Summary: Radioisotopes in Diagnostics and Therapy

Ulli Köster
Institut Laue Langevin, Grenoble, France

‘Star’ Radionuclides for SPECT and PET

Centralized: 5(+x) reactors

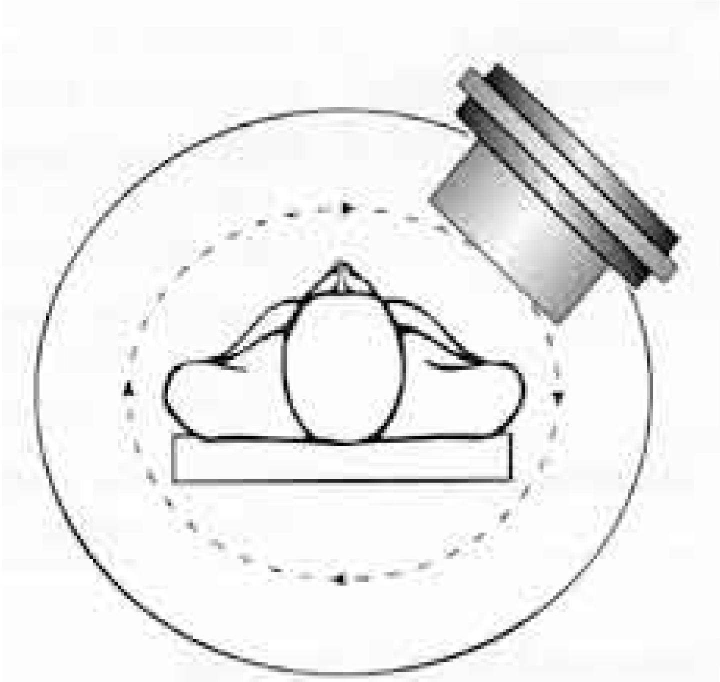
- **^{99m}Tc** 6 h Eγ 140 keV
- from ^{99}Mo-^{99m}Tc generator; ^{99m}Tc supplies from operations in house/central radiopharmacy
- Ideal nuclear features for imaging (gamma camera, SPECT) and patient dose
- Versatile coordination chemistry of technetium
- Multi-disciplinary synergy → products for specific functional imaging
- Easy, abundant, economic availability ***(? since 2008***)

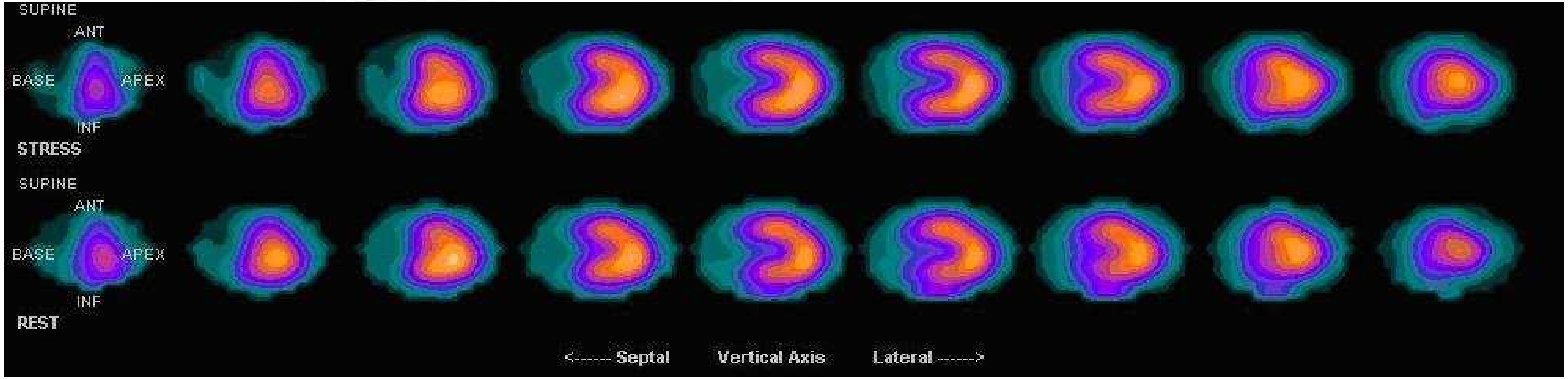
Decentralized: 671 cyclotrons

- **^{18}F** 110 min β^+ (0.635 MeV)
- ^{18}O(p,n) Ep 10-18MeV; 20-40uA
- Decentralised facilities for production and supplies
- Compatible to label organic and biological molecules or analogs
- Suitable for PET, PET-CT
- $T_{1/2}$ advantage over ^{11}C, ^{13}N, ^{15}O
- **Success of ^{18}FDG**
- several pharmaceuticals containing fluorine
- Relatively more expensive

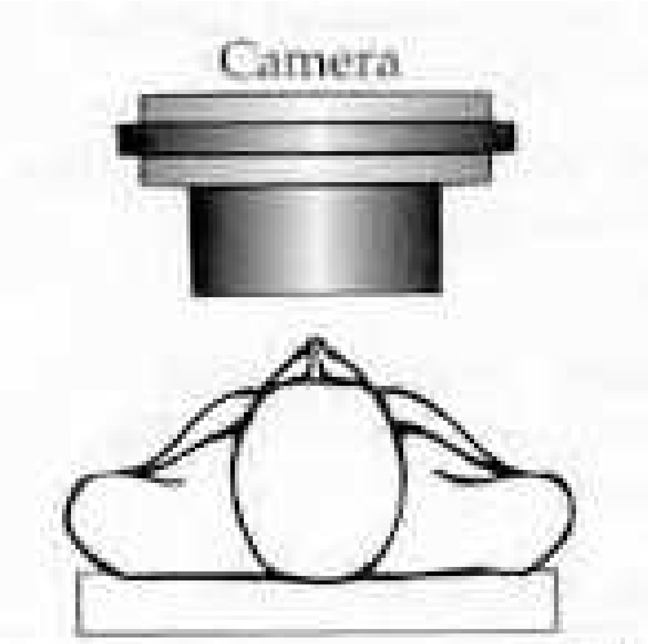
Ischemic heart disease

- **diagnose by ECG and cardiac stress test with SPECT**

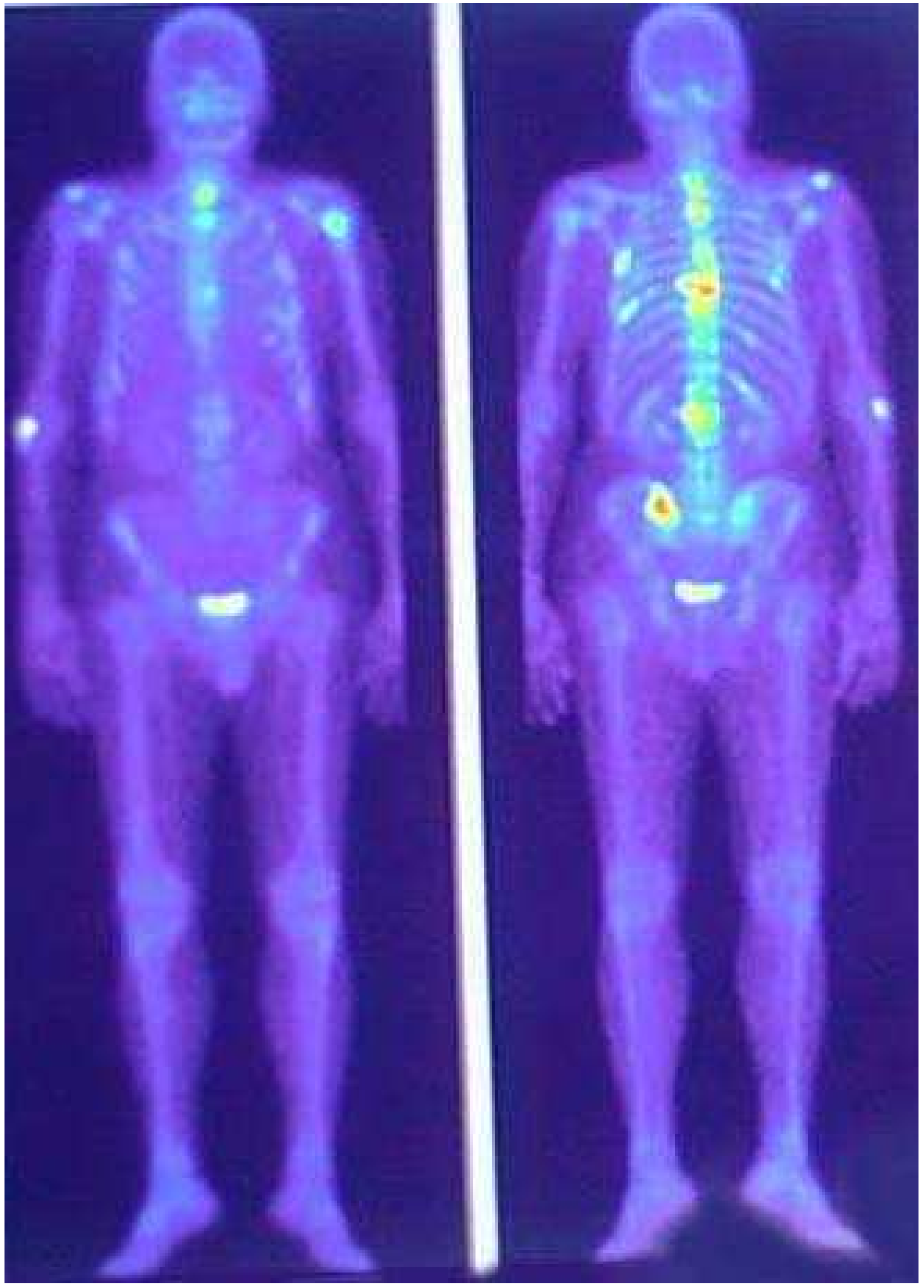




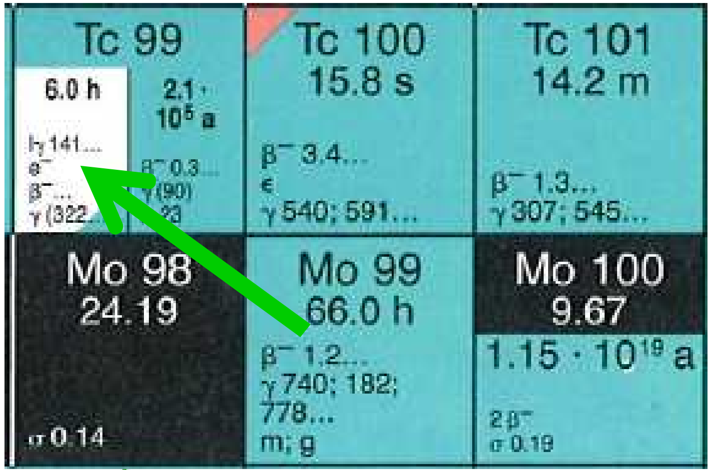
Bone metastases from (prostate) cancer

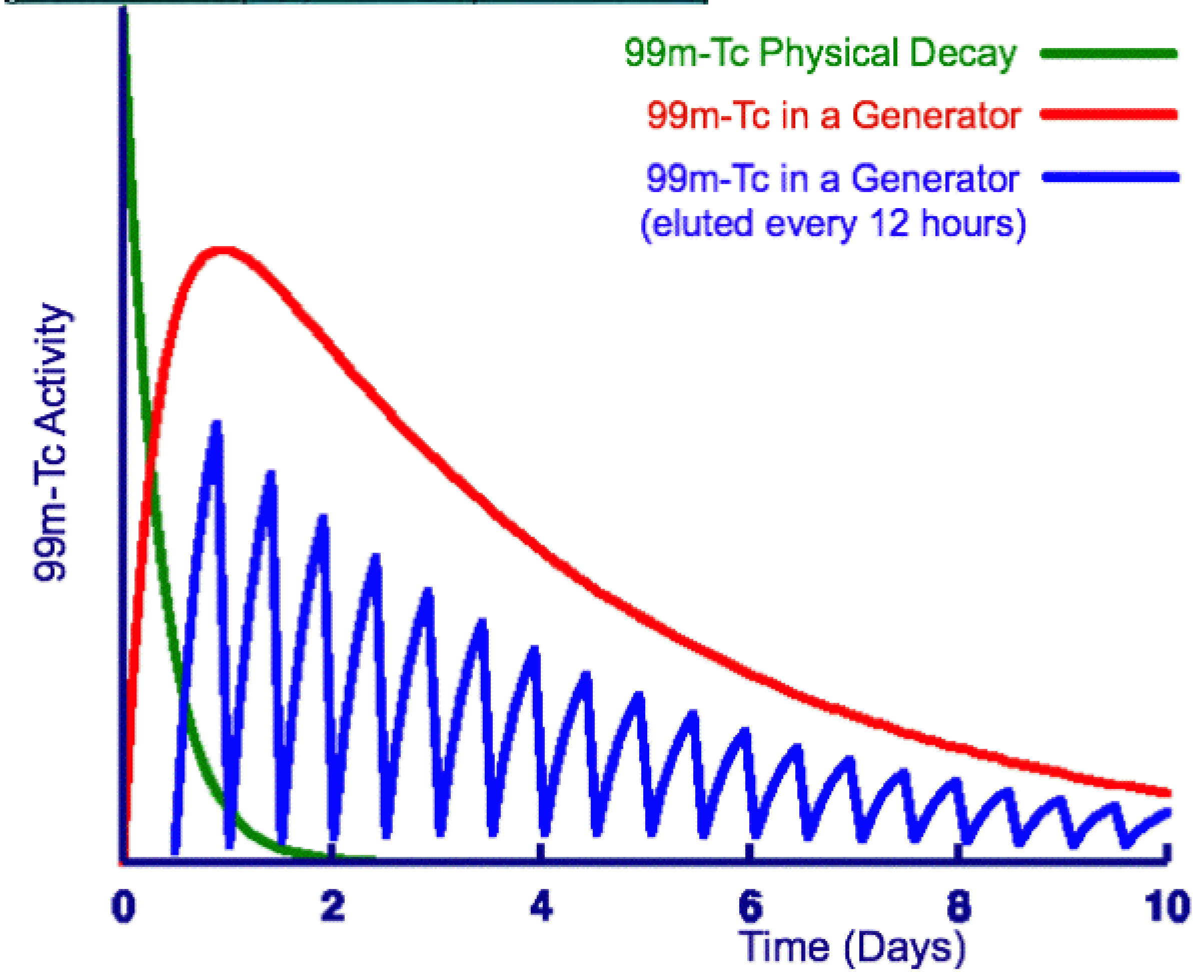


- **planar or SPECT scan for bone metastases**



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

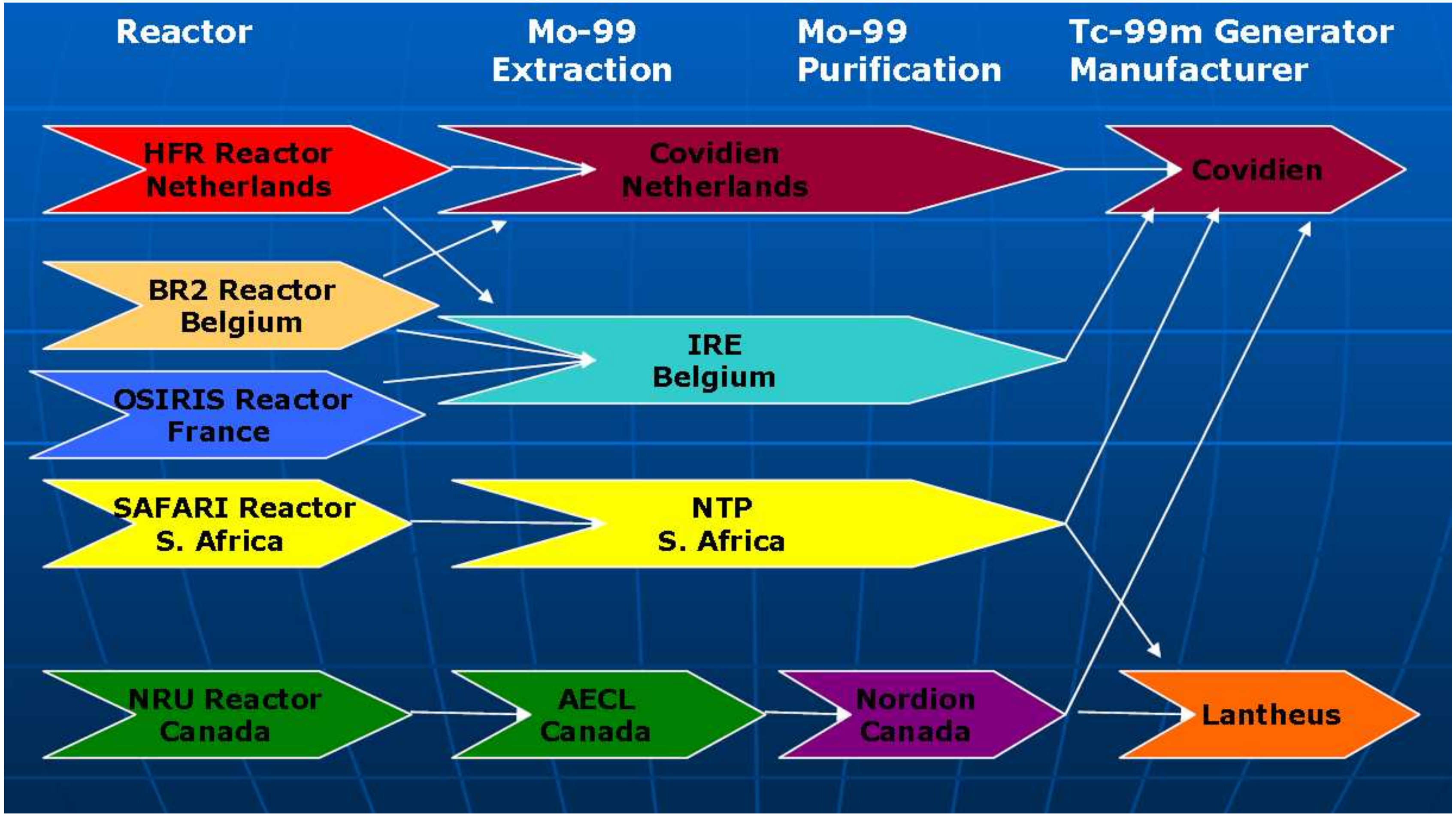




- simple
- reliable
- portable
- cheap

World market for $^{99}Mo/^{99m}Tc$

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



NRU Reactor, Canada

- **15 May 2009: D_2O leak**
- **stopped till spring 2010+**
- **license till October 2011**

HFR Petten, NL

- **extended maintenance stop from 19 February 2010**

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%

MAPLE reactors MMIR-1, MMIR-2

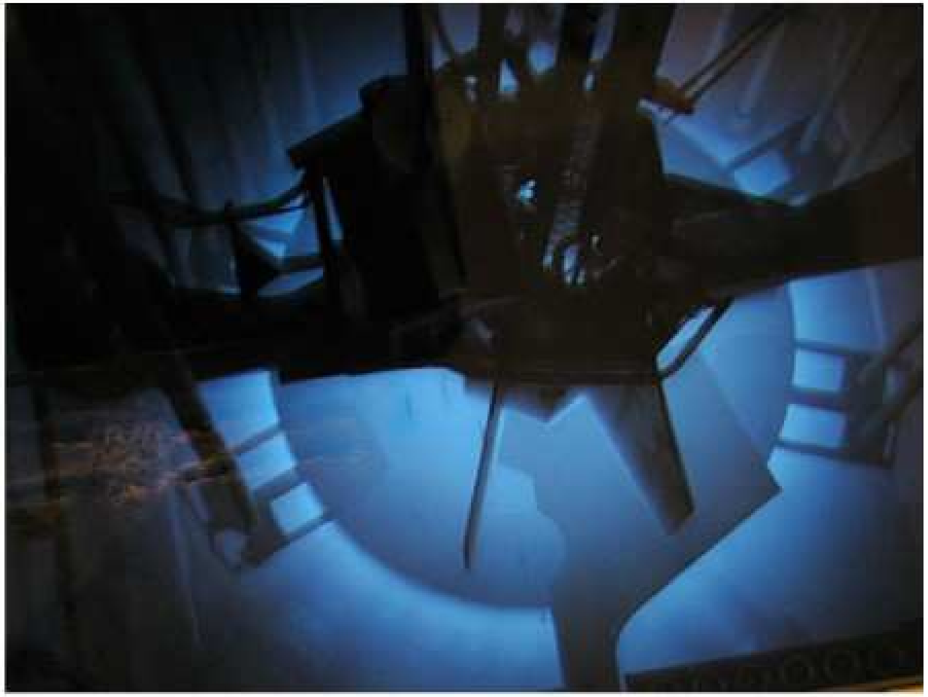
Power coefficient:
Designed as: –0.12 mk/MW
Found as: +0.28 mk/MW

MAPLE 1 and 2 reactors, and New Processing Facility, at AECL Chalk River Laboratories (NRU and NRX reactors are behind, on the left and right, respectively).

Project officially stopped!

Correction should be possible.
Costs? Delays?

30 MW MAPLE-type reactor HANARO operates nicely in Korea

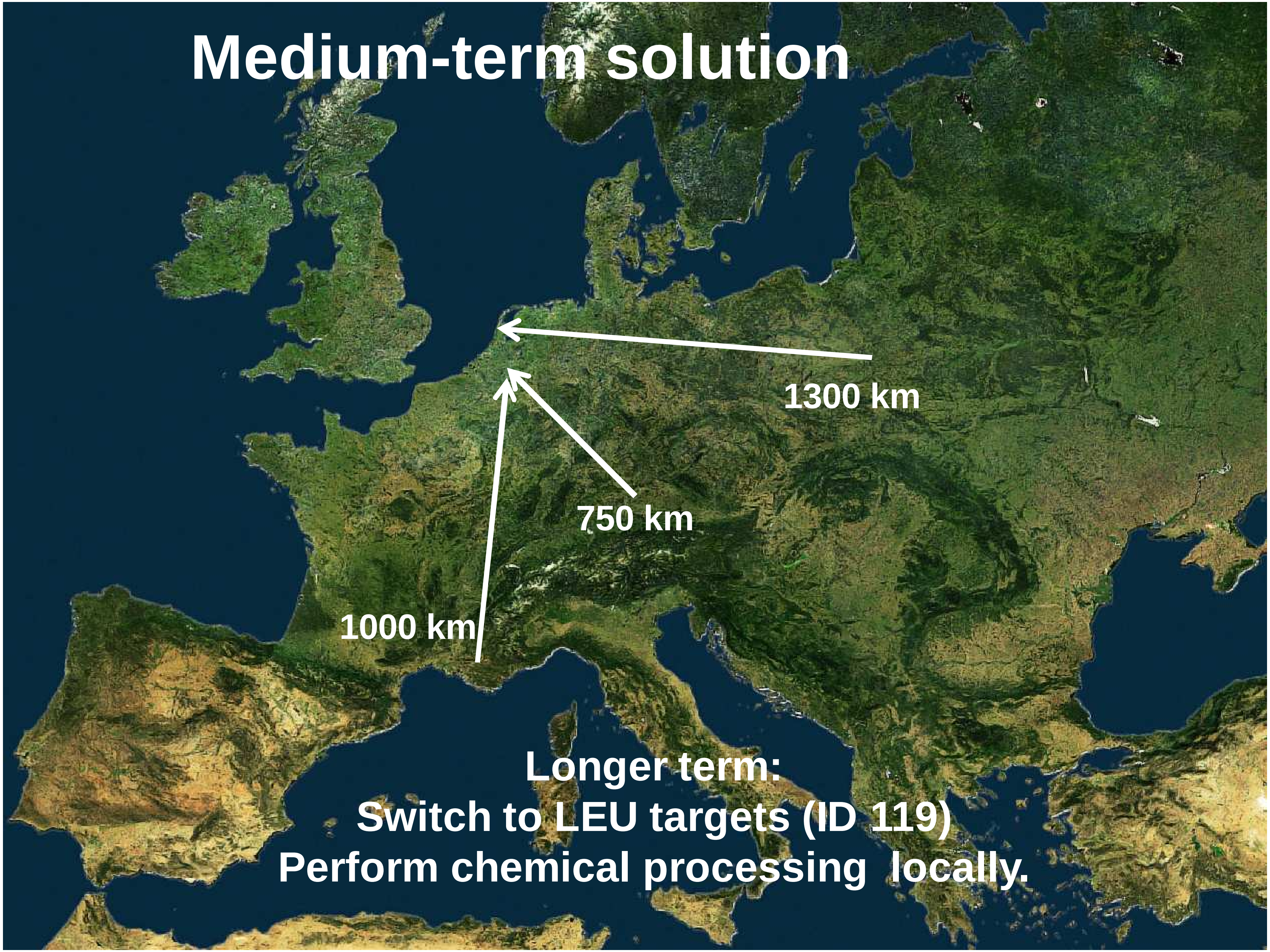


Blue "Cerenkov radiation" from MAPLE 1 reactor core during commissioning tests at high power (8 MW). The Cerenkov glow is caused by high-speed electrons (beta particles or secondary electrons due to the core's operation) slowing down in the surrounding water.

Reactors foreseen for future ^{99}Mo production with HEU targets

Reactor	Location	Country	Power (MW)	Fuel	Operation (days per year)	Operation	Potential ^{99}Mo world market share
MARIA	Warsaw	Poland	20-30	LEU	138	1974 Mo: 2010+	
FRM2	Garching	Bavaria	20	HEU	240	2004 Mo: 2014+	(13%)
RJH	Cadarache	France	100	LEU		2014+	(12-25%)
PALLAS	Petten?	Nether-lands	(45)	LEU	>300	2016+	
MAPLE	Chalk River	Canada	2x10	LEU	→ 365	?	(100%)

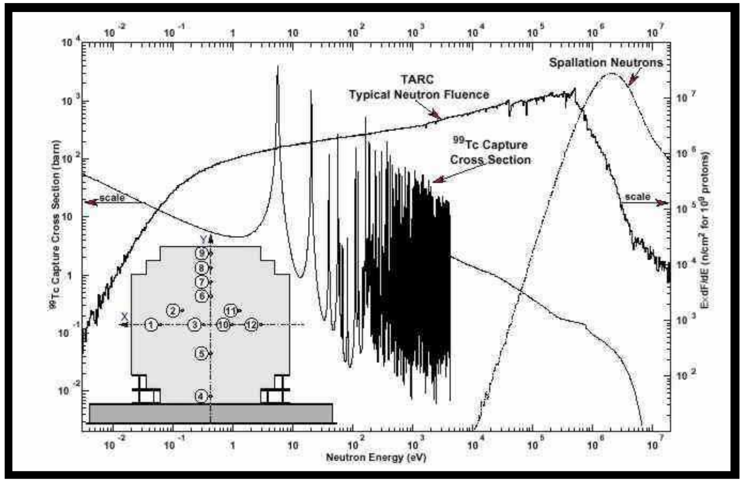
Medium-term solution



Longer term:
Switch to LEU targets (ID 119)
Perform chemical processing locally.

Alternative methods of producing ^{99}Mo

1. Neutron irradiation (n,γ)
2. Liquid core reactor (n,f)
3. Cyclotron bombardment (p,2n)
4. Photo-nuclear reaction (γ,n)
5. Photo-fission reaction (γ,f)
6. Spallation source (neutrons) ID94
7. Spallation source (resonance crossing) ID47
8. Neutron generator fission



Cost of new projects has to compete against depreciated subsidized reactors.

"Parasitic" operation interesting to generate backup capacity.

“Value” of ^{99m}Tc

Typical SPECT exam in Switzerland:

Medical service	167.42 CHF	114 €	18%
Technical service	729.73 CHF	495 €	78%
700 MBq ^{99m}Tc activity`	32.30 CHF	22 €	3%
Kit DPD	9.45 CHF	6 €	1%
Total	938.90 CHF	637 €	100%

Compare:

“AeroChamber” 50.10 CHF

34 €

plastic tube with two
rubber end caps

Milk, fossile fuel and ^{99m}Tc are too cheap
$\Rightarrow$ not sustainable!

From diagnostics

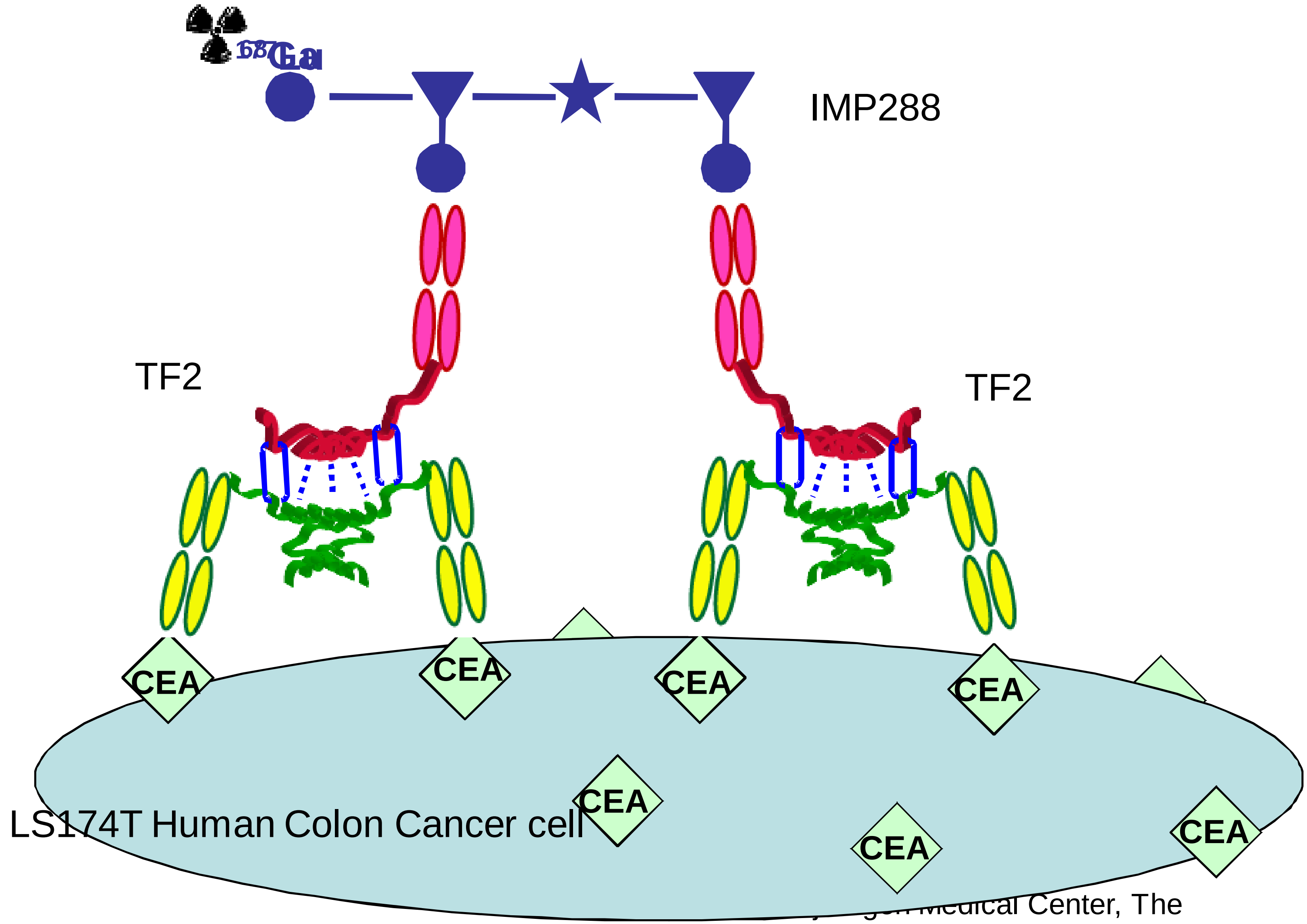
to therapy

Selectivity towards cancer cell

Biotracer	Example	Mass (u)
Element	I^- (24 h), F^- (1 h), Sr^{2+}, Ra^{2+}	18 .. 223
Small molecule	TcO_4^{2-} (20 min), FDG (1 h), MIBG	100..300
Peptides	DOTATOC, DOTATATE,... (1-4 h)	1000-1500
mab	Ibritumomab, Tositumomab, Rituximab, Cetuximab,... (days)	150000

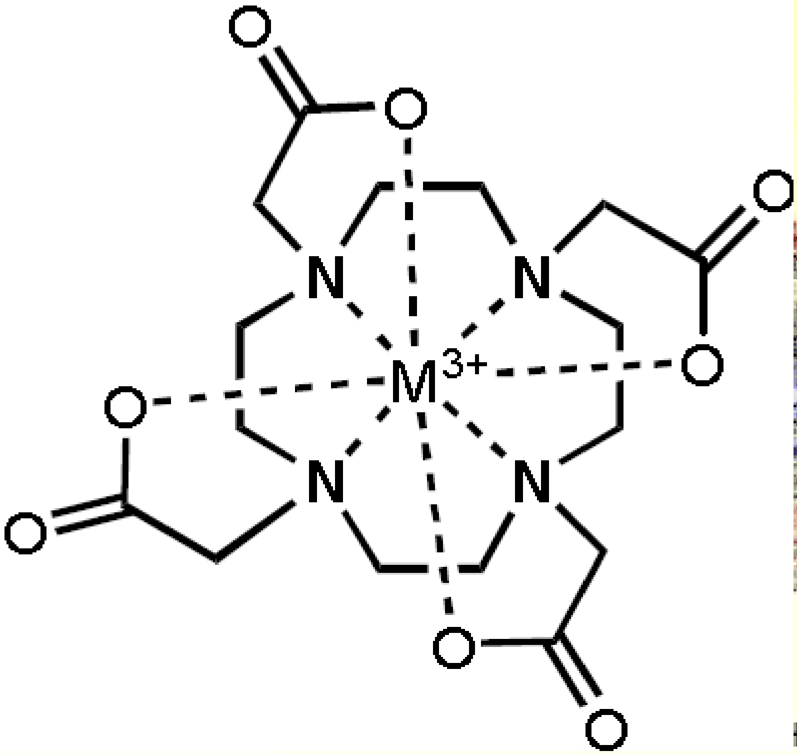
slower heavier

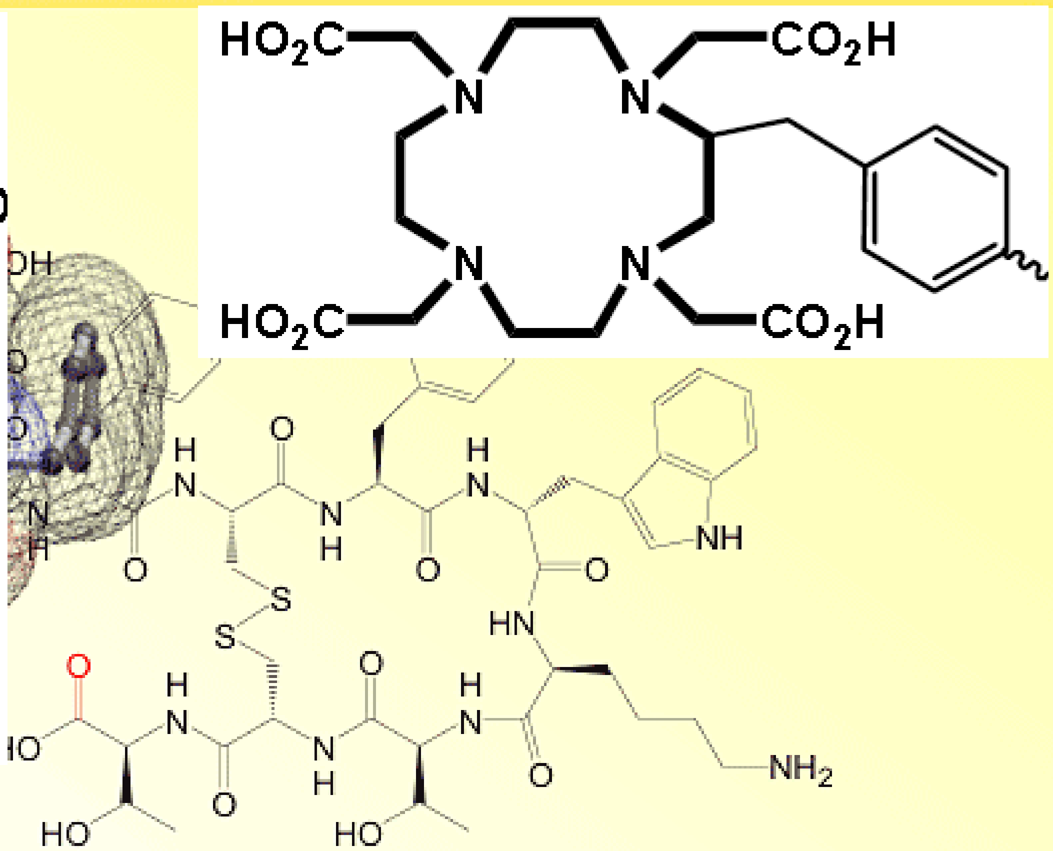
Pretargeted immunoPET imaging



Medical Center, The
Netherlands

Structural Formula of DOTA-TOC/TATE





DOTA-TATE

1,4,7,10-tetraazacyclododecantetraacetate

^{111}In ^{90}Y

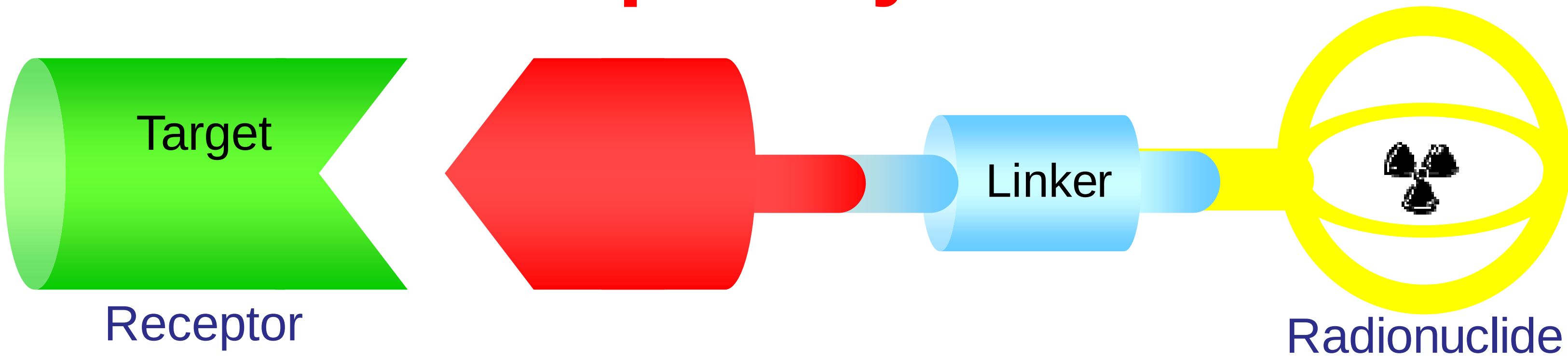
^{67}Ga ^{177}Lu

^{68}Ga ^{213}Bi

IC$_{50}$ (Y^{III}) = 1.6 ± 0.4 nM

Helmut Maecke, EANM-2007.

Interdisciplinary research



Structural biology

Coordination chemistry

Nuclear physics and radiochemistry

- **photon diffraction**
- **neutron diffraction**

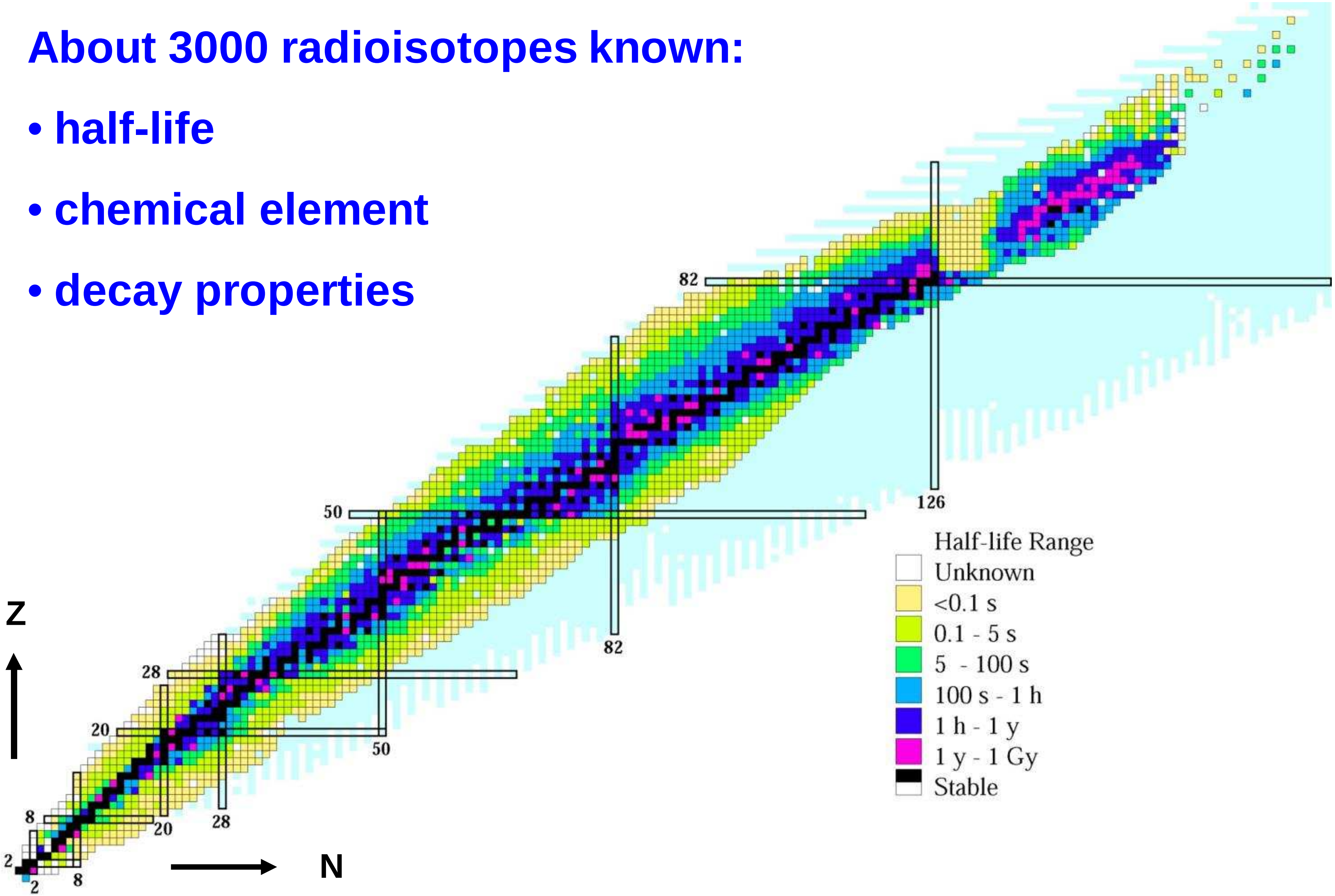
?

User facilities: ESRF, ILL, EMBL

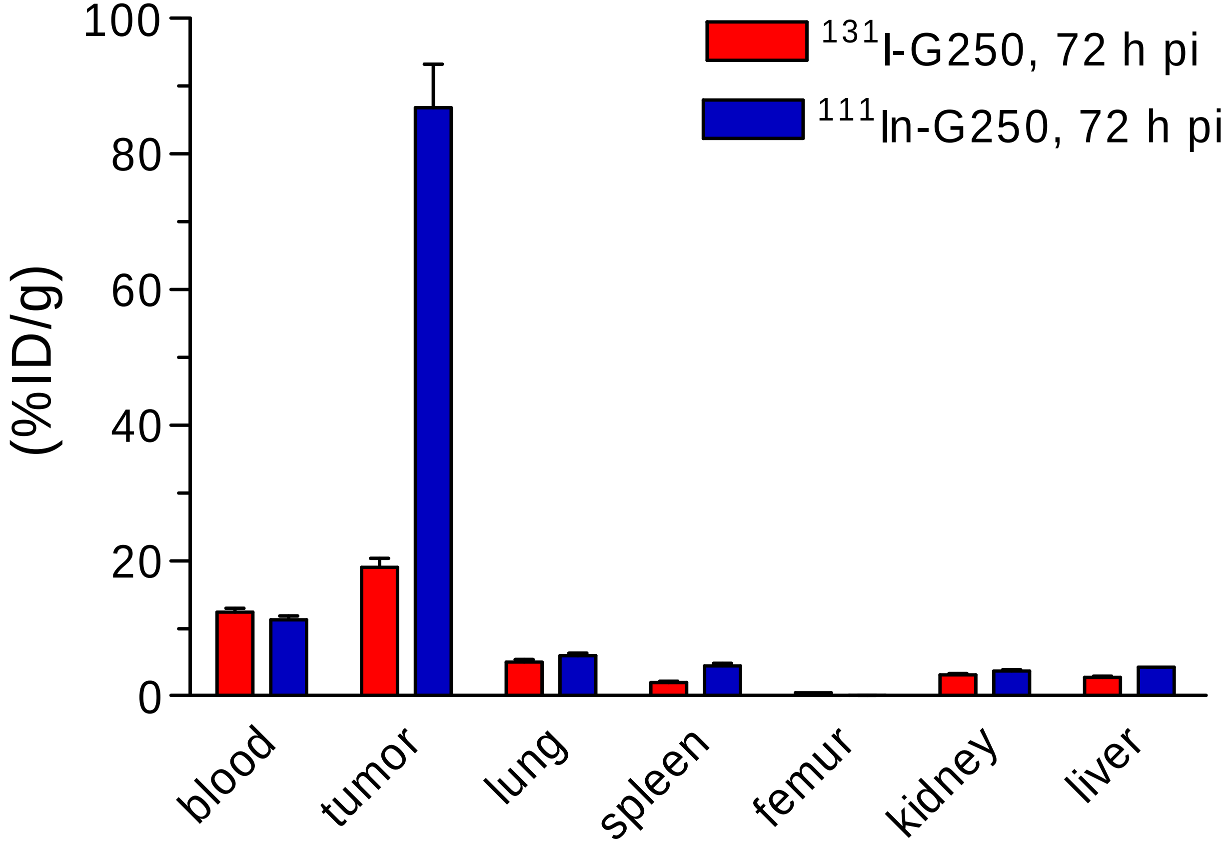
The quest for the optimum isotope

About 3000 radioisotopes known:

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

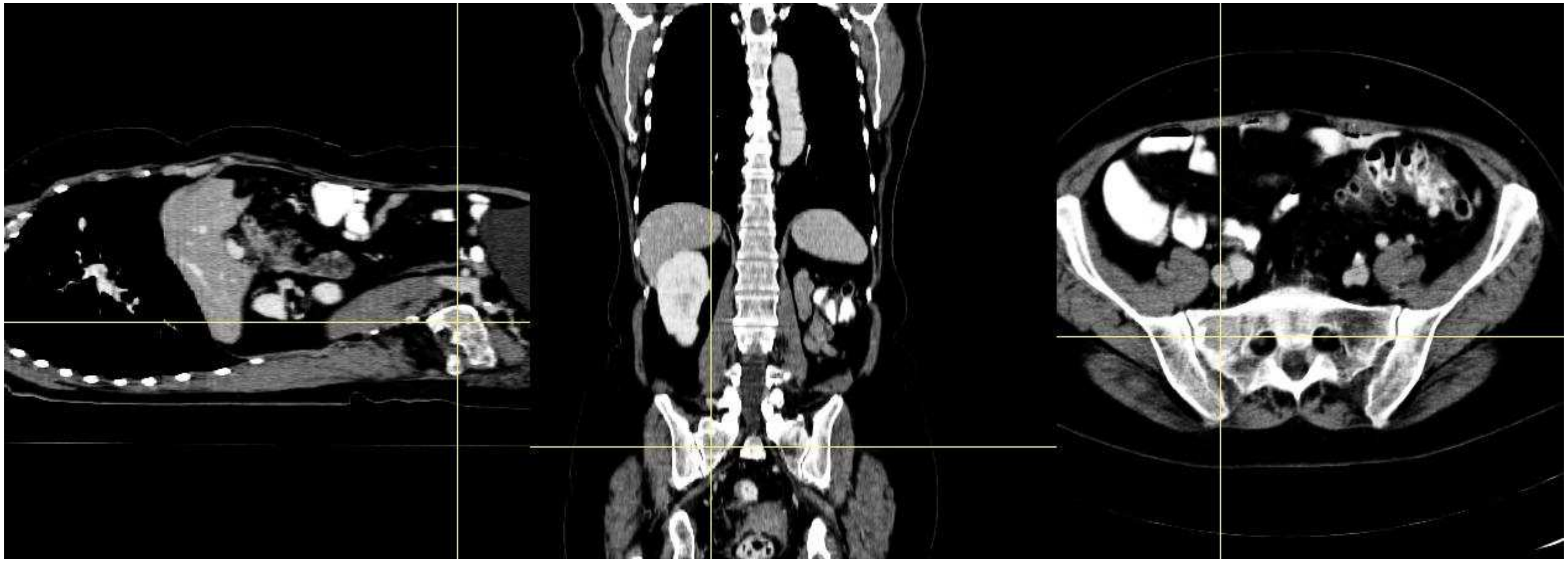


The Quest for the optimal radionuclide for RIT



Radboud University
Nijmegen Medical
Center, The Netherlands

Radioimmunotherapy of RCC with ^{177}Lu-cG250



Radboud University
Nijmegen Medical
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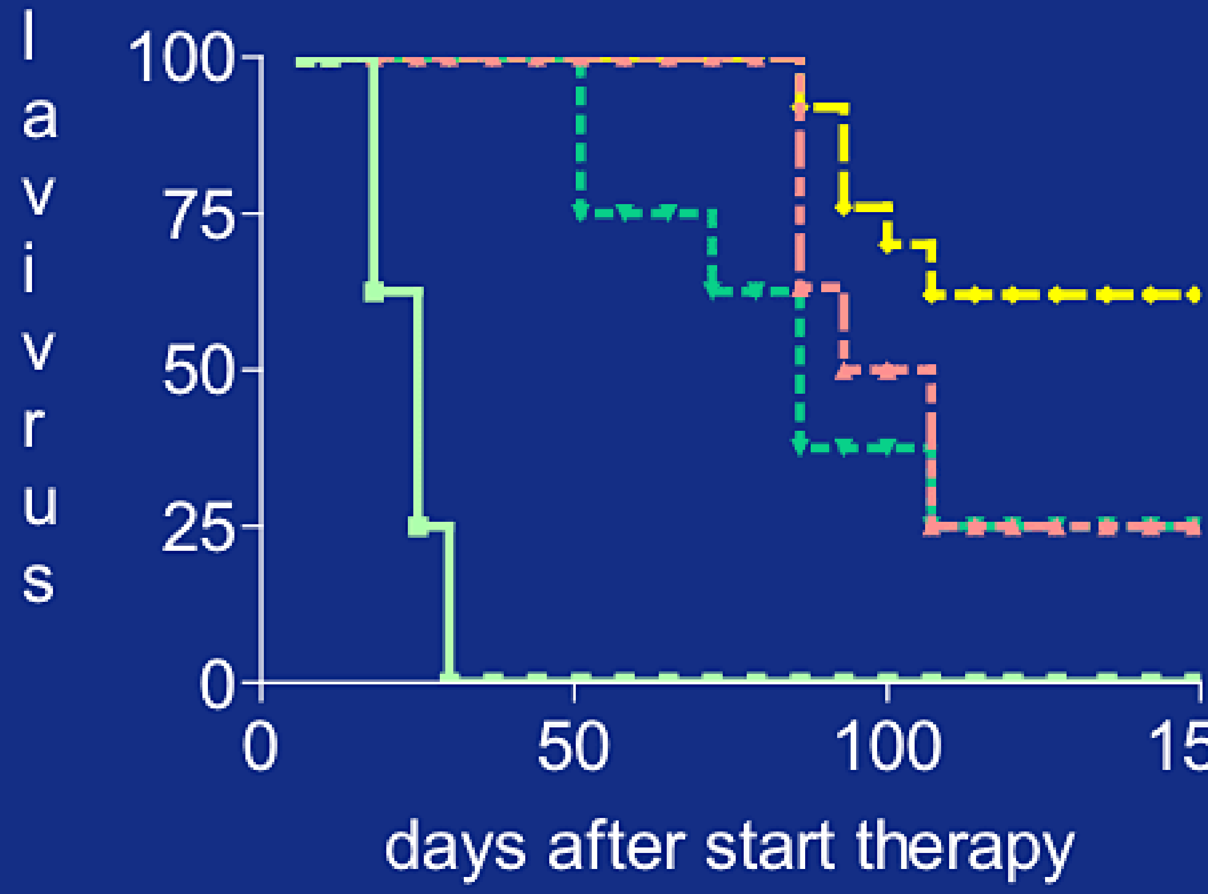
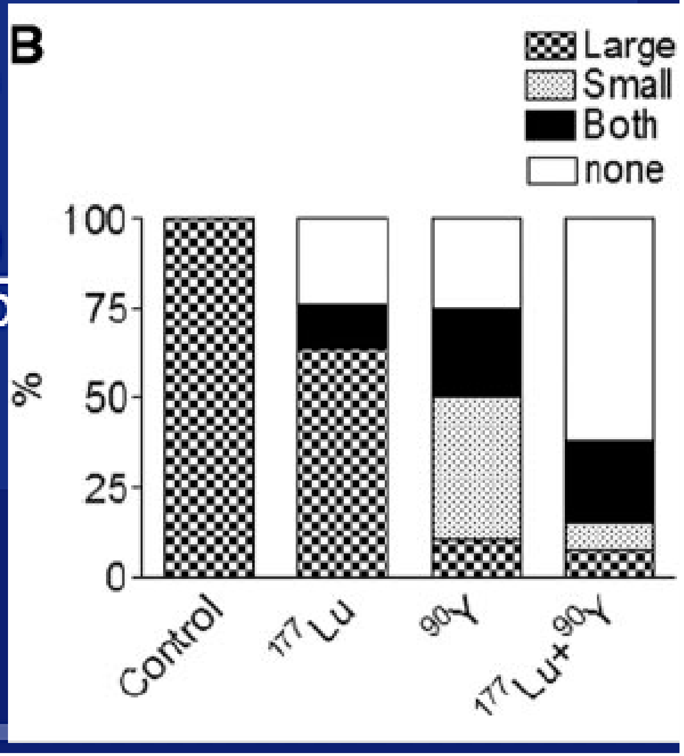
Survival





J Nucl Med 2005, Suppl 1, 13S

Radionuclides for radioimmunotherapy

Radio-nuclide	Half-life	E mean (keV)	Eγ (keV)	Range
Y-90	64 h	934 β	-	12 mm
Re-188	17 h	763 β	155	11 mm
I-131	8 days	182 β	364	3 mm
Lu-177	7 days	134 β	208, 113	2 mm
Tb-161	7 days	154 β 5, 17, 40 e^-	75	2 mm 1-30 µm
At-211	7.2 h	5870 α	-	45 µm
Tb-149	4.1 h	3967 α	165,..	25 µm

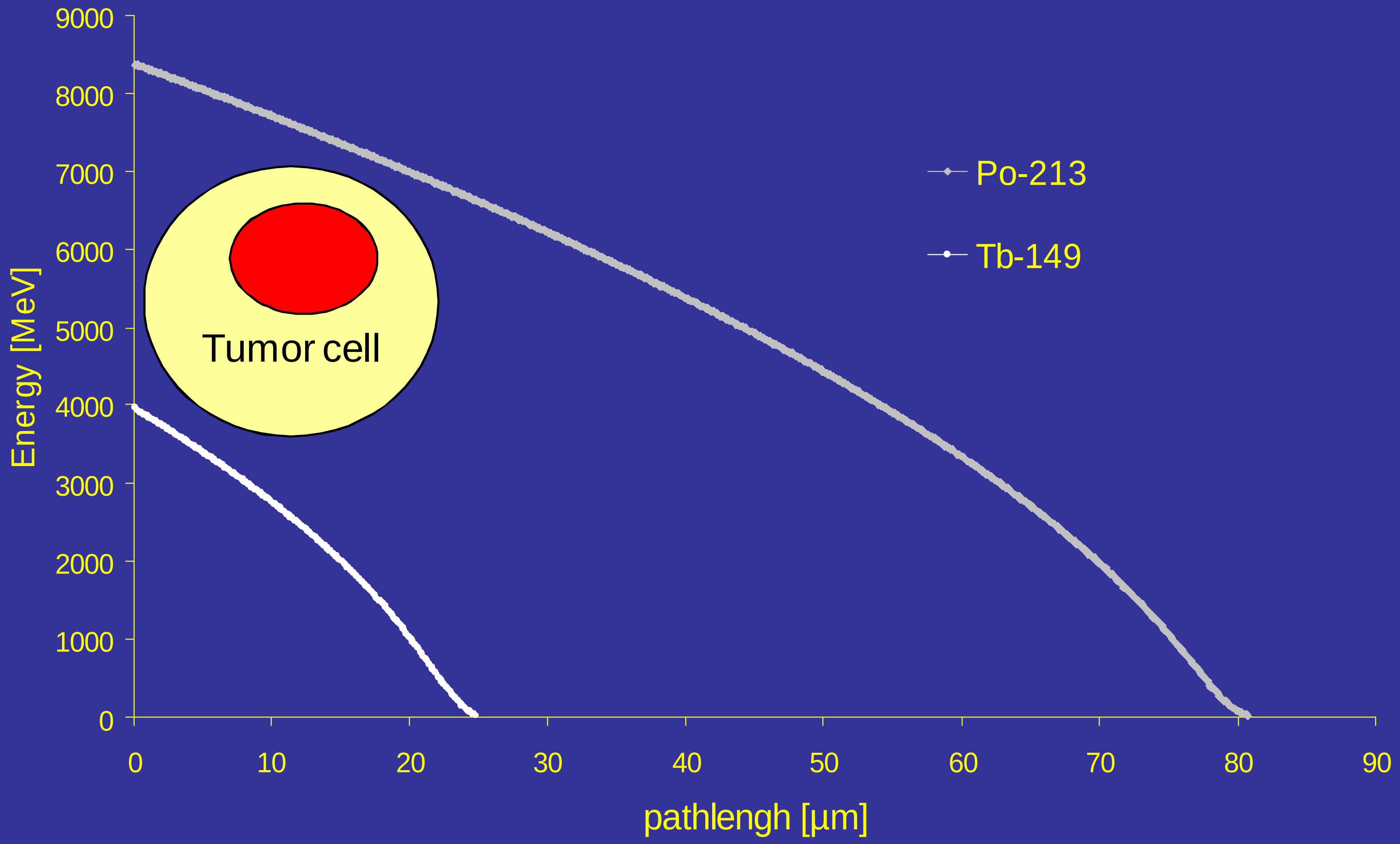
cross-fire

localized

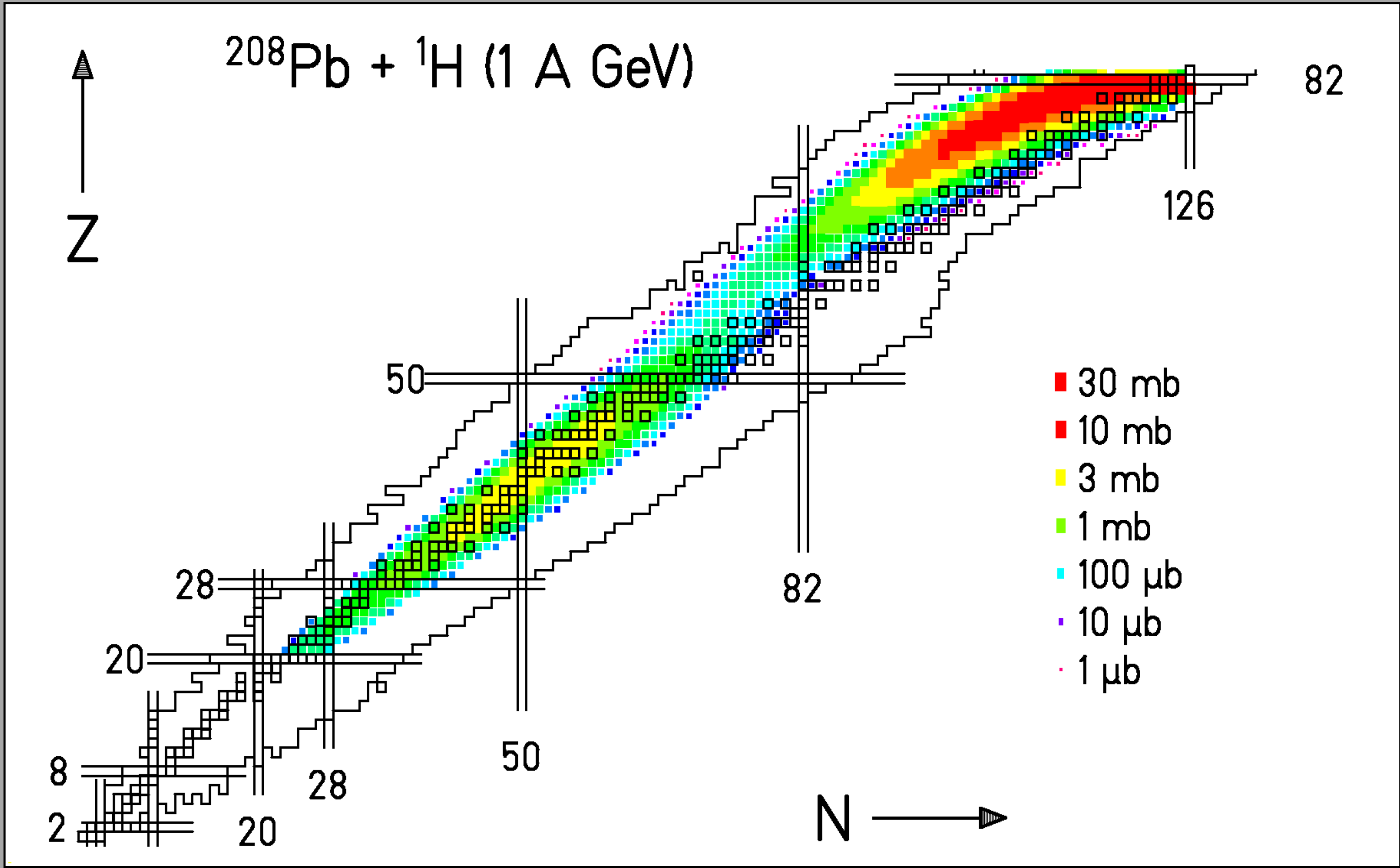
Isotopes for targeted alpha therapy

^{149}Tb for targeted alpha therapy

Alpha track in relation to cancer cells

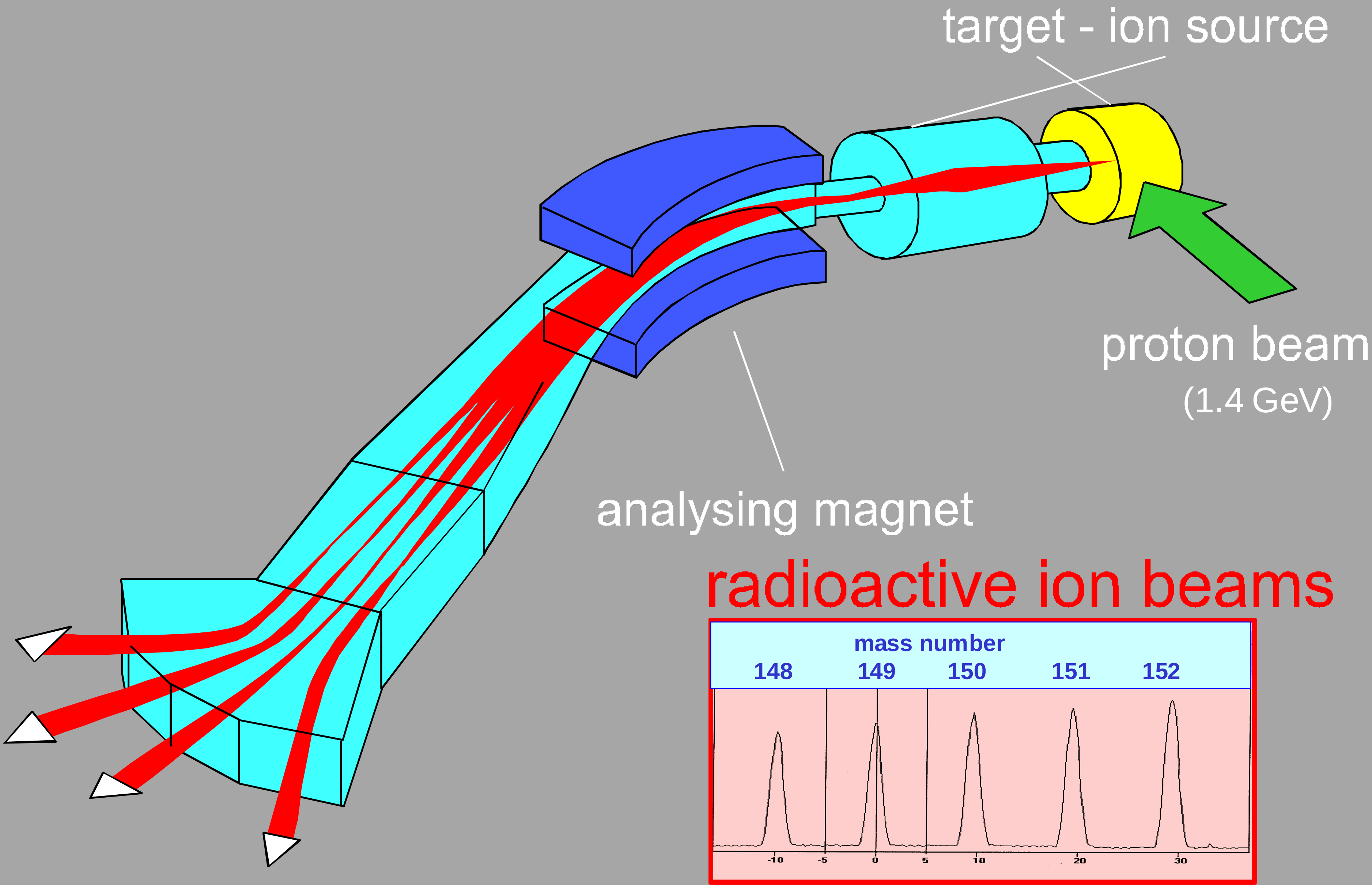


High-energy proton induced reactions

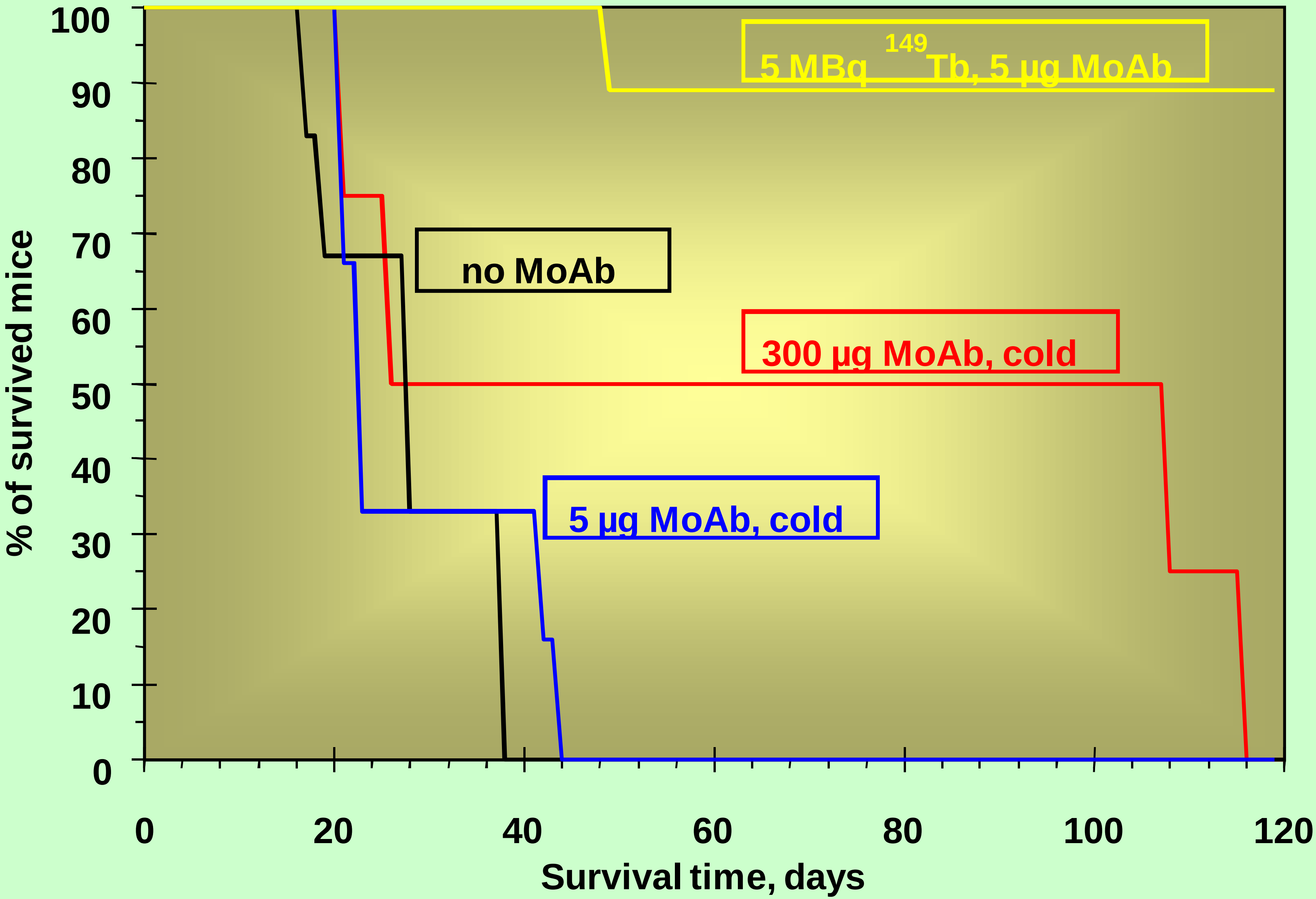


High-energy proton induced reactions can produce most of the isotopes of the chart of nuclides.

Isotope Separation On-Line



Survival of SCID mice



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

Terbium: a unique element

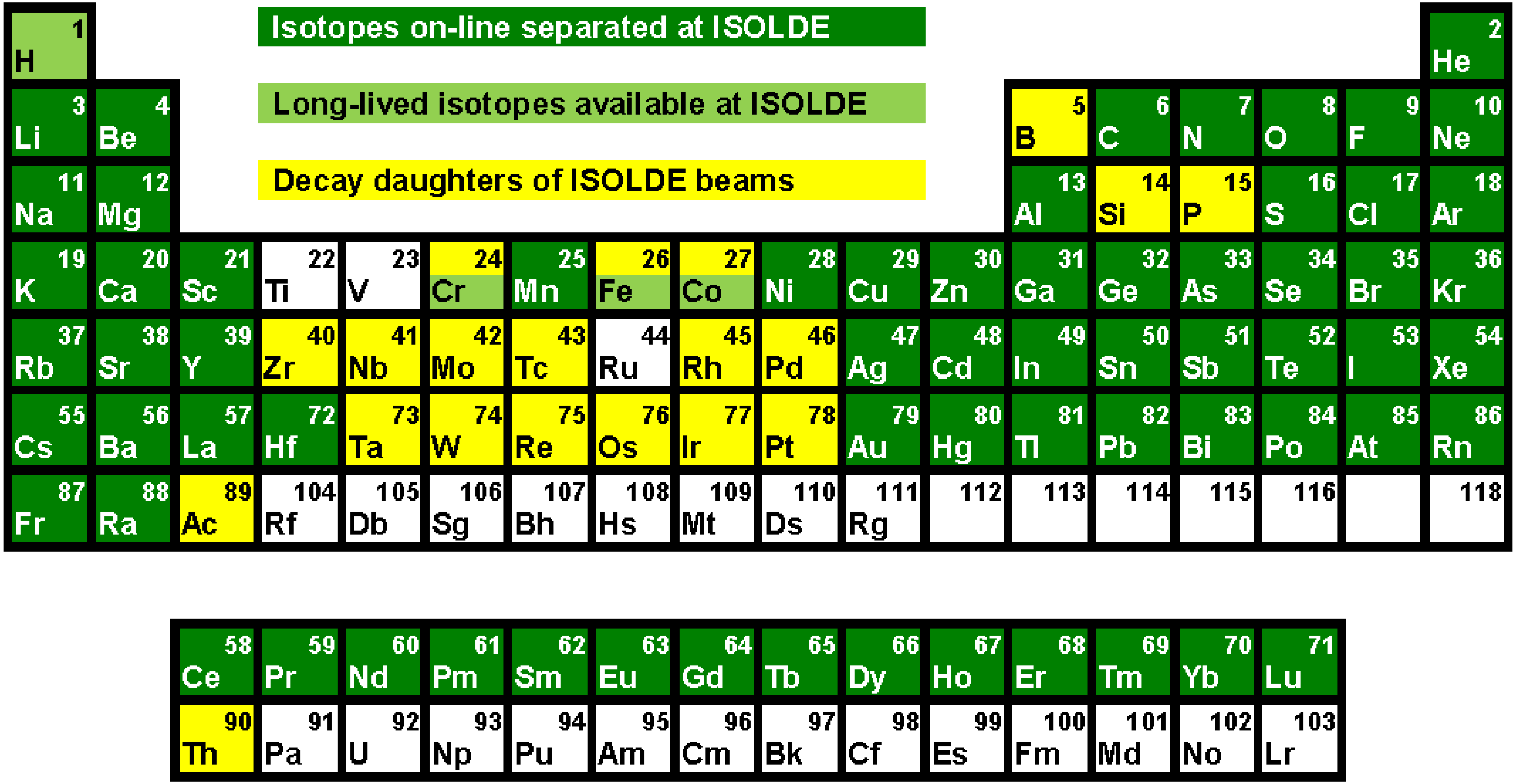
ID101
^{149}Tb
α-RIT

ID92
^{152}Tb
PET

^{155}Tb
SPECT

ID97
^{161}Tb
β/e^{-} RIT
SPECT

Radioisotopes available at ISOLDE-CERN



Currently available: more than 1000 different radioisotopes

Saturation activities of longer-lived radioisotopes: GBq and more

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

Isotopes for targeted alpha therapy

Thomson Reuters

Algeta soars on $800 million Bayer drug alliance

09.03.09, 09:13 AM EDT

FRANKFURT, Sept 3 (Reuters) –

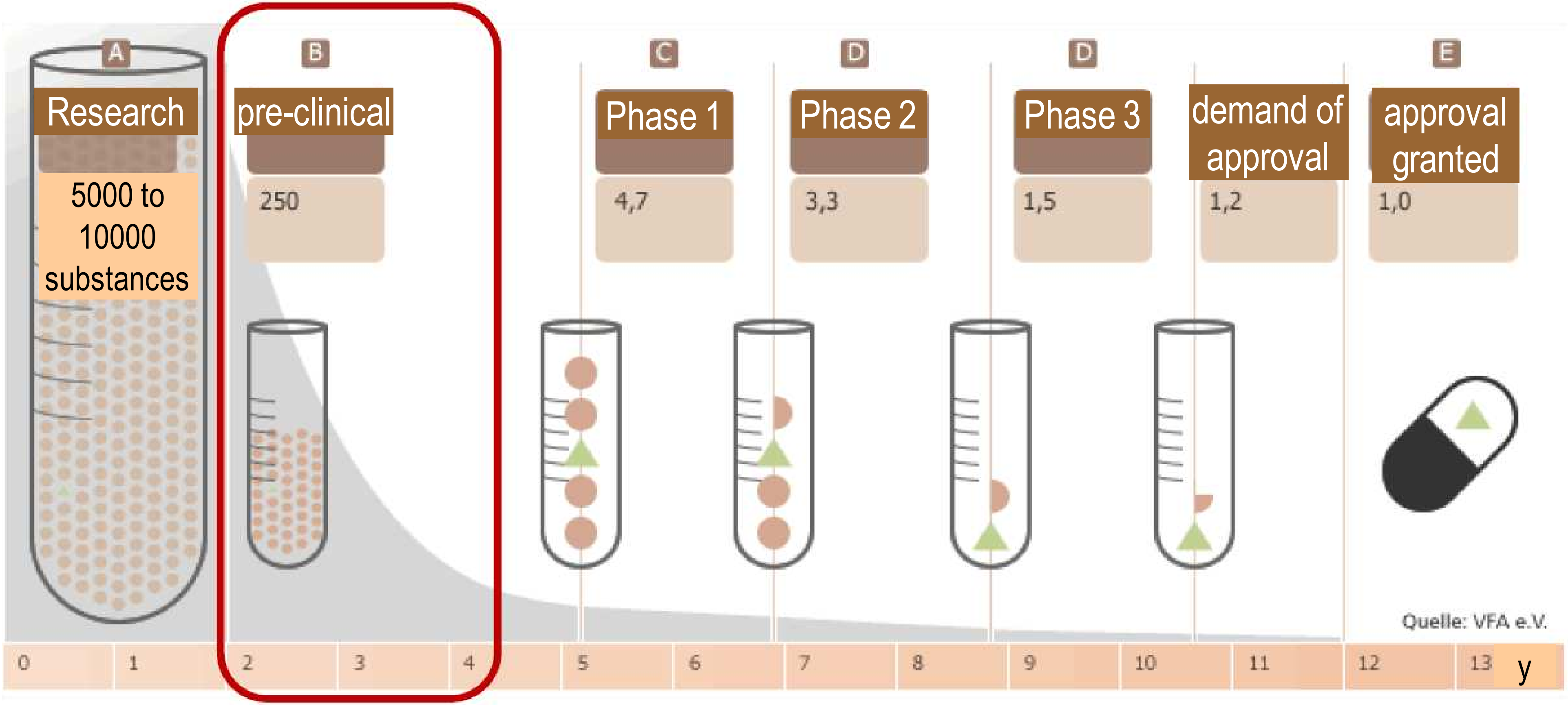
Norwegian biotech company Algeta clinched an $800 million licensing deal for its main experimental drug with German drugmaker **Bayer**, sending its shares soaring on Thursday.

Algeta expects **peak annual global sales of $1.3-$1.9 billion** for the cancer drug, dubbed **Alpharadin,** which clings to **cancerous bone cells** because it has some properties of calcium and **destroys them via alpha rays**.

The deal is potentially worth 560 million euros ($800 million) to Algeta, including an upfront payment of 42.5 million from Bayer and payments depending on development and commercial milestones, the two companies said.

Algeta, founded in 1997 by two **Norwegian radiochemistry researchers**, will also get double-digit royalties on future sales. It also has an option in the U.S. market, by far the largest for Alpharadin, to switch from royalties to sharing profit equally with Bayer.

Development of pharmaceuticals



Screening

in vitro tests
animal exp.

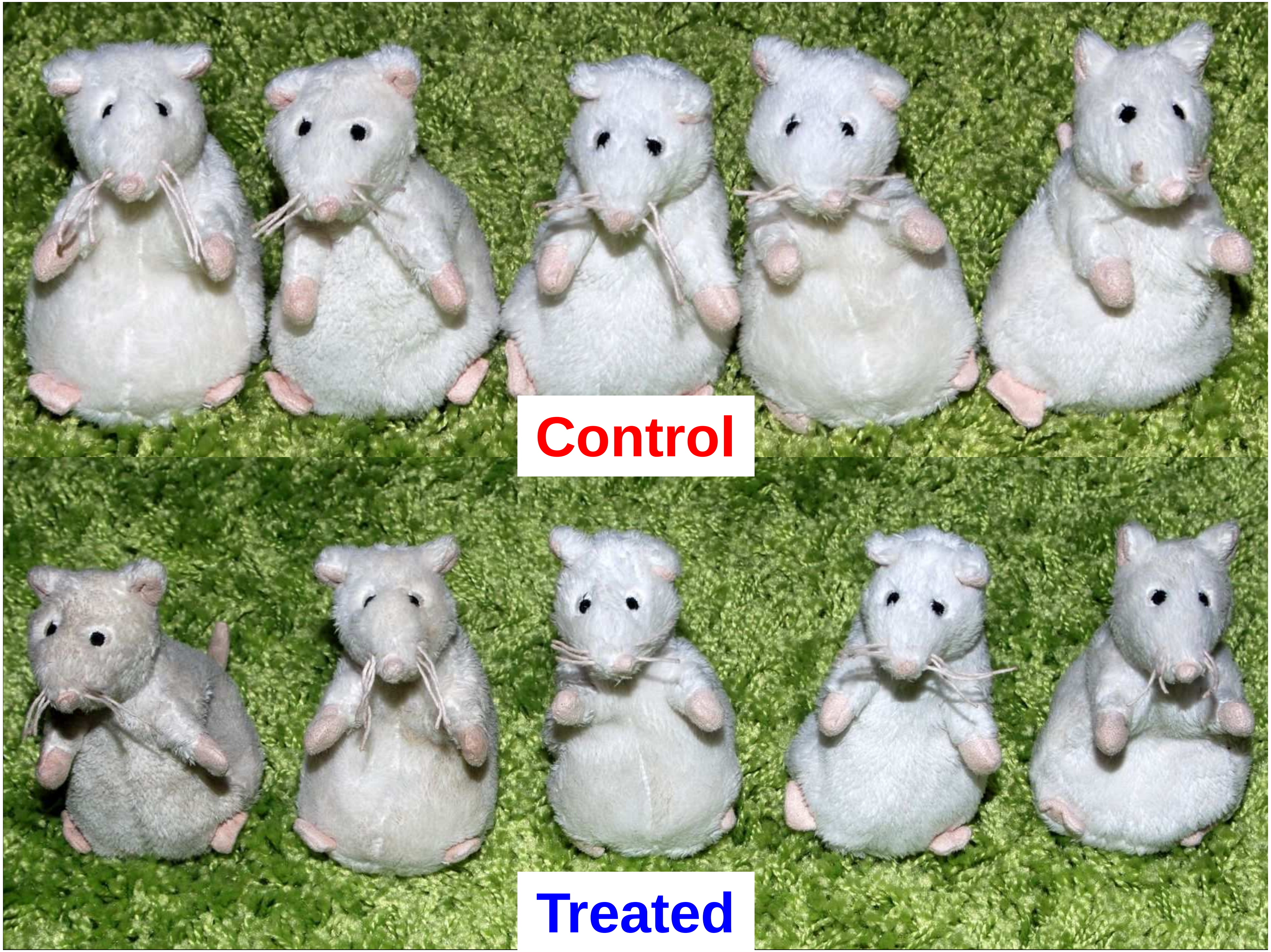
tests with humans

toxicity side effects	wanted effect	comparison with standard
20-80 healthy volunteers	100-300 patients	x00-x000 patients

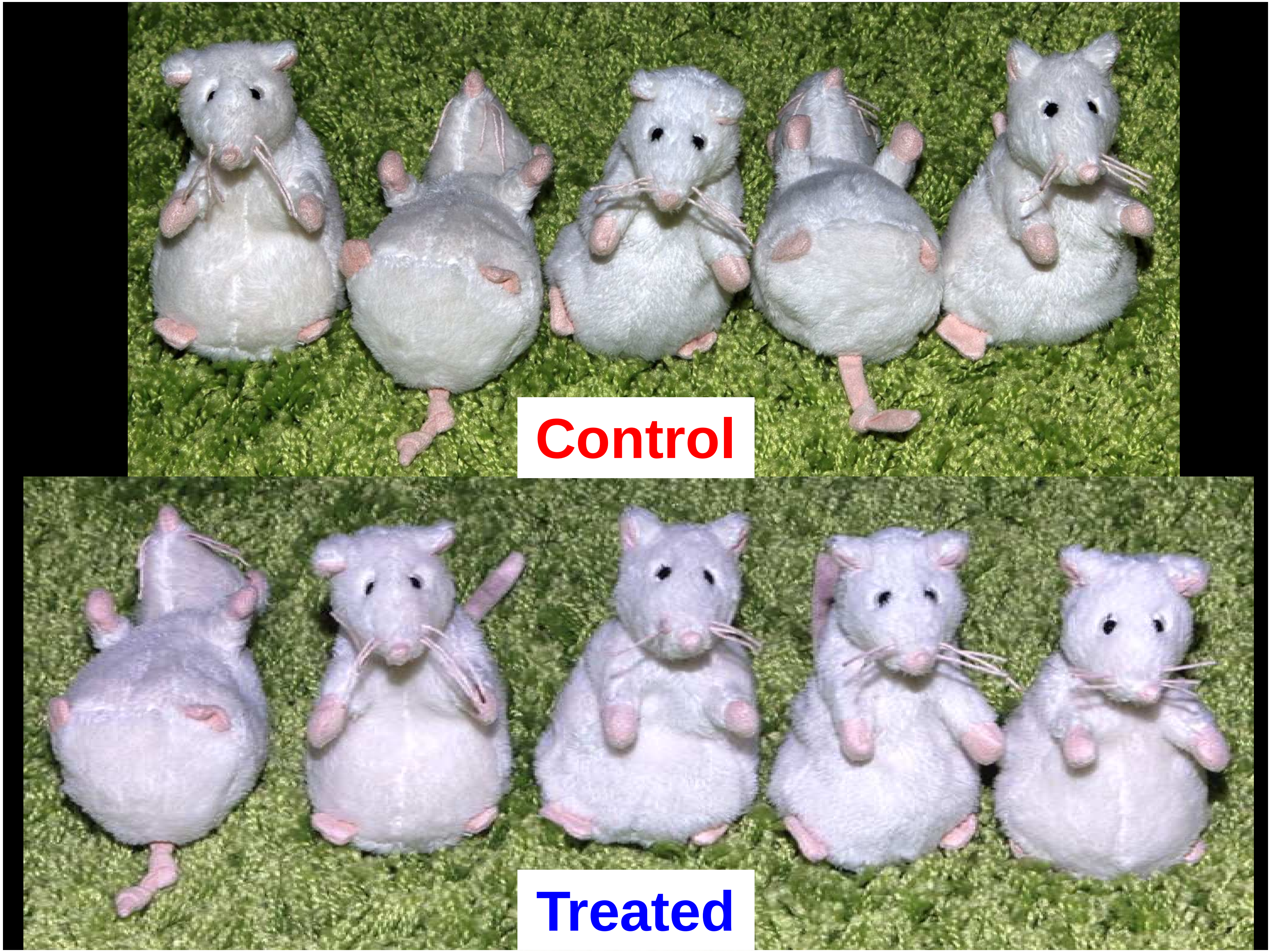
Pre-clinical studies (1)

Pre-clinical studies (2)

Pre-clinical studies (3)


Control
Treated


Control
Treated


Control
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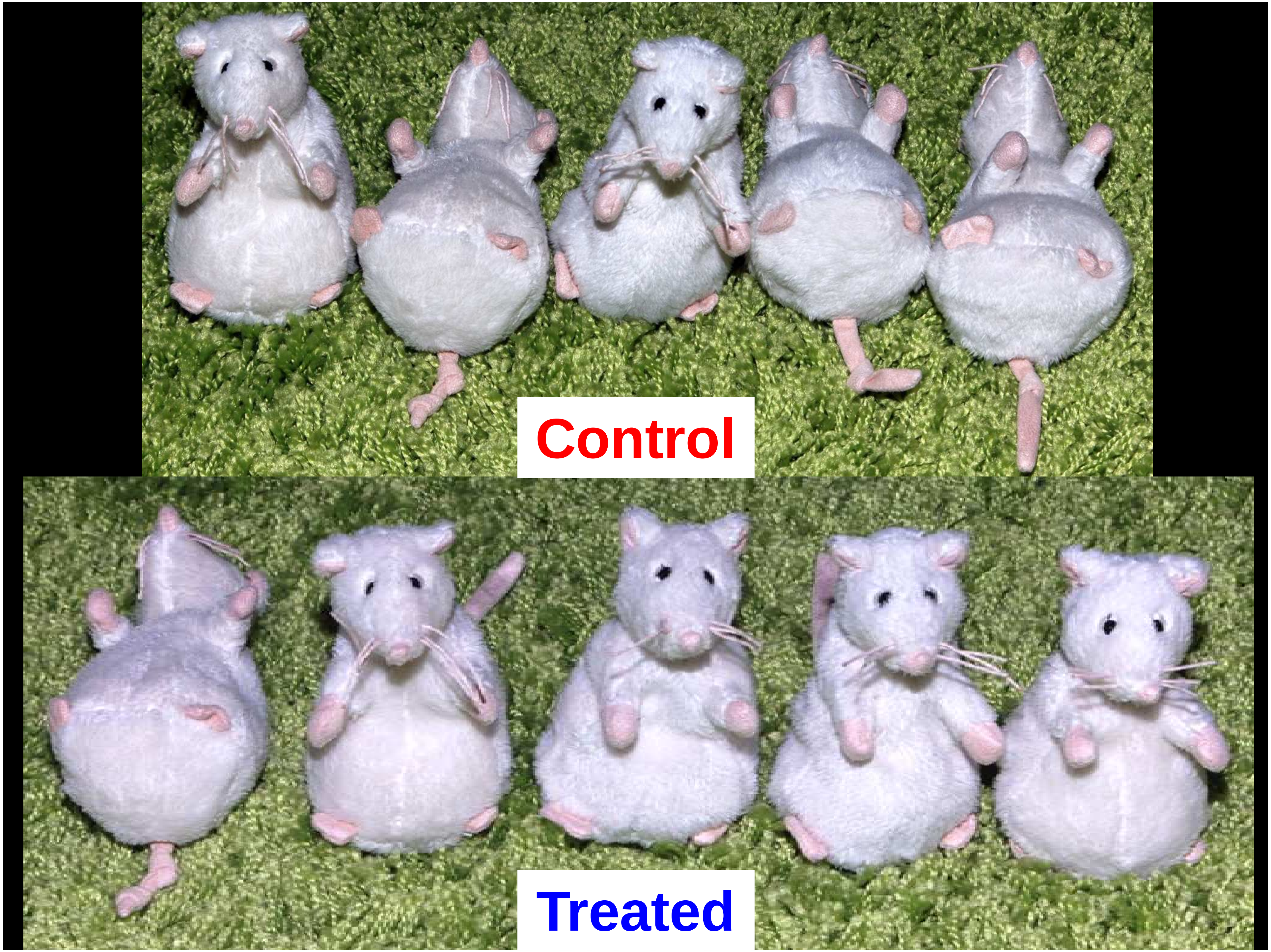
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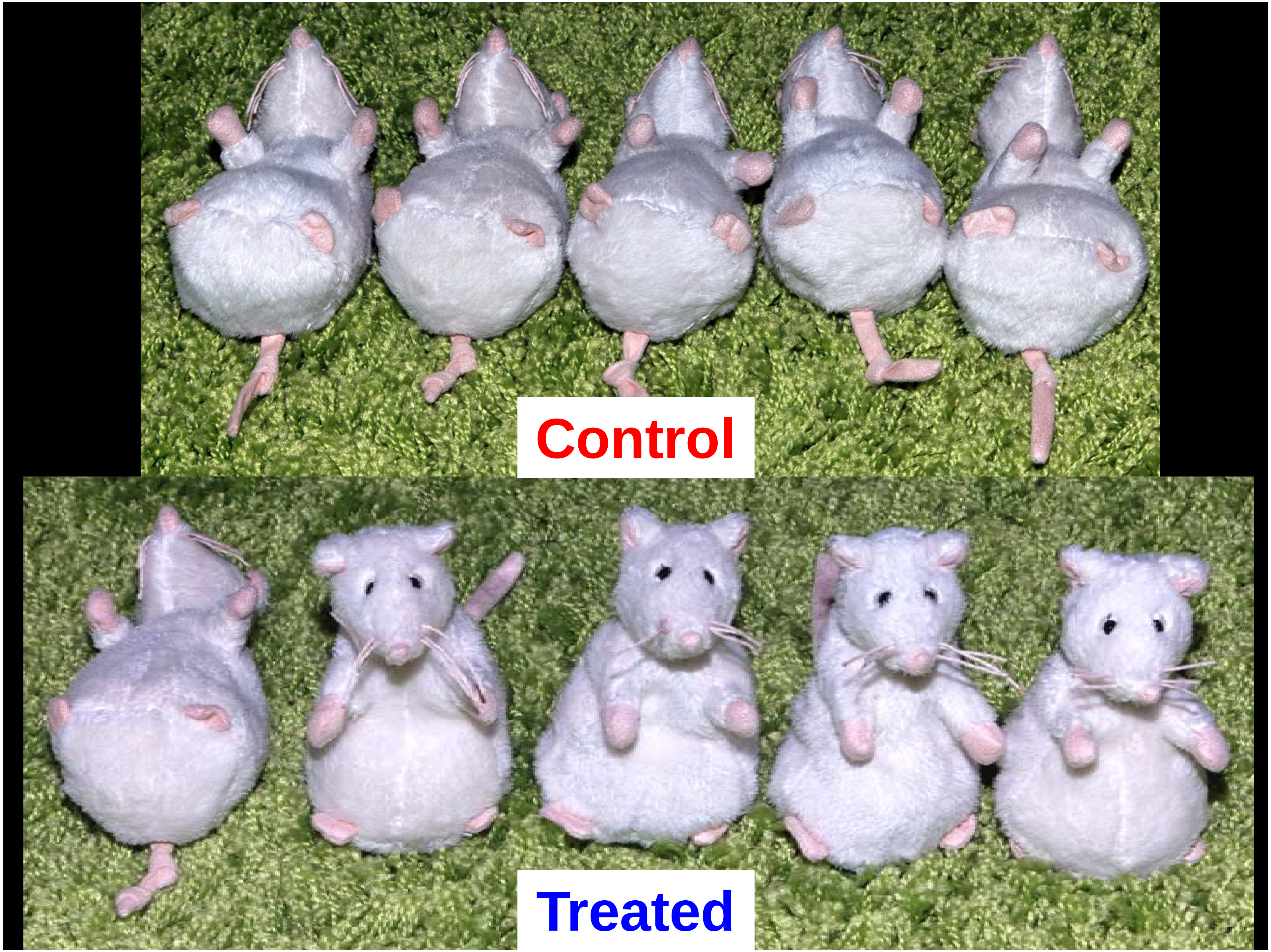
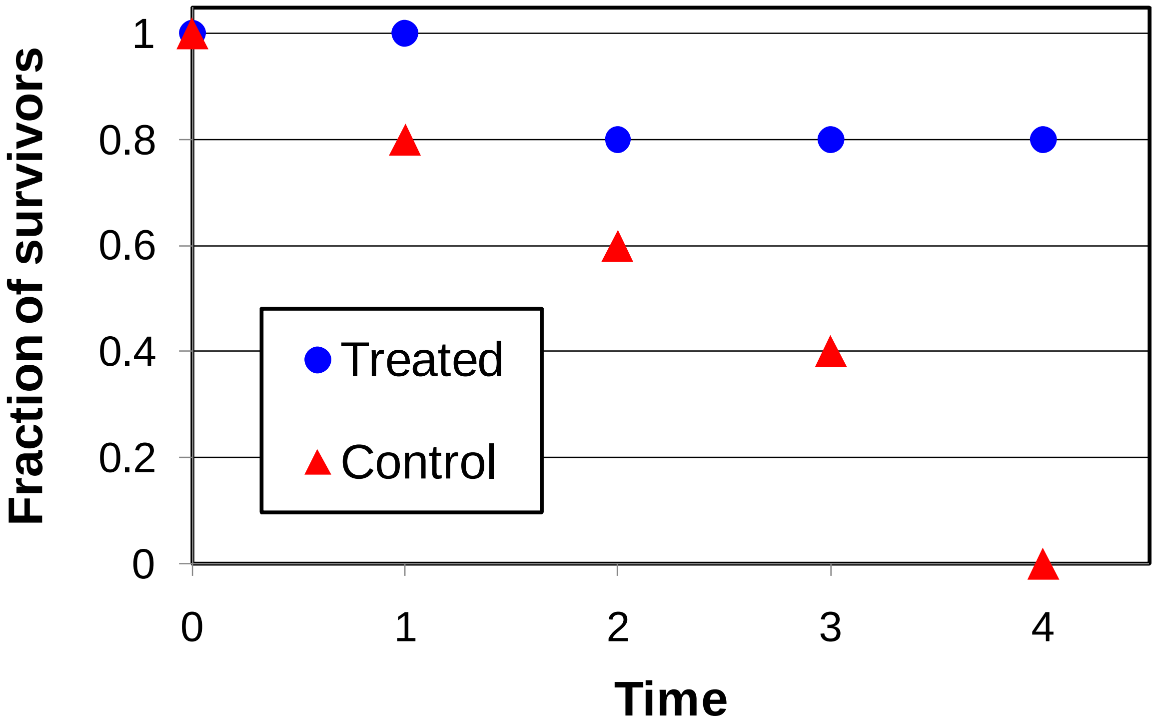
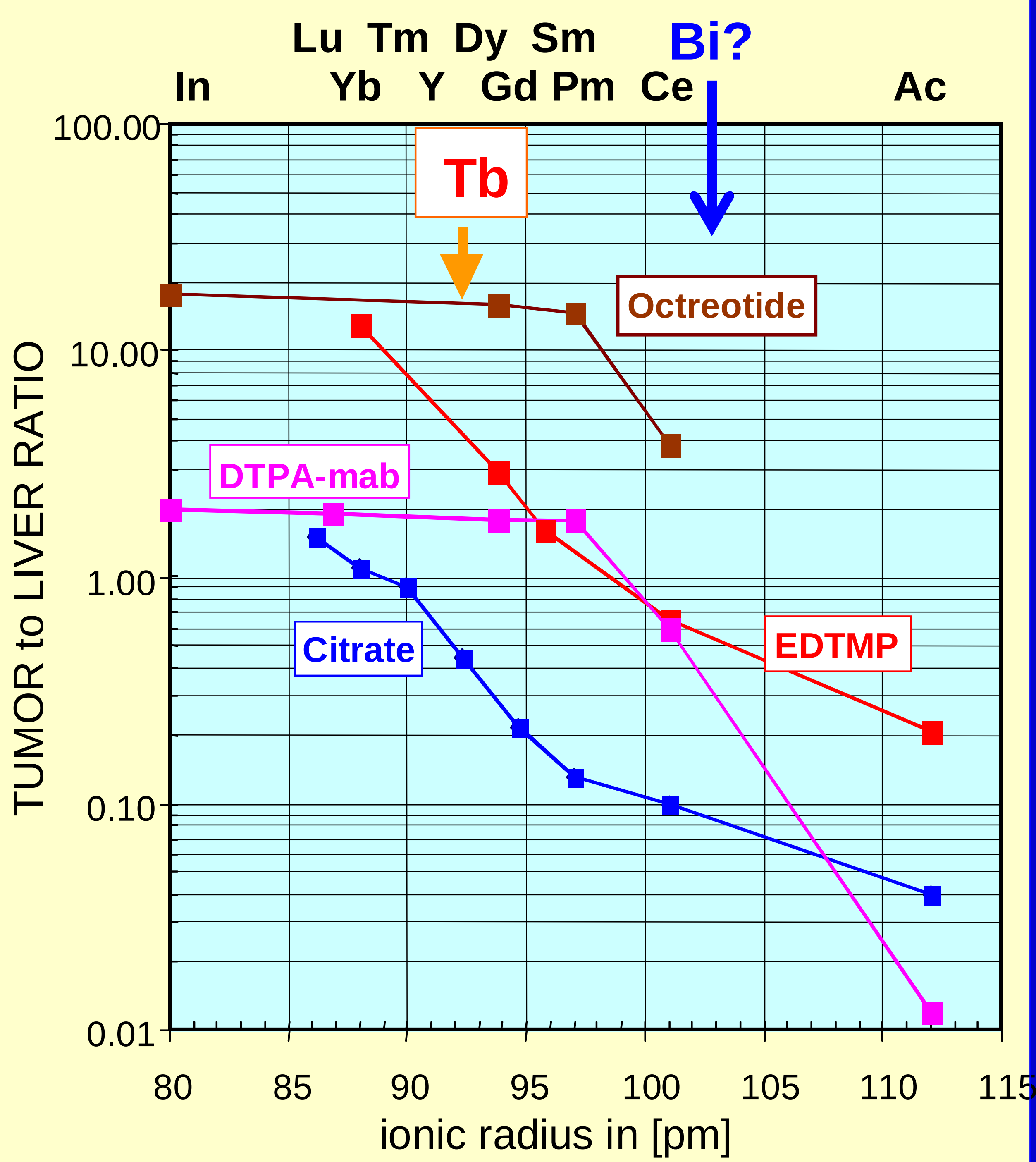

Control
Treated

Survival curve



- **medium survival time, median survival time, survival benefit**
- **shows final benefit but not detailed mechanism**

- **more information from bio-distribution studies**
- **preferentially on-line with suitable radiotracers and small animal SPECT or PET**



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

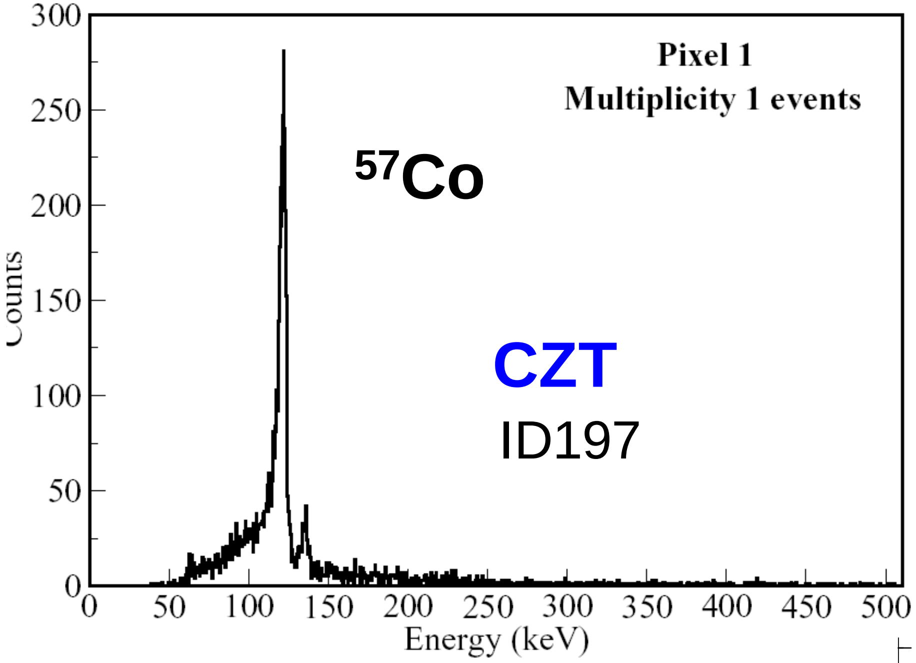
Mab

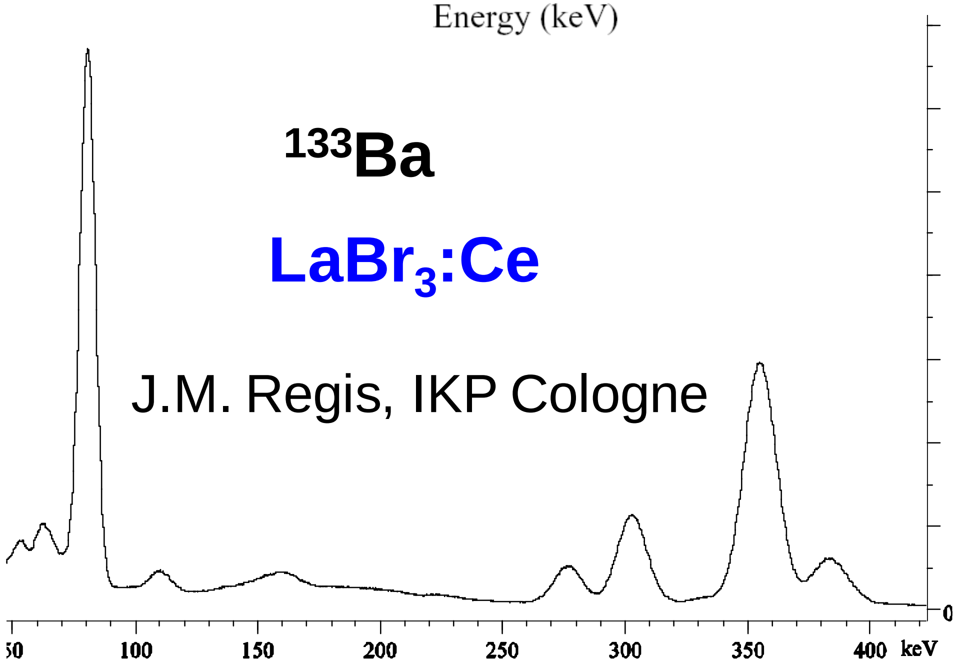
Linker:

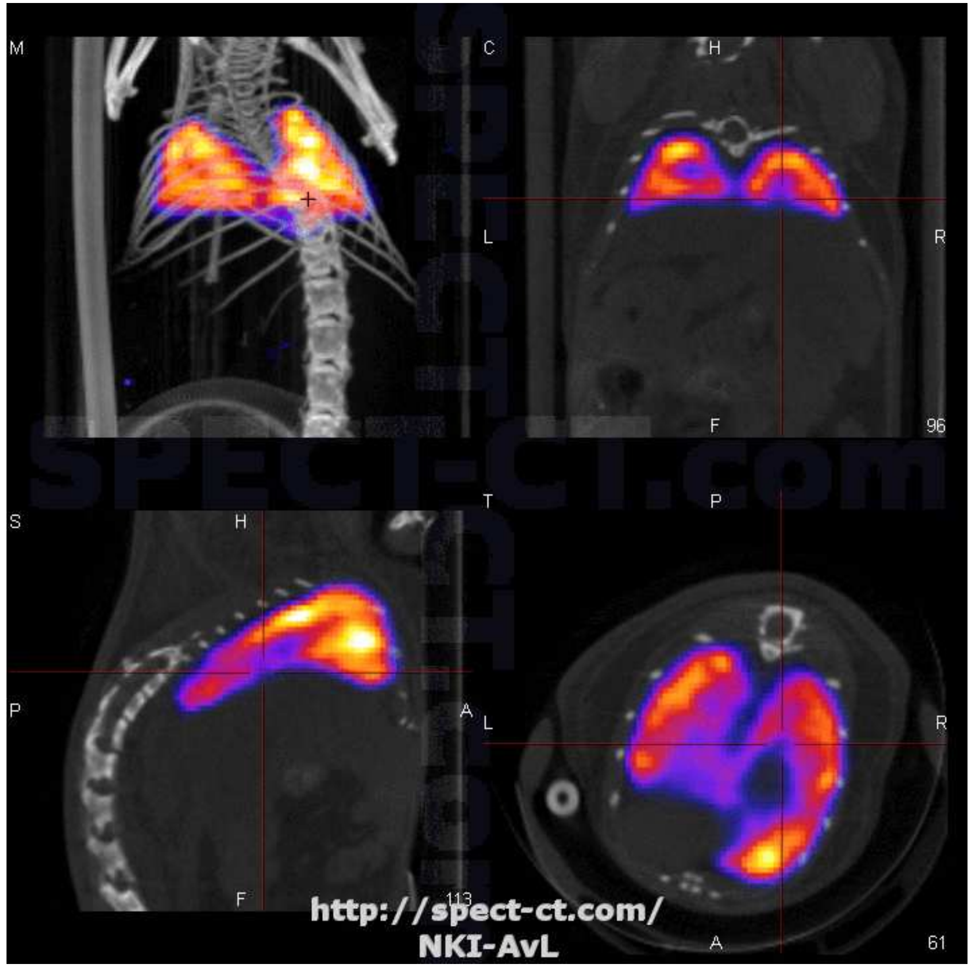
Aminobenzyl-DTPA

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

New generation of small animal SPECT

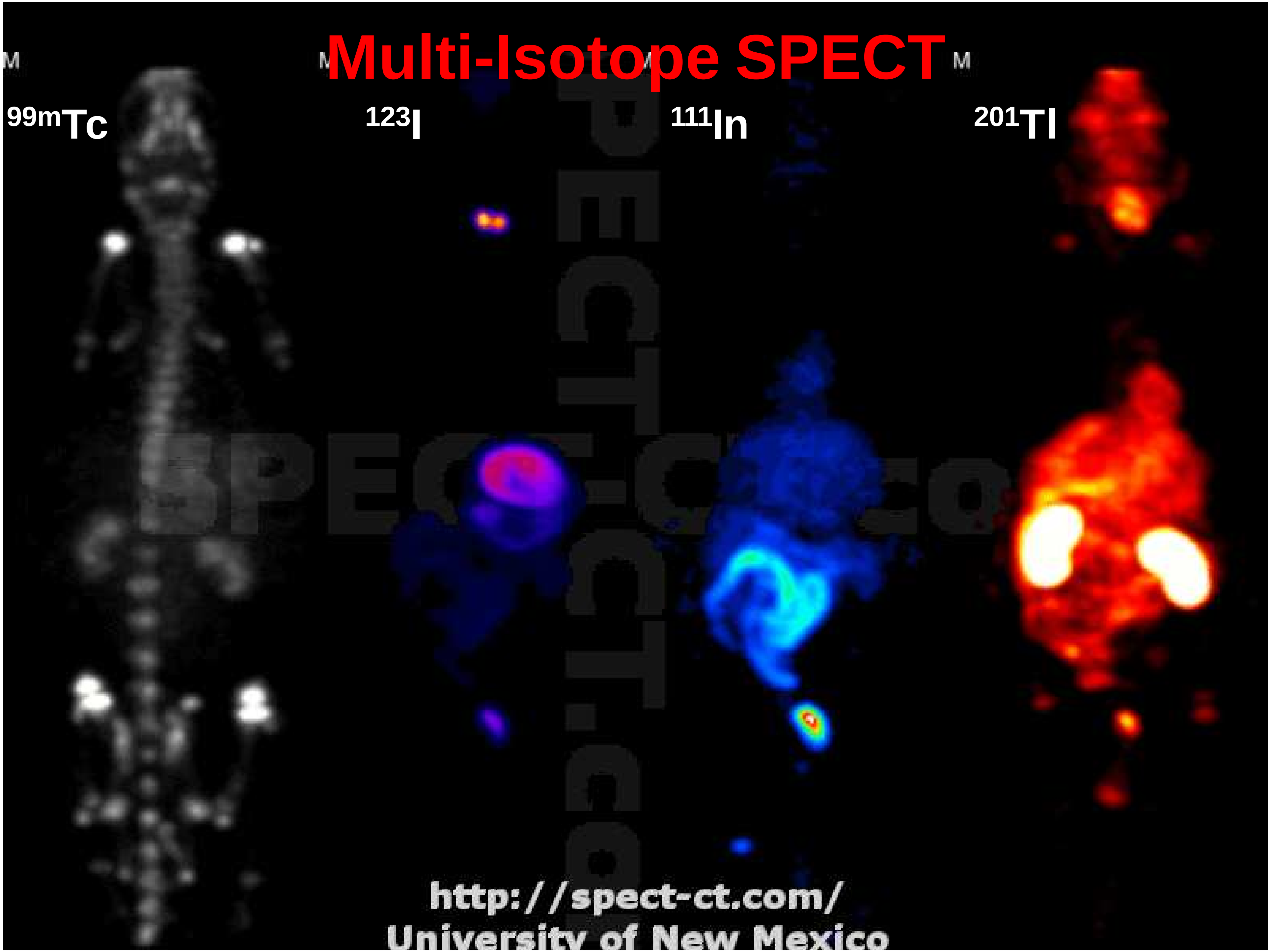




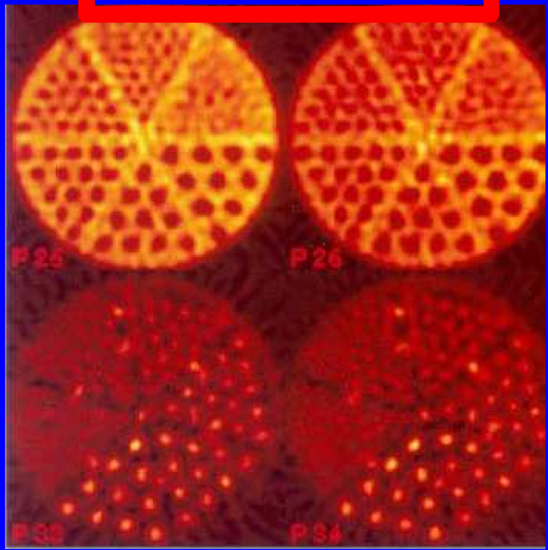


systematic biodistribution studies with different radiotracers become possible with dedicated small animal SPECT

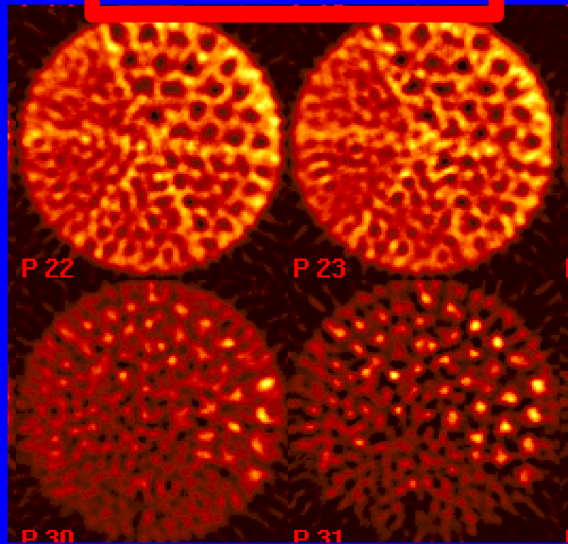
Multi-Isotope SPECT



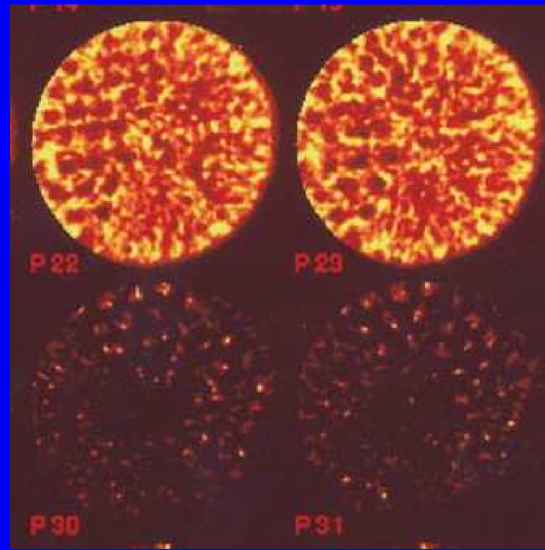
76 h ^{134}Ce/La



81 h ^{140}Nd/Pr

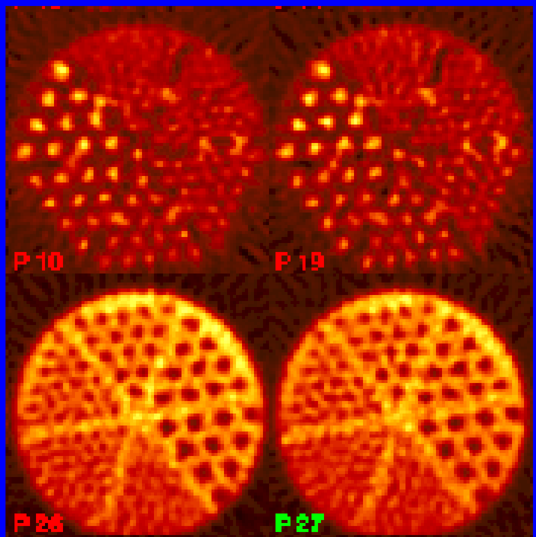


^{149}Tb



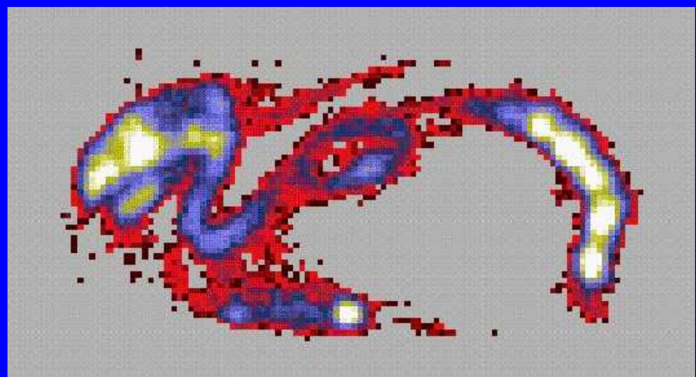
Positron emitting radiolanthanides

PET phantom studies

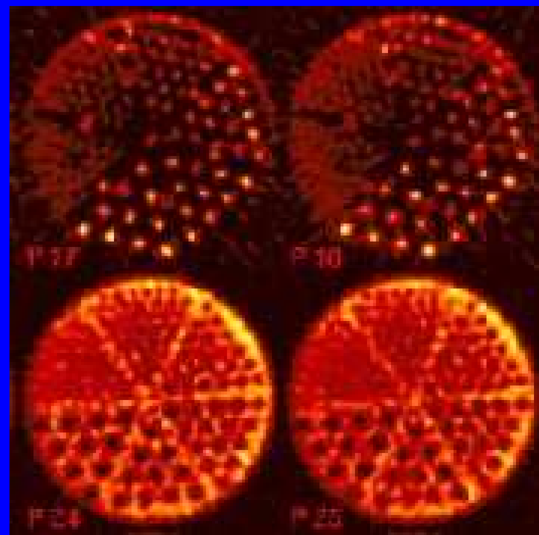


^{138}Nd/Pr

^{142}SmEDTMP in vivo study

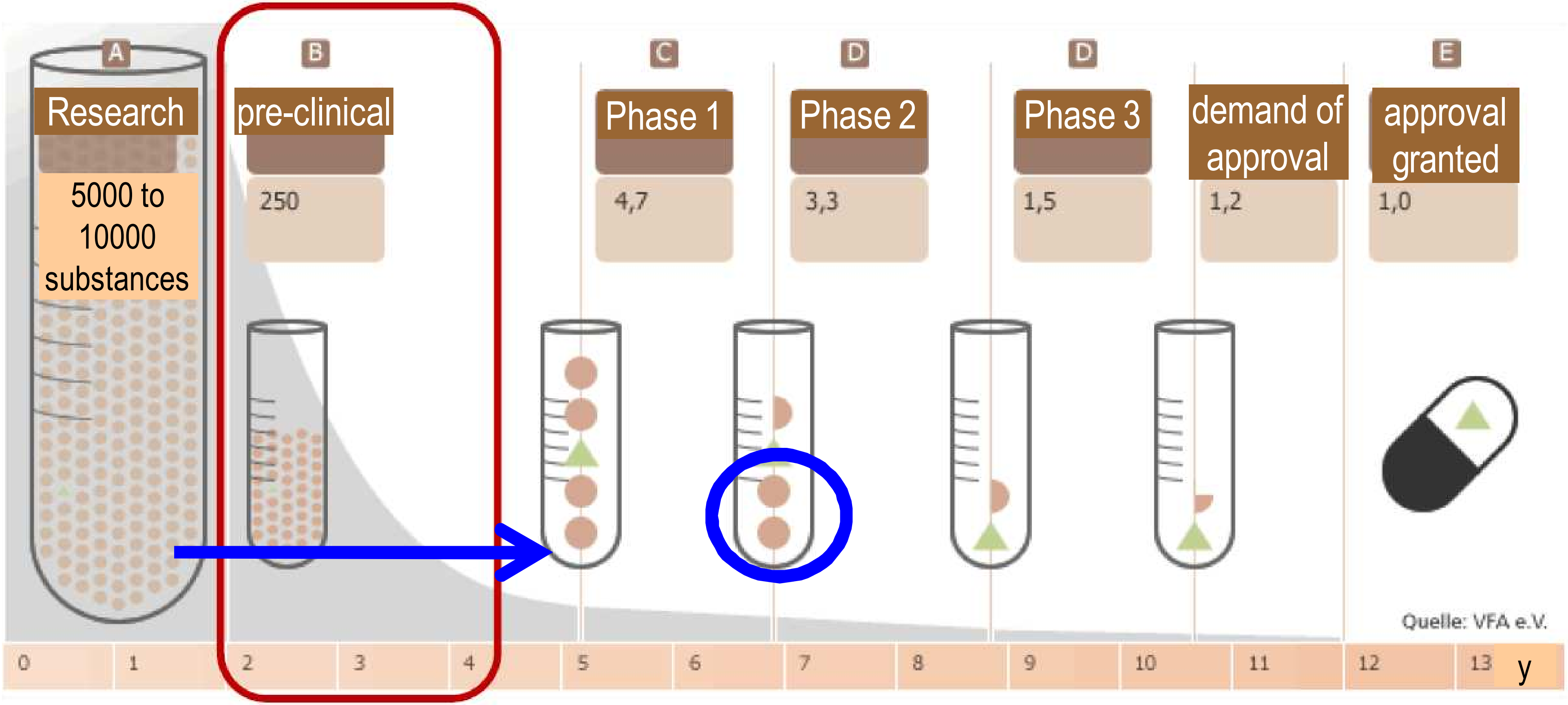


^{142}Sm/Pm



17.5 h ^{152}Tb

Development of pharmaceuticals



Screening

in vitro tests
animal exp.

- **Multi-isotope studies**
- **Long-lived PET tracer**

tests with humans

toxicity side effects	wanted effect	comparison with standard
20-80 healthy volunteers	100-300 patients	x00-x000 patients

Classification of Isotopes for Medicine

1. **Established isotopes** — “industrial” suppliers
   ^{99m}Tc, ^{18}F, $^{123,125,131}I$, ^{111}In, ^{90}Y
   supply security
   optimization of production/scale effects > cost reduction

2. **Emerging isotopes** — “small” innovative suppliers
   ^{68}Ga, ^{82}Rb, ^{89}Zr, ^{177}Lu, ^{188}Re
   quality, GMP, certification

3. **R&D isotopes** — research labs
   $^{44,47}Sc$, $^{64,67}Cu$, ^{134}Ce, ^{140}Nd,
   $^{149,152,155,161}Tb$, ^{166}Ho, ^{195m}Pt,
   ^{211}At, $^{212,213}Bi$, ^{223}Ra, ^{225}Ac,...
   availability at affordable cost

“Small” innovative suppliers in tight collaboration with universities & research labs

AAA	**CERN, Uni Geneva, Uni Lausanne, CERIMED,...**
ITG	**FRM2, TU Munich**
ITD	**FZR, TU Dresden**
(ARRONAX	**Subatech, Univ. Nantes)**

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   ^{211}At, $^{212,213}Bi$, ^{223}Ra, ^{225}Ac,...
   availability at affordable cost

Innovative Radioisotopes for Medicine

Proposal for a European user facility providing R&D isotopes for (pre-)clinical studies + logistics.

Potential Suppliers:

- **ILL Grenoble** **($1.5 \cdot 10^{15}$ n./cm^2/s high flux reactor):**
  ^{161}Tb, ^{166}Ho, ^{169}Er, ^{186}Re, ^{195m}Pt,... highest spec. activity
- **ISOLDE-CERN** **(1.4 GeV protons + mass separation):**
  ^{149,152,155}Tb, ^{140}Nd, ^{134}Ce,... + many others carrier-free!
- **PSI Villigen** **(1 MW SINQ + cyclotron + radiochemistry):**
  ^{44}Ti/^{44}Sc, ^{64,67}Cu, ^{117m}Sn,...
- **ARRONAX Nantes** **(70 MeV high power cyclotron):**
  ^{44,47}Sc, ^{64,67}Cu, ^{211}At,...
- **Open for additional contributors...**

Opportunity and duty for large scale research infrastructures!

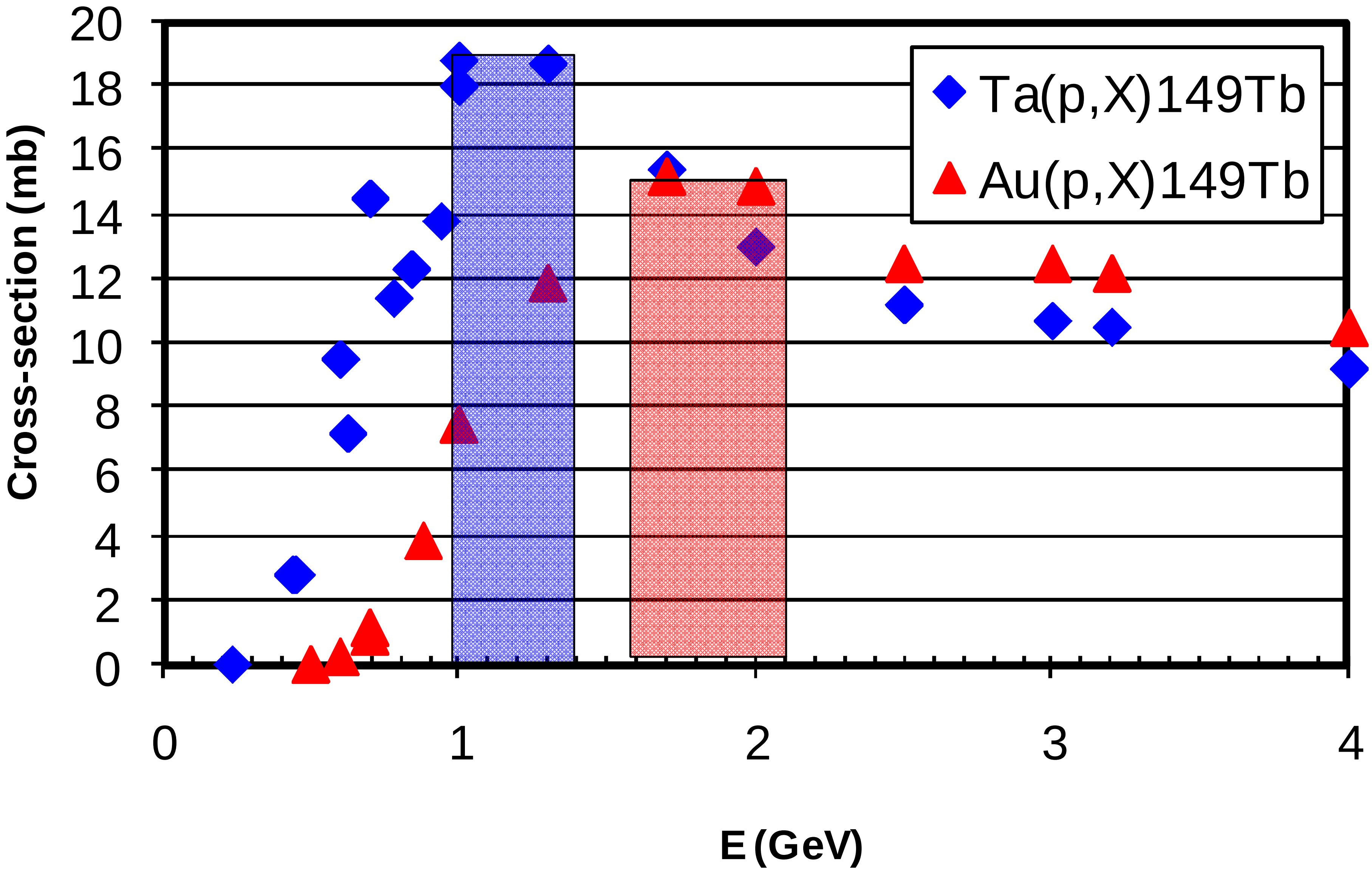
Future of ISOLDE Isotopes for Nuclear Medicine

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).**

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

Spallation production of ^{149}Tb



BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

Which radioisotopes will we need in 2030?

DATE: December 4, 1958

TO: Addressees Below

FROM: Daniel M. Schaeffer, Head
BNL Patent Office

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

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

"The method of producing carrier-free molybdenum-99 from fission products is disclosed in U. S. Patent Application S.N. 732,108, Green, Powell, Samos & Tucker (BNL Pat No. 58-17). It is noted that molybdenum-99 may be separated from its radioactive daughter, technetium-99, by absorption of a solution of molybdenum-99 on alumina and subsequent elution of its daughter with .1 nitric acid. While this method is probably novel, it appears that the product will probably be used mostly for experimental purposes in the laboratory. On this basis, no further patent action is believed warranted."

...

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