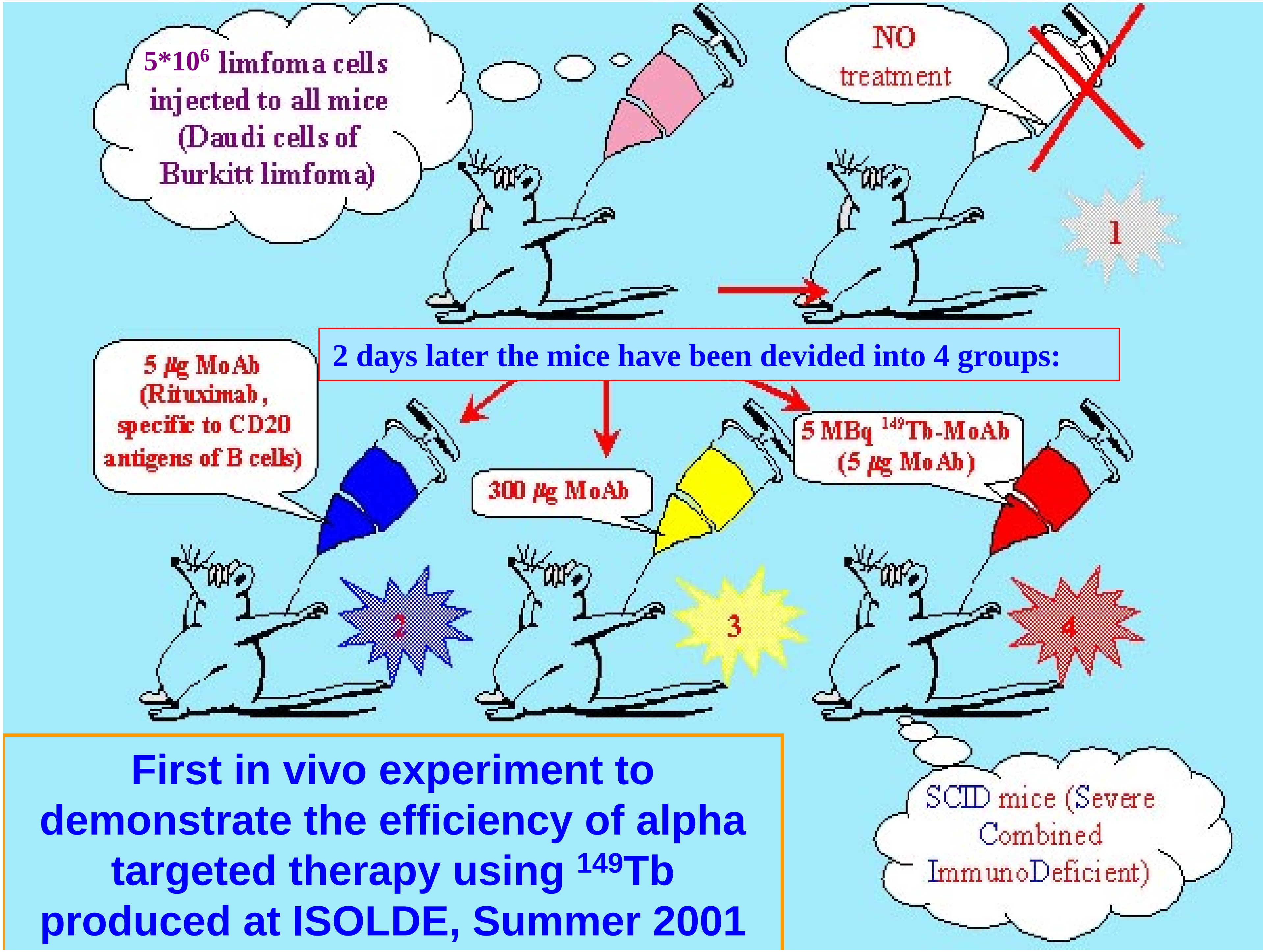


^{142}Sm/Pm

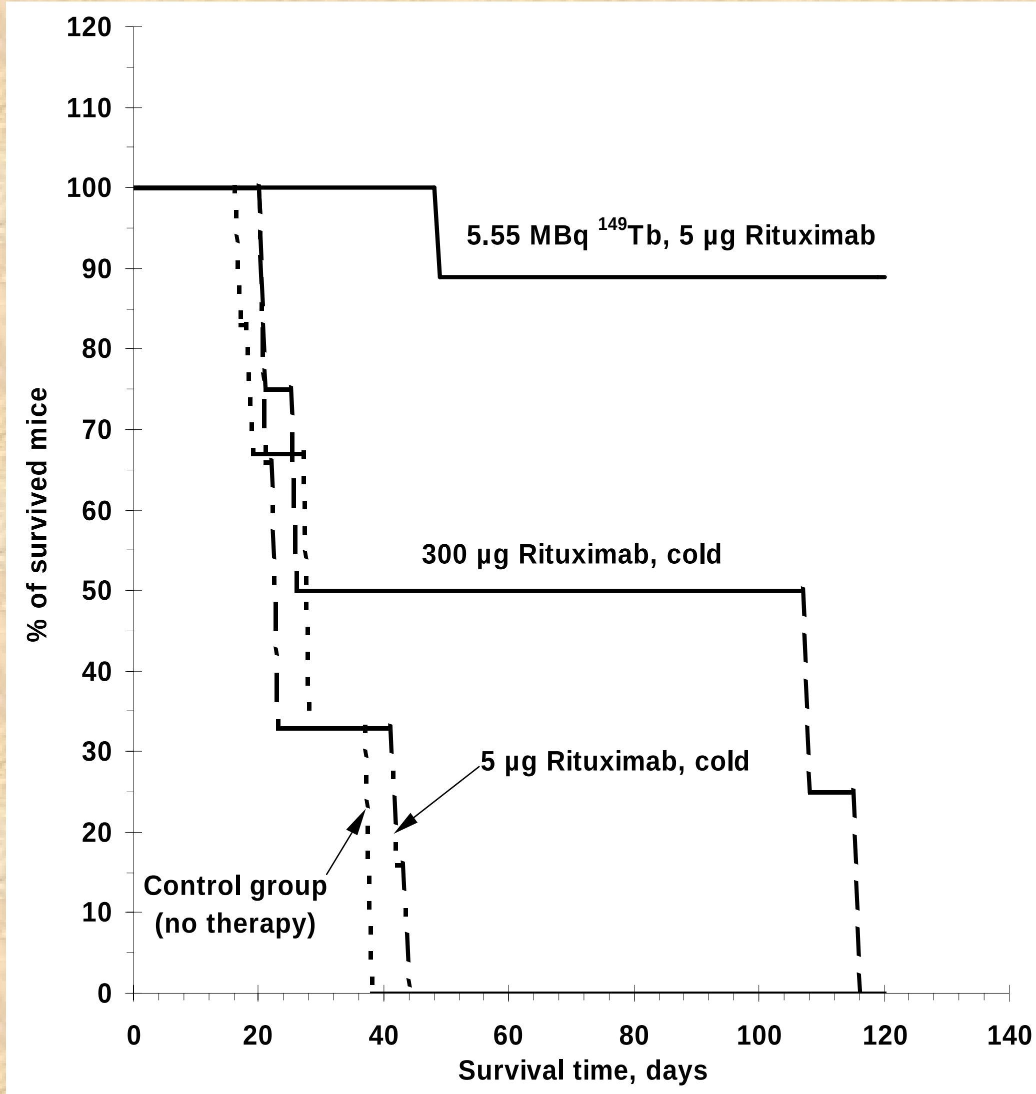


^{152}Tb

α-emitters for therapy


5*10^6 limfoma cells injected to all mice (Daudi cells of Burkitt limfoma)
NO treatment
1
2 days later the mice have been devided into 4 groups:
5 µg MoAb (Rituximab, specific to CD20 antigens of B cells)
300 µg MoAb
5 MBq 149Tb-MoAb (5 µg MoAb)
2
3
4
SCID mice (Severe Combined ImmunoDeficient)
First in vivo experiment to demonstrate the efficiency of alpha targeted therapy using 149Tb produced at ISOLDE, Summer 2001

Targeted Alpha Therapy (TAT) in vivo – direct evidence for single cancer cell kill using ^{149}Tb-Rituximab



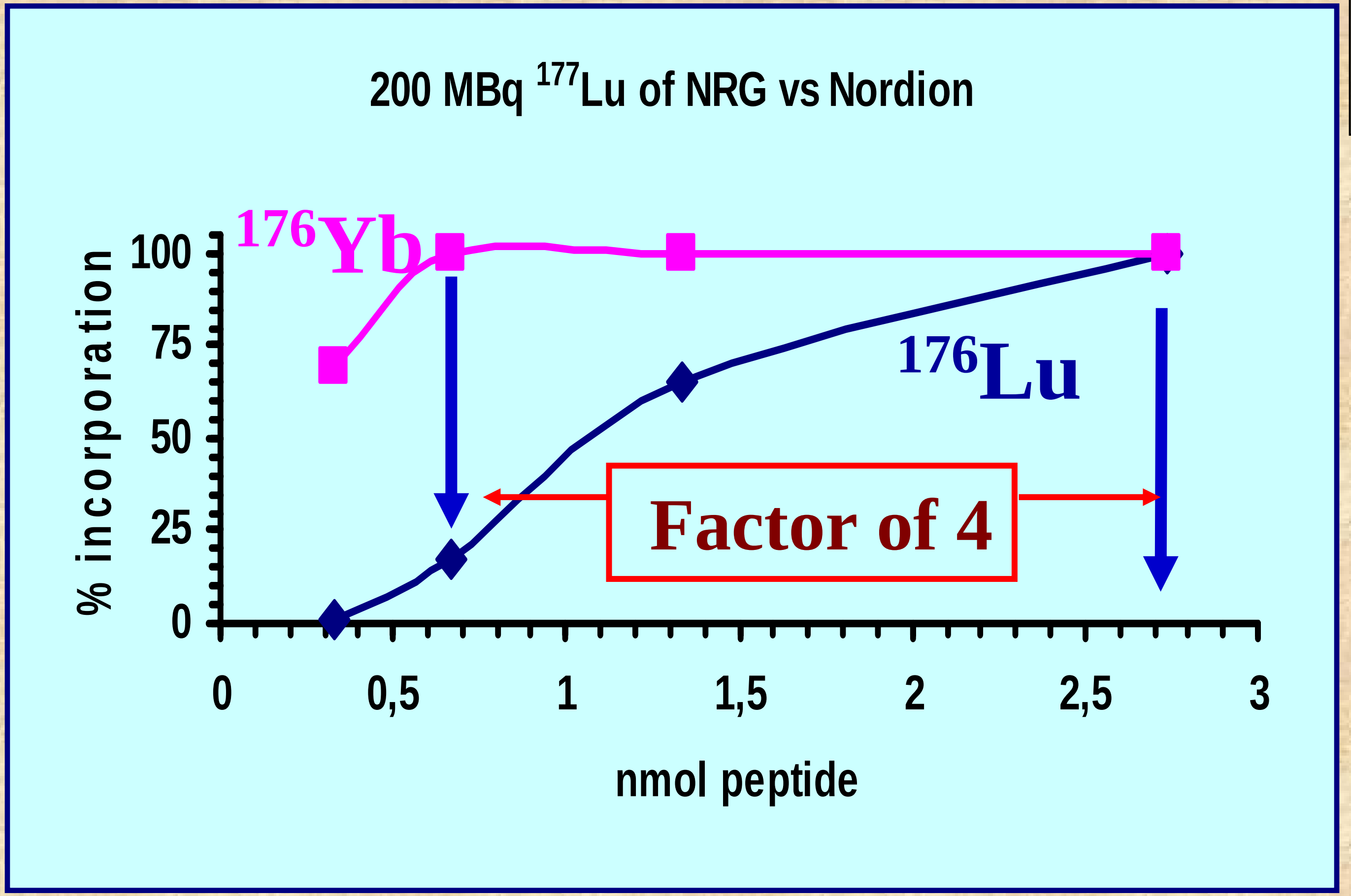
G.-J. Beyer, M. Miederer, S. Vranješ-Đurić, J.J. Čomor, G. Künzi, O. Hartley, R. Senekowitsch-Schmidtke, D. Soloviev, Franz Buchegger and the ISOLDE Collaboration,
Eur.J.Nucl.Med. and Molecular Imaging **33**(4), 547-554, (2004)

Why is high specific activity that important?

- The receptor density is low for peptide ligands
- The infusion speed is limited for certain therapeutical approaches
- We do not wont to delute our biospecific ligands with inactive atoms

Influence of production mode for ^{177}Lu
^{176}Lu-route versus ^{176}Yb-route

Wouter A.P. Breeman
Erasmus MC Rotterdam
The Netherlands



200 MBq ^{177}Lu
incubation:
pH = 4.5
T = 80 oC
T = 20 min
Peptide variation

Low carrier - shorter infusion time

Radioisotopes for:

- Diagnosis:
- „Classical Radioisotopes“,
  Market more or less saturated,
  slow increase for ^{99}Mo, strong increase for ^{18}F

- Therapy:
- Fast growing demand (15 % per year),
  (other source: 100 fold until 2020 y)
  new isotopes required, β^-, α , Auger-
  new quality parameters: carrierfree

- **R&D:**
- **R&D nuclides (metallic β^+, γ), not available for reasonable prices, development of new radiopharmaceuticals hampered**

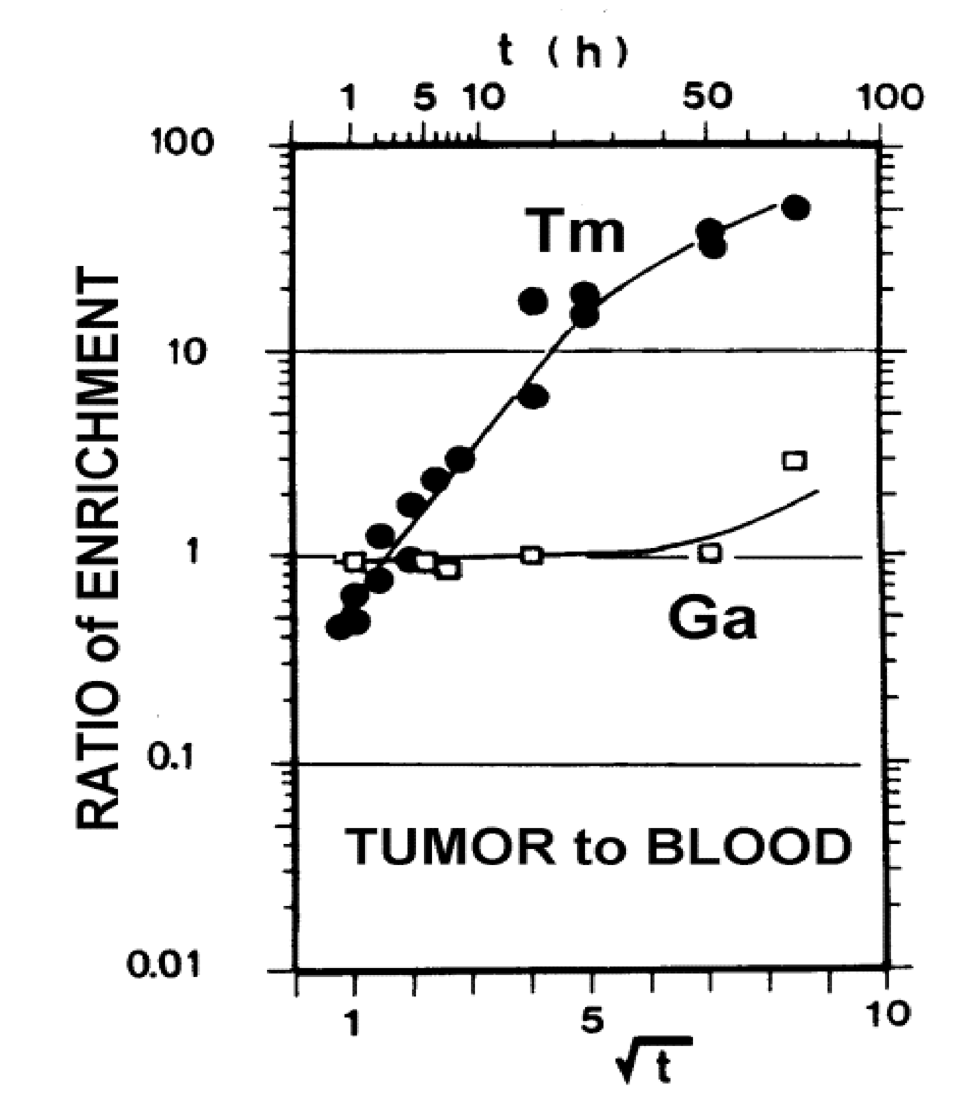
Alterantive and universal Production Route:

high energy proton induced Reactions:

Spallation

Fission

Fragmentation



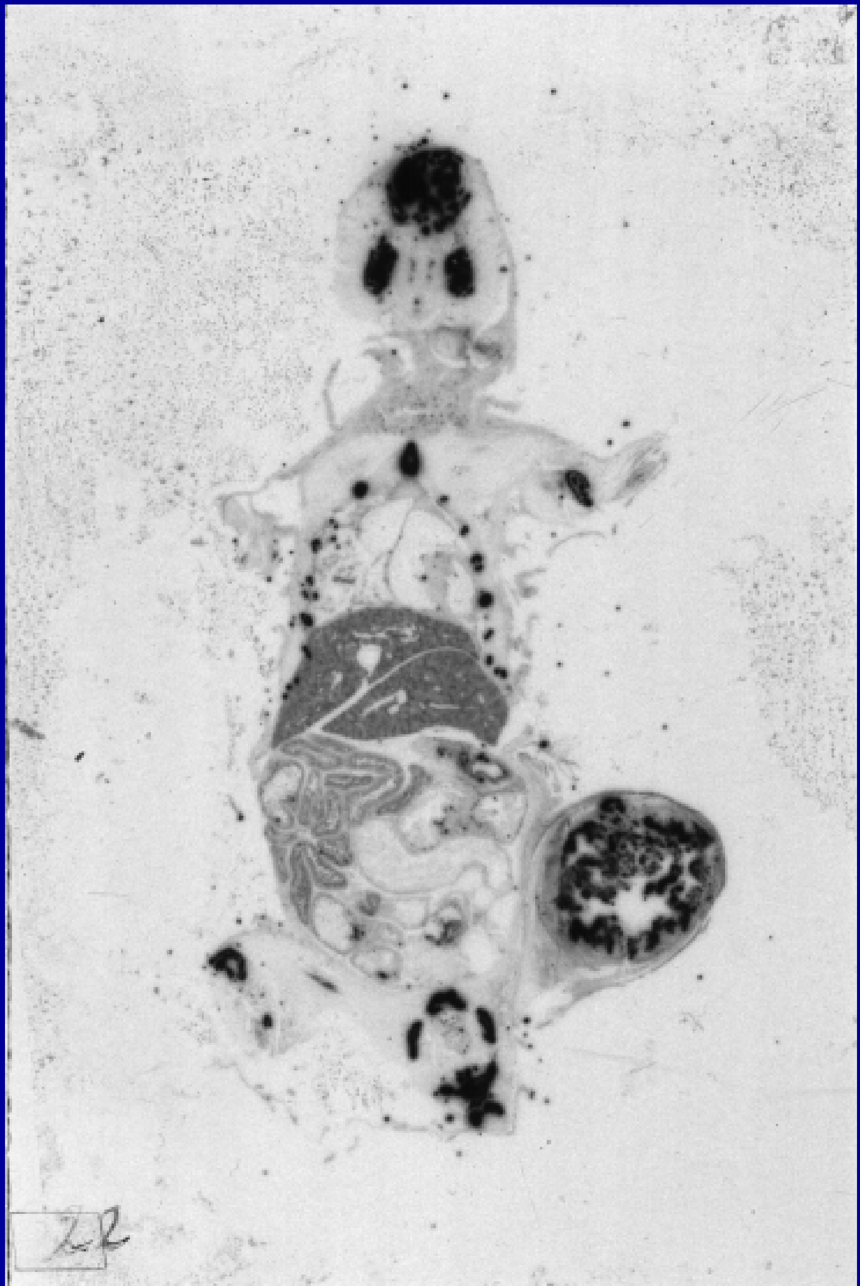
Direct comparison

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

in
tumour 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 mice 24 hours after injection of 0.4 MBq of ^{167}Tm-Citrate

Lanthanides are unspecific tumor seaking tracers

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

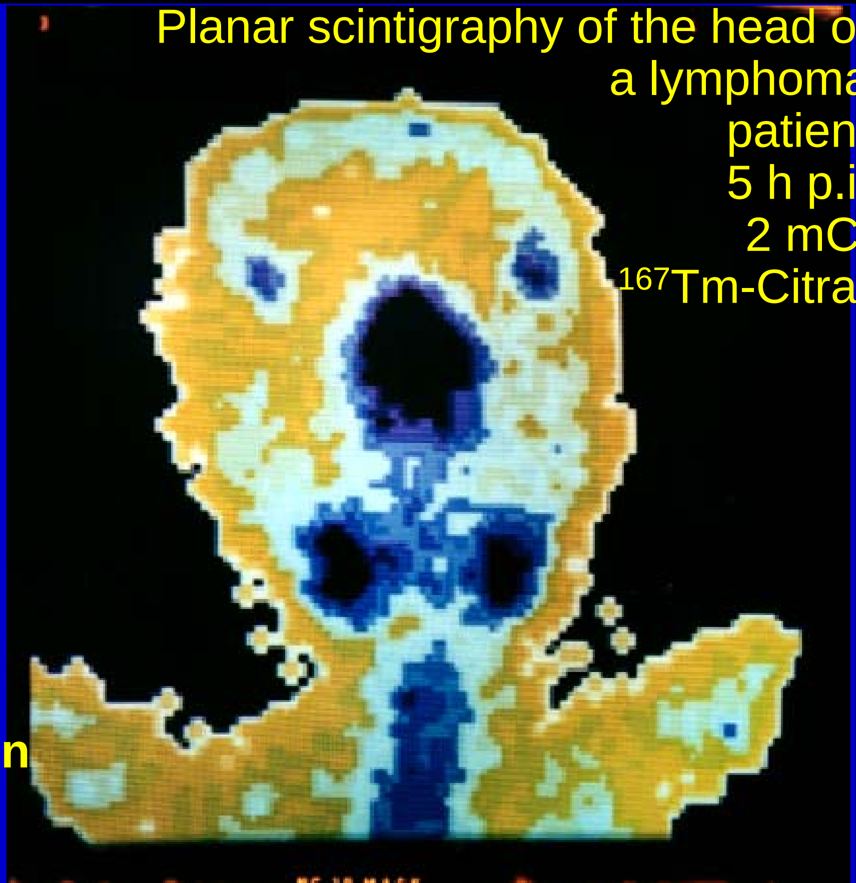
1980

^{167}Tm-citrate

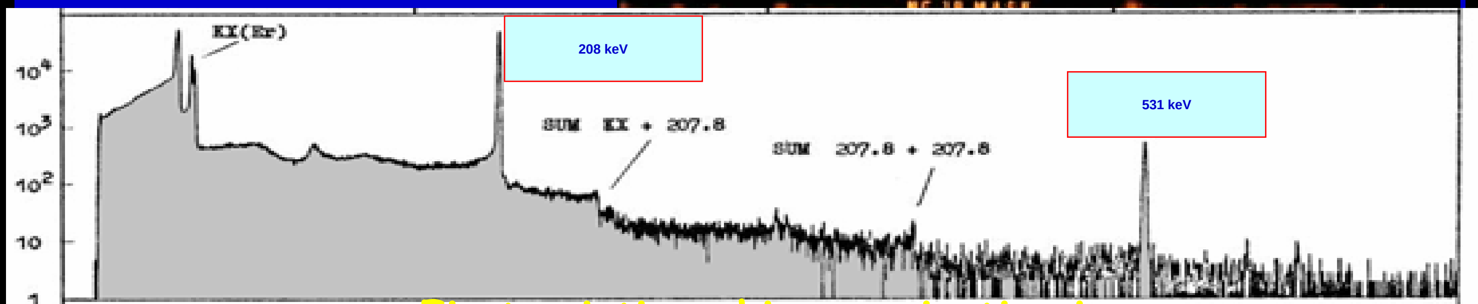
$T_{1/2}$ = 9.25 d
EC = 100 %
γ: 208 keV, 41.7 %
γ: 531 kev, 1.6 %

Production route:

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

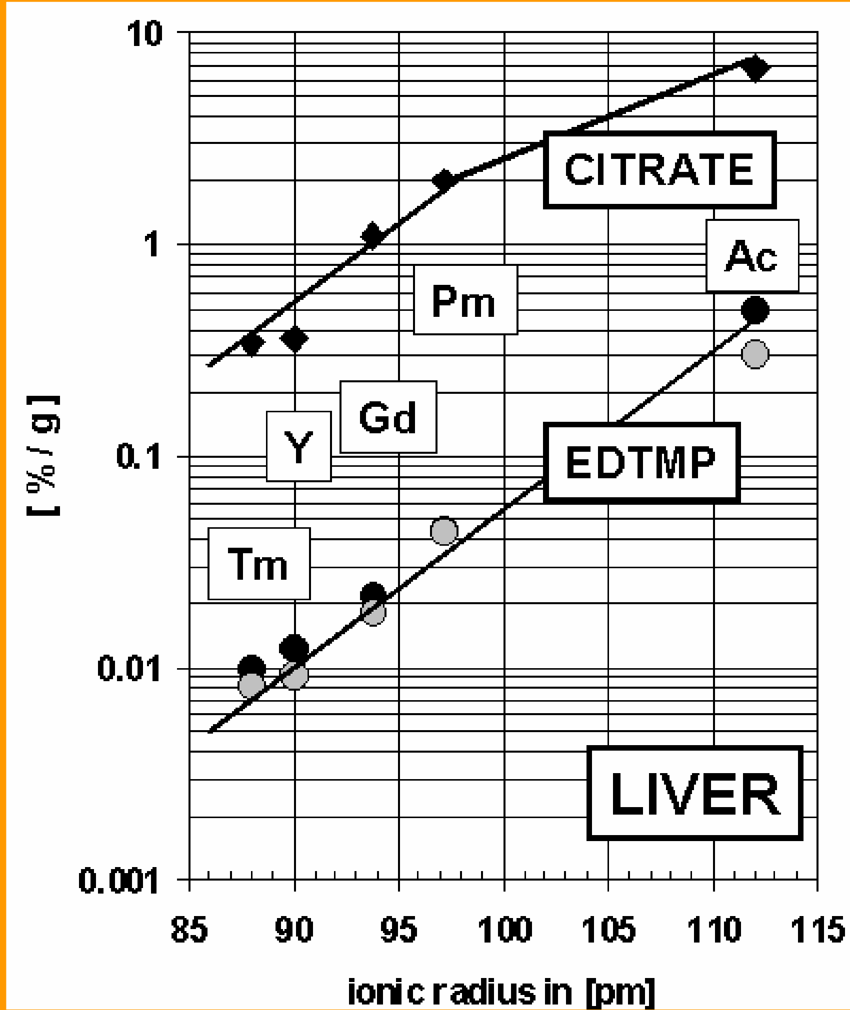


Planar scintigraphy of the head of a lymphoma patient
5 h p.i.
2 mCi
^{167}Tm-Citrat



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

Simultanous injection of an isotope cocktail of rare earth isotopes

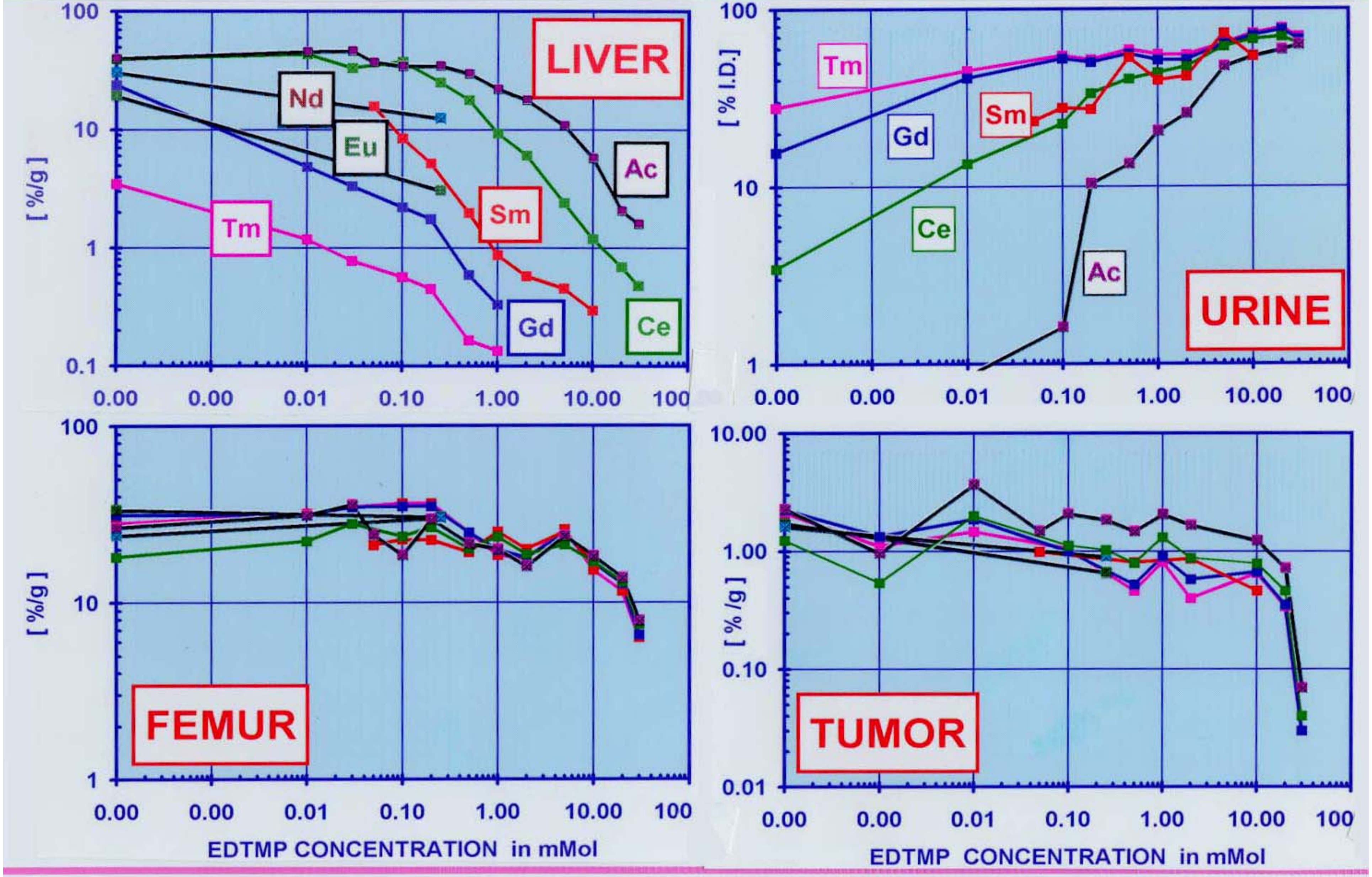


Liver uptake of ^{225}Ac and a mixture of carrier-free radio-yttrium and

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

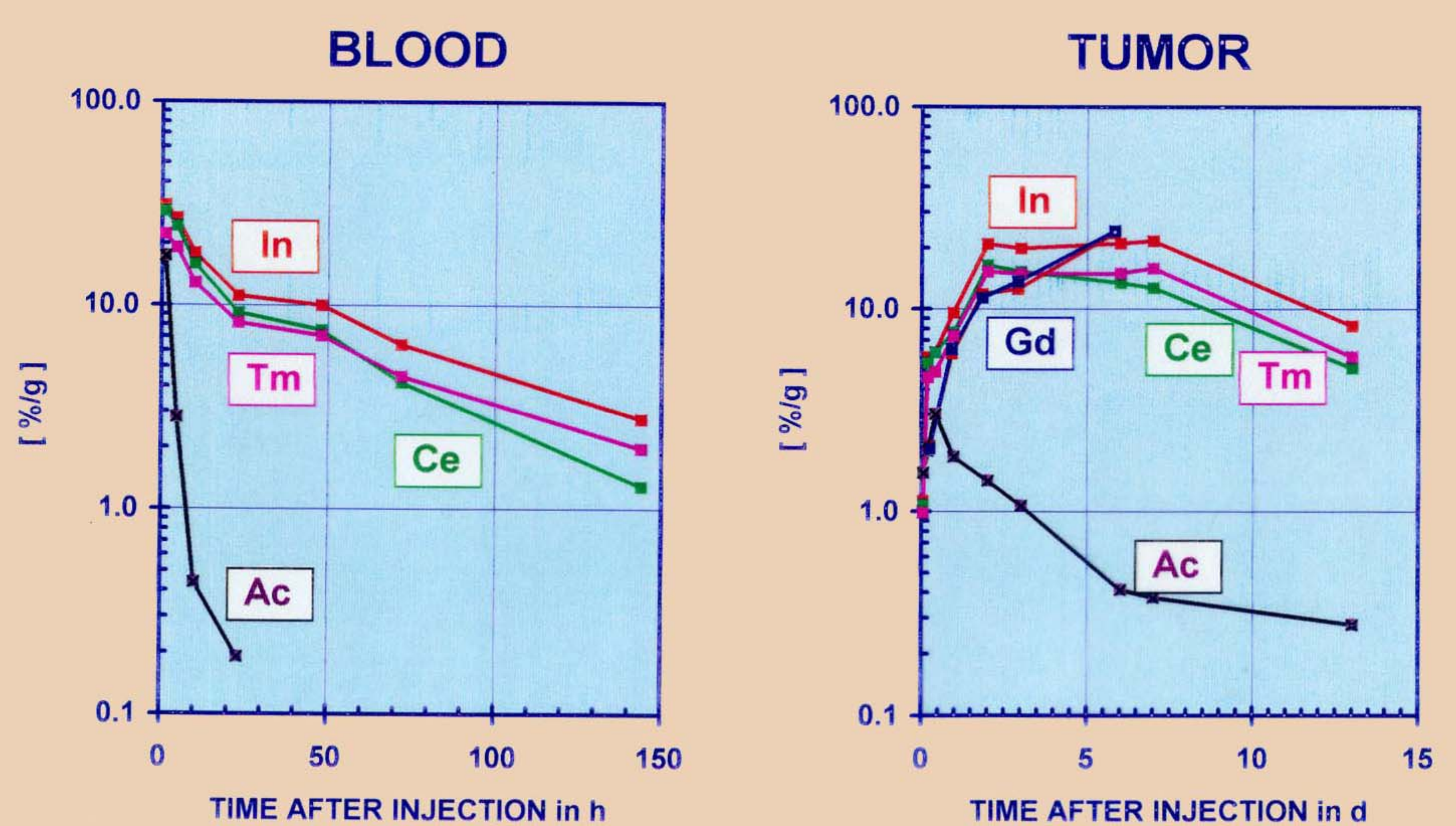
G.J.Beyer, R.Bergmann et al., Isotopenpraxis **26**,111 (1990)

LOW MOLECULAR WEIGHT CHELATORS: EDTMP BIODISTRIBUTION

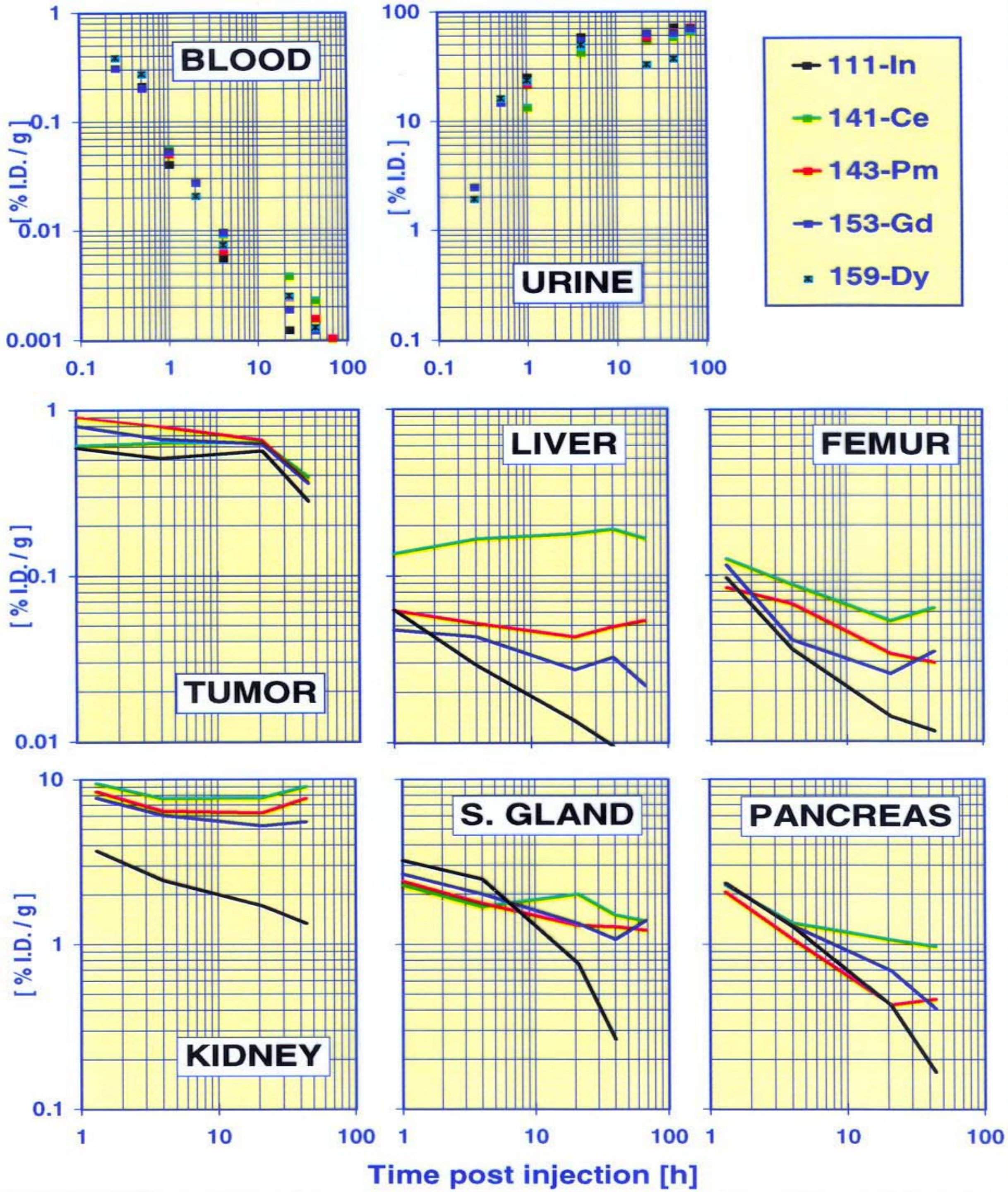


G.J.Beyer, R.Offord, G.Künzi et al. Nuclear Medicine and Biology **24** : 367-372, (1997)

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



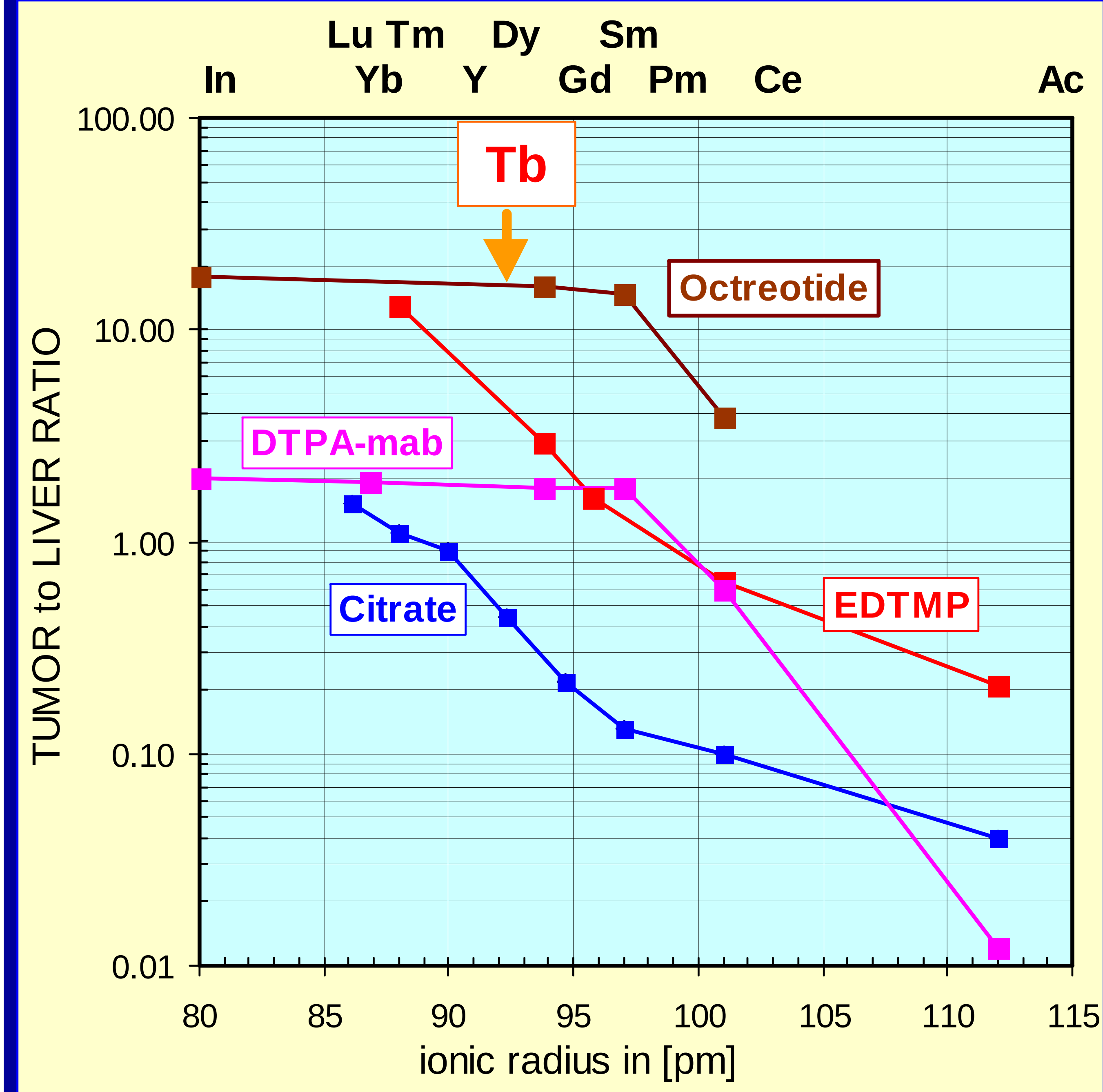
G.J.Beyer, R.E.Offord, G.Künzi et al. Journal of Labelled Compounds and Radiopharmaceuticals, **XXXVI**I, 292, (1995)



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)



CERN experiment IS 363

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)

Radiolanthanides at ISOLDE

spallation or fission

1 or 1.4 GeV protons

pulsed beam, 3 10^{13} p/pulse (~1µA)

Ta-foil- or U-carbide target

Surface ionization ion source

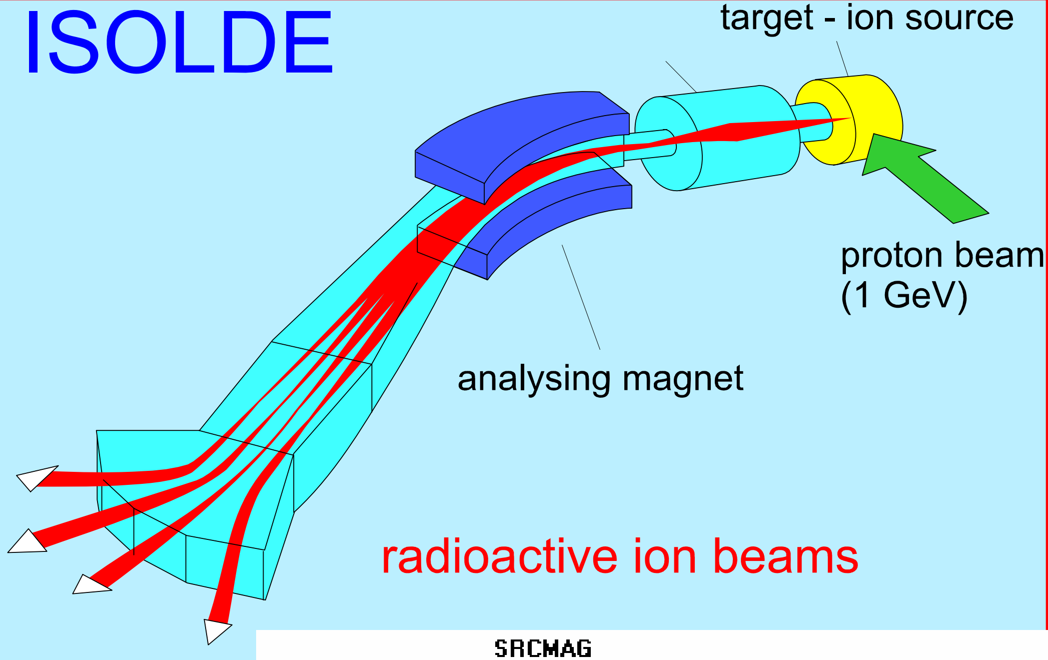
122 g/cm^2 Ta (rolls of 25 µm foils)

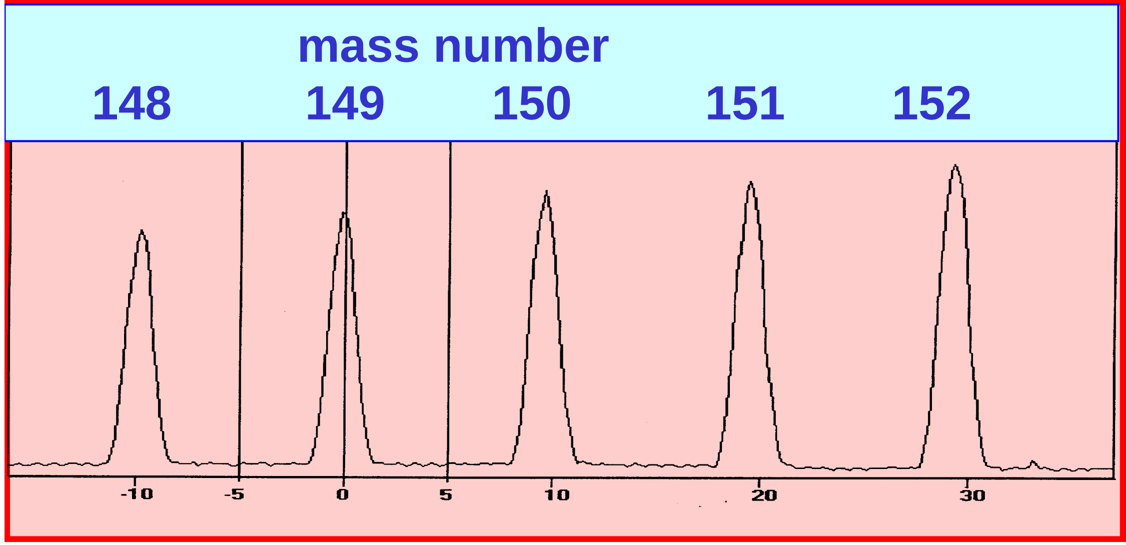
at 2400 ^{o}C

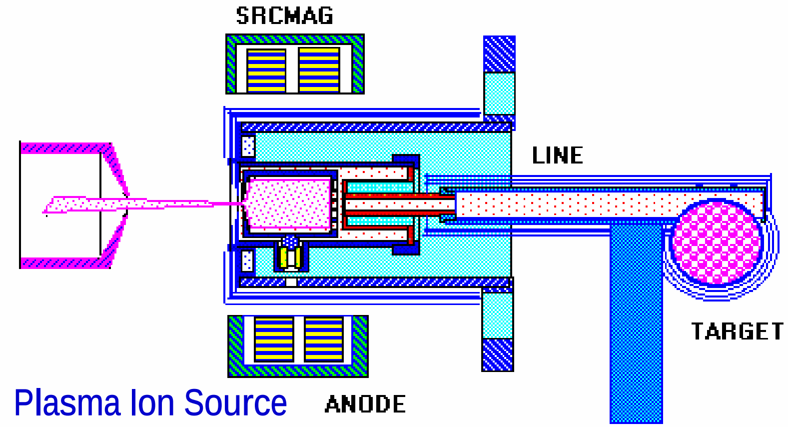
W-tube as ionizer at 2800^{o}C

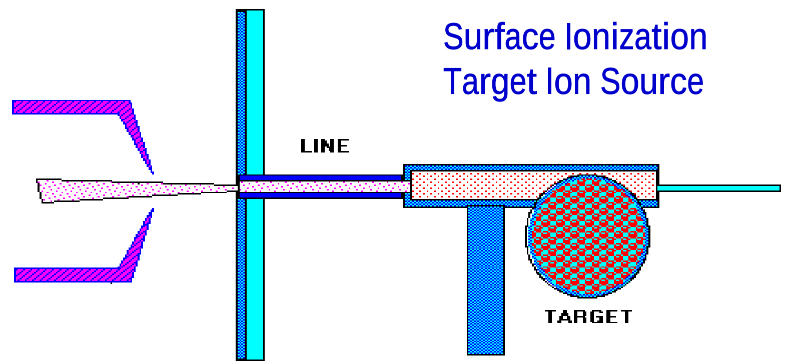
Radioactive Ion Beams of

40 elements possible today









IP with cyclotrons today:

Mass separation process → enriched target material

Irradiation at cyclotron → selective nuclear reaction

Radiochemical separation → one single pure product

One target → one product
100 products → 100 targets

IP with accelerators tomorrow:

one „universal“ target → unspecific nuclear reaction

Parasitic production at high energy p-drivers (~1GeV, ~5 mA)

Radiochemical separation → off-line or on-line

One target → > 100 products

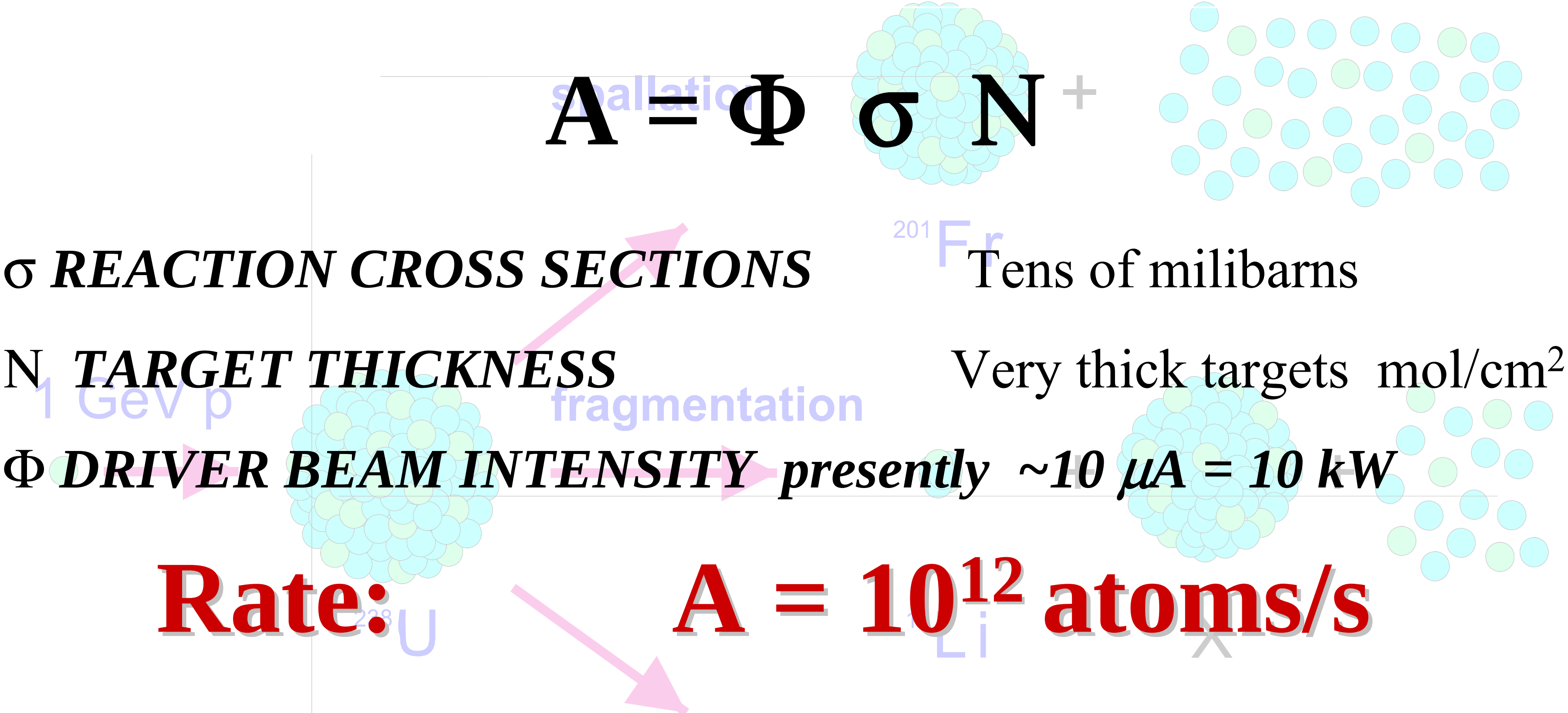
Mass separation process on-line / off-line →

mono-isotopic preparations

carrier-free

Production rate in the target

$$A = \Phi \ \sigma \ N$$



σ ***REACTION CROSS SECTIONS*** Tens of milibarns

N ***TARGET THICKNESS*** Very thick targets mol/cm^2

Φ ***DRIVER BEAM INTENSITY presently ~10 μA = 10 kW***

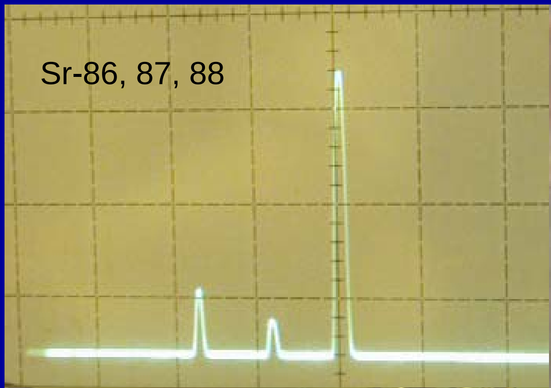
Rate: A = 10^{12} atoms/s

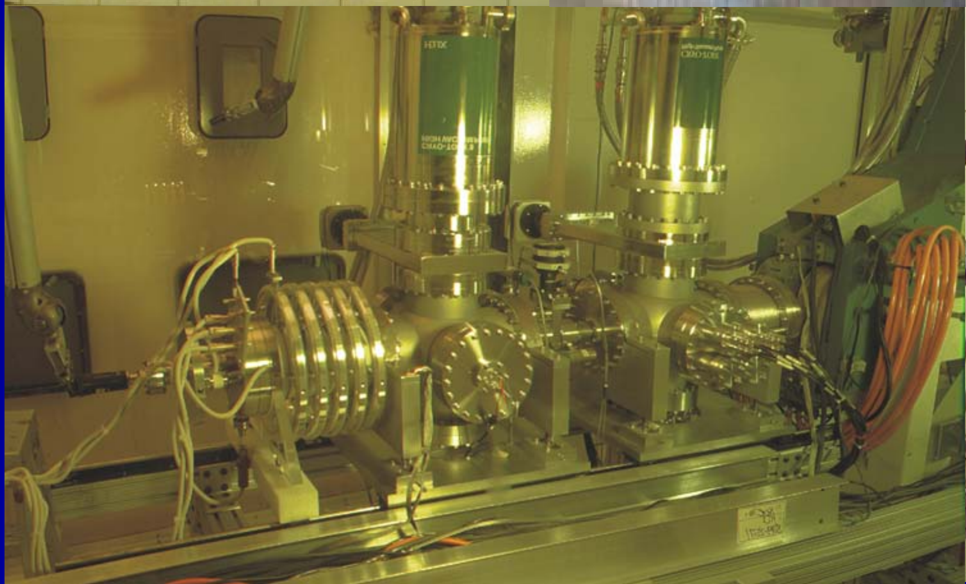
Multi MW Proton drivers
(several mA 1-1.5 GeV protons)
are under construction
~10^{14} Atoms/s possible in a parasitic mode

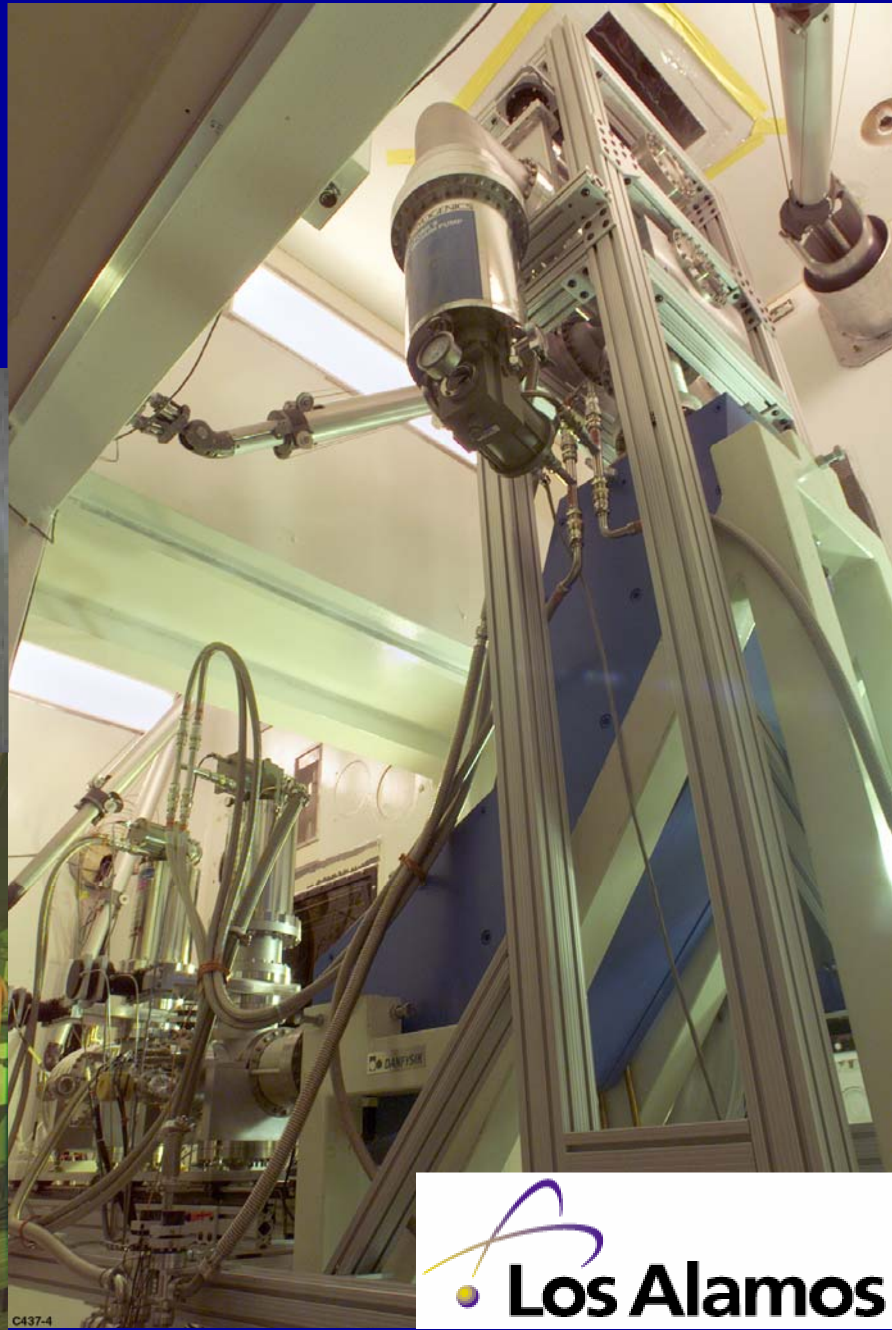
Radioactive Sample Isotope Separator (RSIS)

Wayne Taylor *et al.*

(~50 μA separator in a hot cell)







Los Alamos

Applied Radiation and Isotopes
Volume 63, Issue 2 , August 2005, Pages 157-178

doi:10.1016/j.apradiso.2005.03.004 Cite or Link Using DOI

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[c] and Edward B. Silberstein[h]

Abstract

Since their introduction in the 1940s, peaceful use of stable isotopes and radioisotopes in the United States has expanded continuously. Today, new isotopes for diagnostic and therapeutic uses are not being developed, critical isotopes for national security are in short supply, and demand for isotopes critical to homeland security exceeds supply. While commercial suppliers, both domestic and foreign, can only meet specific needs, the nation needs a consistent, reliable supply of radioactive and stable isotopes for research, medical, security, and space power applications. **The national isotope infrastructure, defined as both facilities and trained staff at national laboratories and universities, is in danger of being lost due to chronic underfunding.** With the specific recommendations given herein, the US Department of Energy may realign and refocus its Isotope Program to provide a framework for a successful National Isotope Program.

Peaceful use of stable and radioactive isotopes in the United States has expanded continuously since their introduction in the 1940s. Traditional industrial use is continuing, and use of radionuclides for food irradiation, sterilization of medical supplies, and other applications is quickly gaining public acceptance. **Approximately 15 M diagnostic procedures and several hundred thousand therapeutic treatments using radionuclides are conducted at medical centers each year in the United States. Significant increases in medical research have increased the need for new research isotopes for advanced applications. Isotopes are a significant component of the US economy, with over $300 billion in sales and 4 M jobs related to their use** (The Untold Story: The Economic Benefits of Nuclear Technologies, 1997).

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. The supply of these stable and radioisotopes for developing new applications has traditionally been the responsibility of DOE. However, the DOE program and its resources have been declining for two decades, and recent policy changes by DOE have significantly worsened the situation and are impeding the development of new isotope applications. In fact, a recent policy change by DOE eliminated all R&D funding for DOE applications and production.

This new requirement for full cost recovery caused DOE to deviate from its original goals for isotope production and distribution by narrowing the range of isotopes produced, concentrating on higher-volume isotopes with profit potential and increasing charges to research users to cover program expenses. This strategy has produced extremely negative results. Despite substantial efforts to operate the Isotope Program on a full-cost-recovery basis, costs have not been met by revenues from sales. The DOE Isotope Program has recently eliminated all R&D funding for radioisotope production and enacted an up-front full and advance prepayment policy. These new policies have resulted in further decline of the DOE Isotope Program and a failure to meet its traditional role in isotope production.

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

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What is the role for science and technology? New science, such as molecular nuclear medicine, is emerging that will require reliable supplies of radionuclides, while the new demands of homeland and national security will spur the development of new technology for radiation detectors and imaging devices, which will ultimately produce new products. Furthermore, the program itself will contribute to the training of a 21st century cadre of radiochemists.

Why now? Over the last 10 years, many studies have identified the need for different components of a National Isotope Program, but their recommendations have never been implemented. We believe that the only way to break the impasse is through coordinated action from the research, provider, and user communities.

What CERN could do?

- Run own specific medical isotope program
- Develope technologies for alternative ways for isotope production
- High-tech radiochemistry
- Integrate physical methods into the isotope programs (mass separation for example)
- Collaboration with bio-chemistry and medicine (oncology, radiology, nuclear med.)
- International collaboration and integration into existing research network

How?

Initiative of G.Beyer, H.L.Ravn, U.Köster, G.Ragnelly

- Creation of a Radiochemical Laboratory at CERN
- 100 % Investment by Industry including the operation of the laboratory (Volume 5-8 Mio EU)
- Main Objective:
  - Development of the technologies for future medical isotope production based on multi MW p-drivers including off-line mass separation
  - maintaining know-how and training of personnal
  - provision of radionuclides for R&D to the radiopharmaceutical orientented research community

First „official“ action:

RADIOISOTOPES
in
MEDICINE:
Requirements – Production - Application

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CERN, ETT Seminar

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https://oraweb.cern.ch/pls/ttdatabase/display.item?itemtable=tt_event&item_id=101

Chronology

- Initiative startet latest in 2001
- „first“ official action: ETT-seminar 2002 (CERN-WEB)
- April 2004 clear statement of investors and industry to invest ~10 Mio CHF into the Radiochemical Laboratory
- Since continous discussion with TT

Results

- Until now no clear position of TT and CERN
- Missing opportunity to put a second floor on building 179 (as suggested)
- Loosing the world leading role of ISOLDE in Application of RIB for medical research and nuclear medical application


Thank you
for your kind attention
Gerd Beyer