RADIOISOTOPES in MEDICINE:

Requirements - Production - Application and Perspectives

1

History

Gerd-Jürgen BEYER
Prof.Dr.rer.nat.habil.
Cyclotron Unit, University Hospital of Geneva, Switzerland
GSG-Int. GmbH, Switzerland
gerd.beyer@cern.ch
gerd.beyer@gsg-int.com

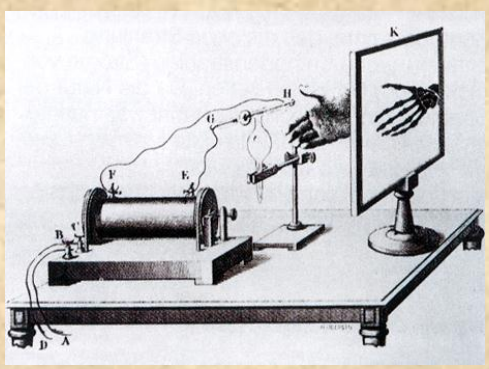
Lecture
JUAS
Joint University Accelerator School
Archamps (France) March 08, 2012

NUCLEAR MEDICINE – HOW IT BEGAN

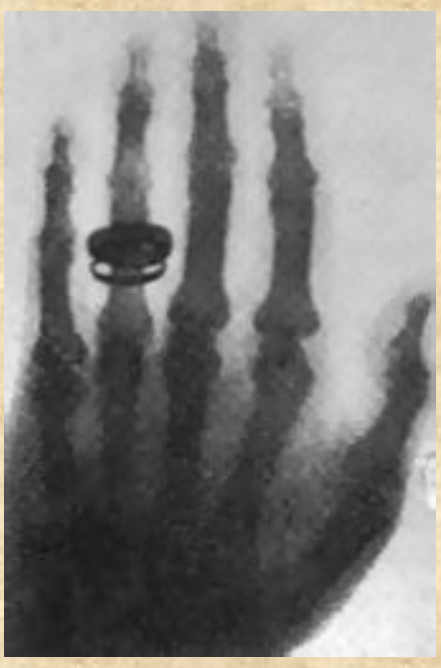
• 1789	Klaproth	Uran
• 1895	Conrad Roentgen	X-Ray
• 1896	Henry Becquerel	Radioactivity
• 1898	M.&P.Curie	**Po** und **Ra**
• 1923	G.Hevesy	Tracer Principle
• 1932	Lawrence	Cyclotron
• 1934	I.&F.Juliot-Curie	Artif.Radiactivity
• 1938	Hahn / Strassmann	U-Fission

W.C. Roentgen discovers X-rays

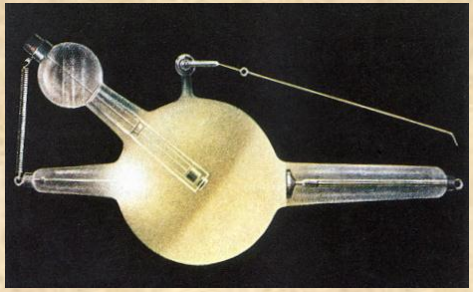
Nov.8, 1895



W.C.Roentgens experiment in Würzburg



Radiograph of Mrs.Roentgens hand, the first x-ray image ever taken, 22.Dec.1895, published in The New York Times January 16, 1896



An early XXth century

X-ray tube

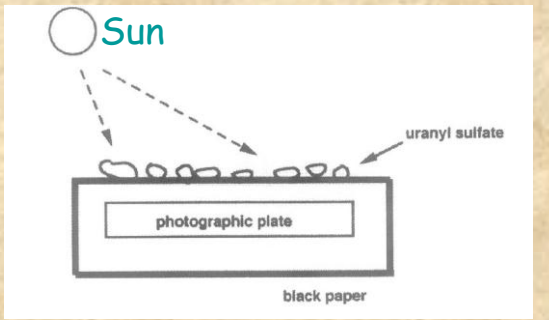
The Académie of Sciences in Paris Monday Meetings in early 1896:

Monday, January 20: **Poincaré's Hypothesis:**

„... Since Roentgen rays seem to emerge from the fluorescence of the wall of the Crookes tube, other fluorescent substances may emit both visible and invisible X-rays."

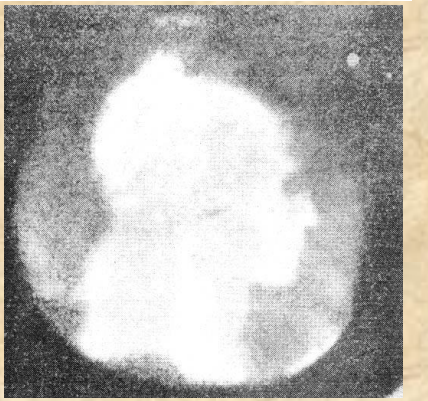
Monday, February 24: **First Becquerel Note:**

first experiments to verify Poincare's hypothesis:
„On radiation emitted by phosphorescence",
Comptes Rendus 122 (1896) 420



Monday, March 2: **second Becquerel Note:**

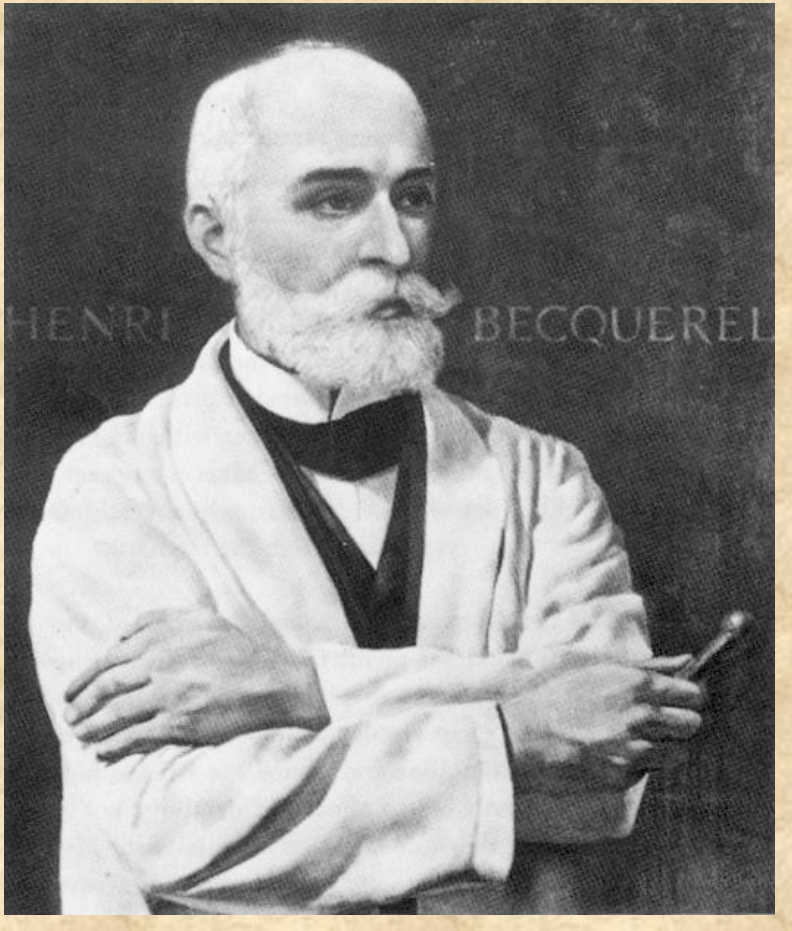
„On the invisible radiation emitted by phosphorescent substances",
Comptes Rendus 122 (1896) 501



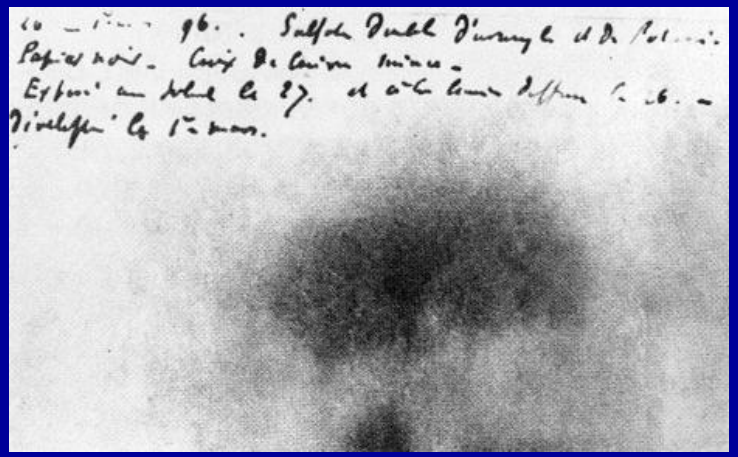
„I had prepared some plates on Wednesday, February 26 and some more on Thursday February 27. Because the sun appeared only intermittently on those days, I had saved the experiments, completely assembled, and returened the plateholders to the darkness of a drawer, leaving the uranium crystals in place. .... Sinse the sun did not reappear during the following days, I did develop the plates on March 1, expecting to find very week images. On the contrary, the silhouettes appeared with great intensity..."

Taken from J.P.Adloff: „Milestones in History of Radioactivity"

1896 RADIOACTIVITY



First image of potassium uranyldisulfate on **24 February 1896** was the discovery of natural radioactivity



Antoine Henry Becquerel

RADIOACTIVITY

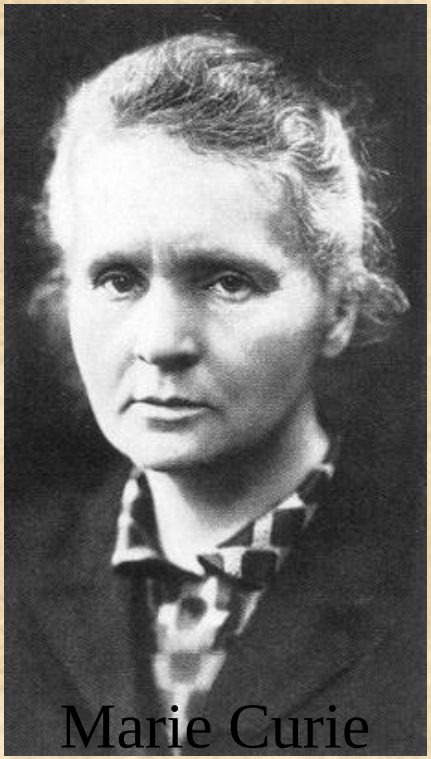
Marie Curie (1867 – 1934) Pierre Curie (1859 – 1906)

Marie and Pierre Curie
with their daughter Irene

1898 **Polonium**
Radium

1903 **Nobel Prize**
together with Pierre and H.Bequerel

1911 **Nobel Prize**
alone



1897 Becquerels friend, Pierre Curie, also Prof. of physics in Paris suggested to his young wife, Marie, that she study the phenomena discovered by H.Becquerel for her thesis. She found soon that some components of Uranium minerals were much more radioactive than Uranium itself. "**We shall call the mysterious rays 'radioactivity'**," she told to her husband Pierre, and the substances that produce the rays "**radioelements**".

1898 Pierre started to join Marie in the study of the mysterious rays. In **July** that year they reported the discovery of **Polonium** (^{210}Po) and in **December** they announced the discovery of the **Radium** (^{226}Ra)

THE TRACER PRINCIPLE 1923

G.V.Hevesy:
The Absorption and Translocation of Lead (ThB) by Plants [ThB = ^{212}Pb]
Biochem.J. **17**, 439 (1923)

Measurements of the tracer's Radioactivity provided thousand fold increases in sensitivity and accuracy over existing chemical assays. The foundation and basic rationale of much of Hevesy visualized that **a radioactive atom might be used as a "representative" tracer of stable atoms of the same element** whenever and wherever it accompanied them in biological systems.

1943 Nobel Prize Chemistry

the father of Nuclear Medicine

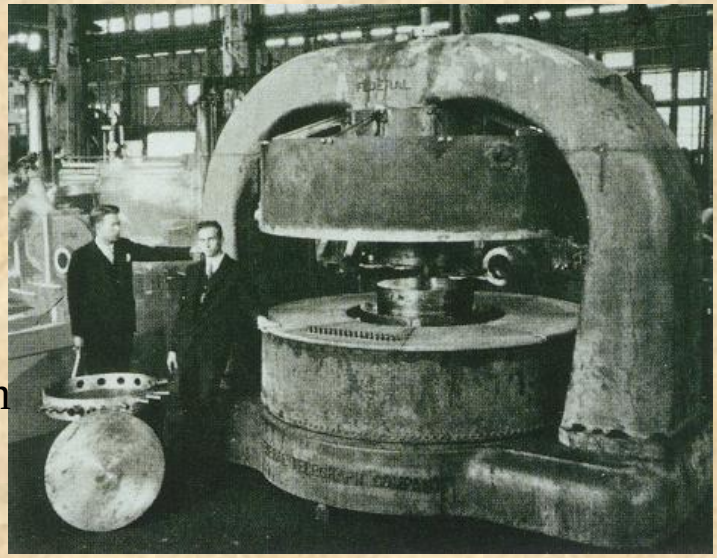
INVENTION of the CYCLOTRON

Ernest O Lawrence and his First cyclotron 1932

1932

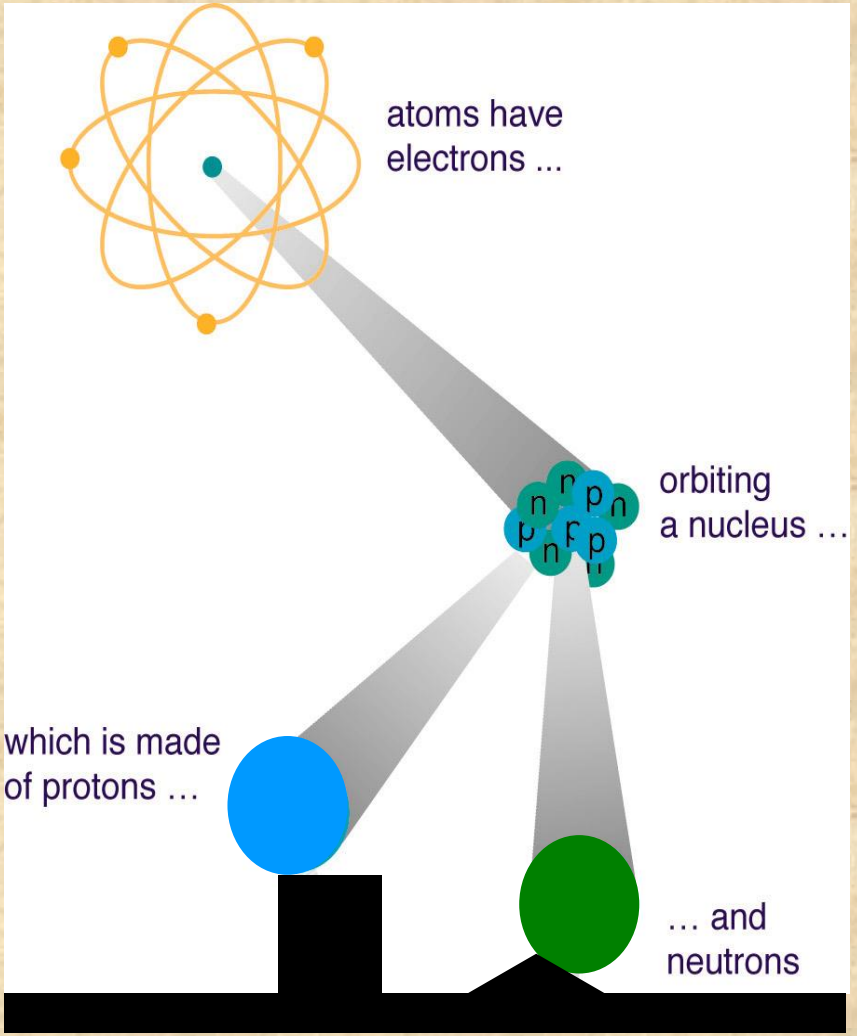
E.O.Lawrence and M.S. Livingston "The production of high speed Light ions without the use of High voltages", A milestone in the production of usable quantities of radionuclides.

E.O Lawrence and M.S.Livingston with the 27-inch cyclotron at Berkeley 1933, the first cyclotron that produced radioisotopes

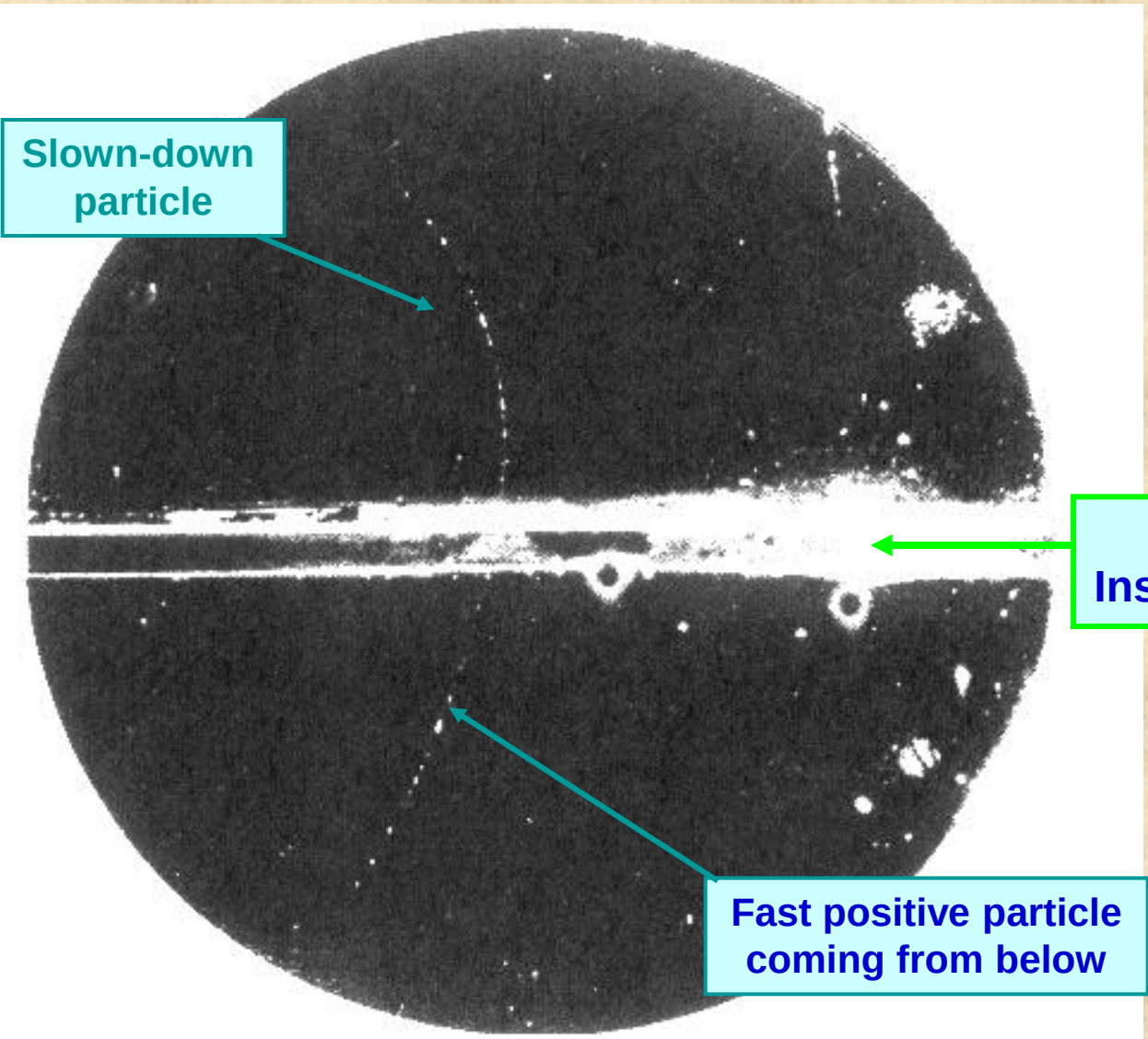


Discovery of the neutron 1932

James Chadwick
(1891 – 1974)



1932 Discovery of the Positron



C. D. Anderson

1934 Artificial RADIOACTIVITY

Irene and Frédéric Joliot-Curie

1934 Nature, February 10
1935 Nobel Prize

"Our latest experiments have shown a very striking fact: when aluminum foil is irradiated on a polonium preparation, the emission of positrons does not cease immediately when the active preparation is removed. The foil remains radioactive and the emission of radiation decays exponentially as for an ordinary radioelement. We observed the same phenomena with boron and magnesium."

$^{27}Al\ (\alpha,n)\ ^{30}P$ and $^{10}B\ (\alpha,n)\ ^{13}N$

The discovery of artificial radioactivity in combination with the cyclotron opened the door to the production of a variety of useful radio-indicators. Practically any element could be bombarded in the cyclotron to generate radioactive isotopes.

1935 Nature **136**, 754 O.Chievitz and G.V.Hevesy
Radioactive indicators in the study of phosphorus metabolism in rats **(^{32}P)**

1937 Radiology **28**, 178 J.G.Hamilton, R.S.Stone:
The administration of radio-sodium (**^{24}Na**)

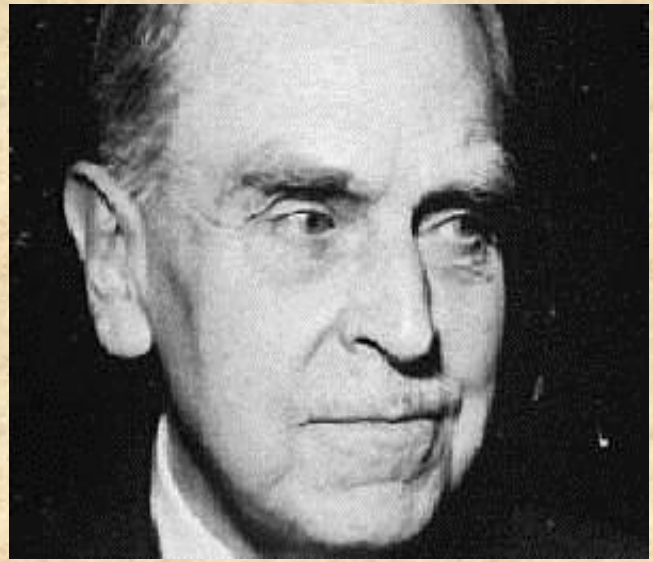
1938 Proc.Soc.Exp.Biol.Med. **38**, 510 S.Hertz, A.Roberts, R.D.Evans
Radioactive iodine (**^{128}I**) – Study of thyroid physiology

1939 Proc.Soc.Exp.Biol.Med. **40**, 694, J.H.Lawrence, K.G.Scott:
Metabolism of phosphorus (**^{32}P**) in normal and lymphomatous animals

1940 Am.J.Physiol. **131**, 135 J.G.Hamilton, M.H.Soley:
Studies of **iodine** metabolism by thyroid in situ

1940 J.Biol.Chem. **134**, 543 J.F.Volker, H.C.Hodge, H.J.Wilson
The adsorption of fluoride (**^{18}F**) by enamel, dentine, bone and hydroxyapatite

1945 Am.J.Physiol. 145, 253 C.A.Tobias, J.H.Lawrence, F.Roughton
The elimination of 11-C-Carbon monoxide from the human body



Otto Hahn, 1944 Nobel Prize

FISSION of Uranium

1938, 17. Dec.

Naturwissenschaften **1**, (1939) 1

O.Hahn und F.Straßmann

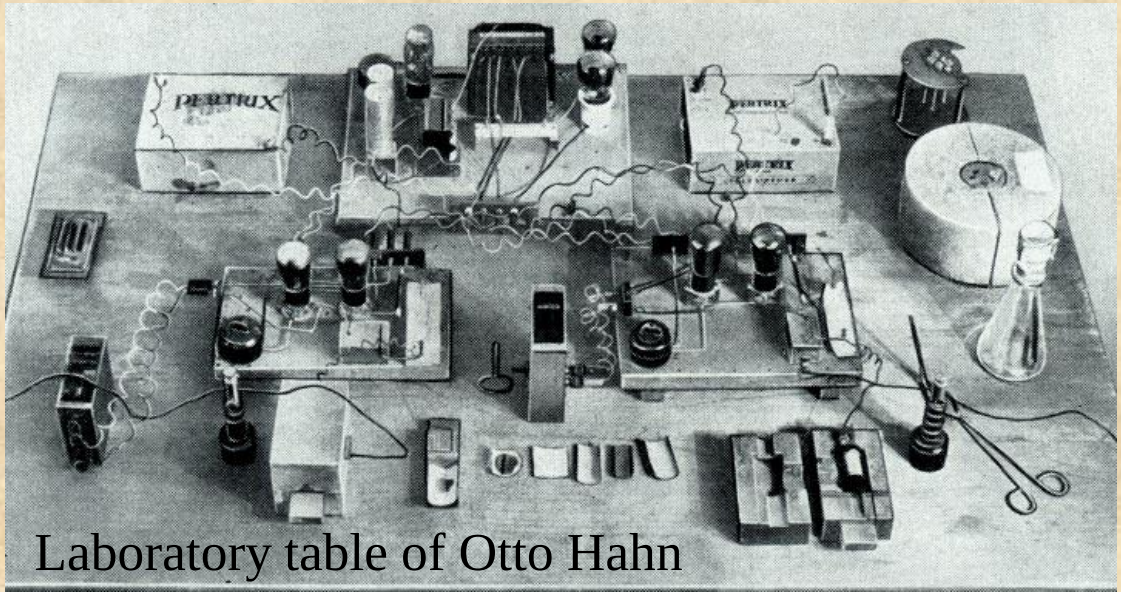
Über den Nachweis und das Verhalten der bei der Bestrahlung des Urans mittels Neutronen entstehenden Erdalkalimetalle

Lise Meitner and O.R Frisch described the Explanation and defined the terminus “FISSION”

Als Chemiker müßten wir … statt Ra, Ac und Th die Symbole Ba, La und Ce einsetzen. Als der Physik in gewisser Weise nahestehende Kernchemiker können wir uns zu diesem, allen bisherigen Erfahrungen der Kernphysik widersprechenden Sprung noch nicht entschließen. Es könnten doch vielleicht eine Reihe seltsamer Zufälle unsere Ergebnisse vorgetäuscht haben.

Niels Bor (Jan.1939)

Mein Gott, wie haben wir das nur so lange übersehen können

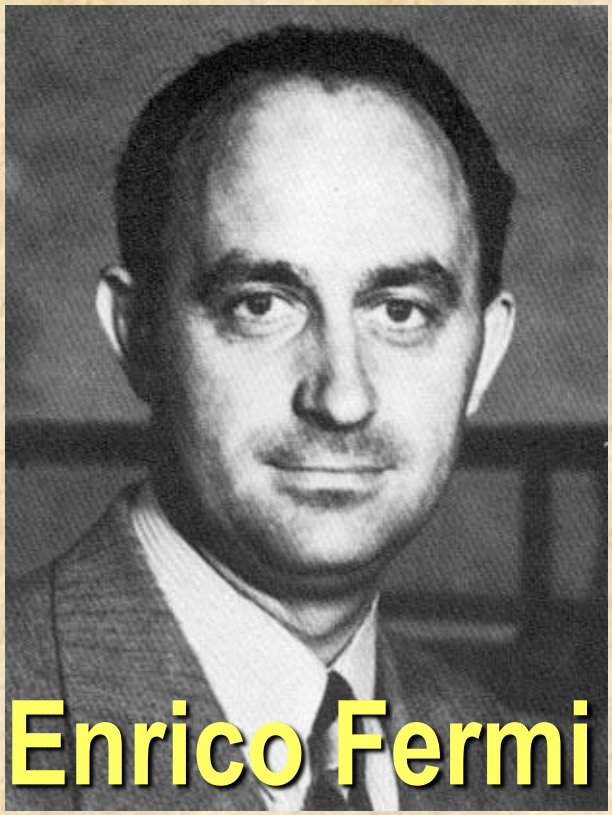


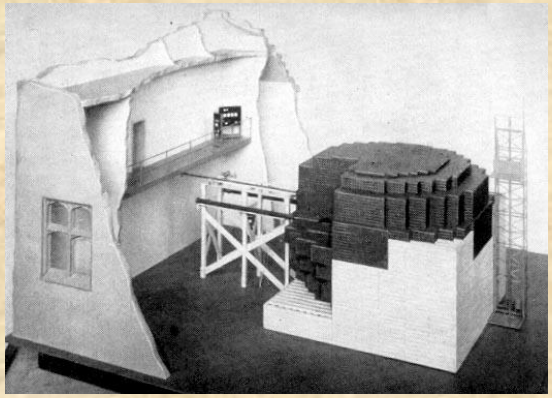
Laboratory table of Otto Hahn

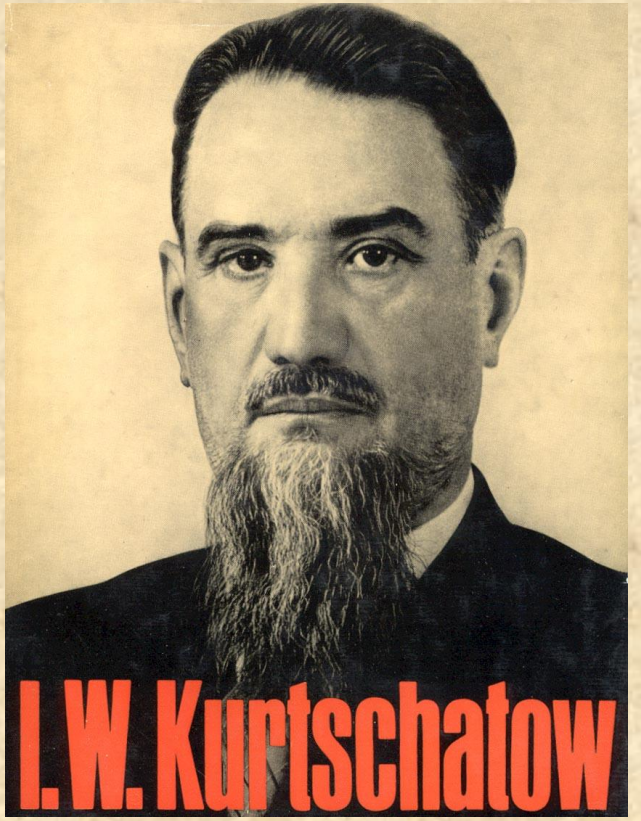
FISSION of Uranium

$$^{235}U + n = [^{236}U] \longrightarrow {}^{140}Ba + {}^{94}Kr + 2\,n + \gamma + \text{Energy}$$

1942 Dec.2, first graphite miler in Chicago

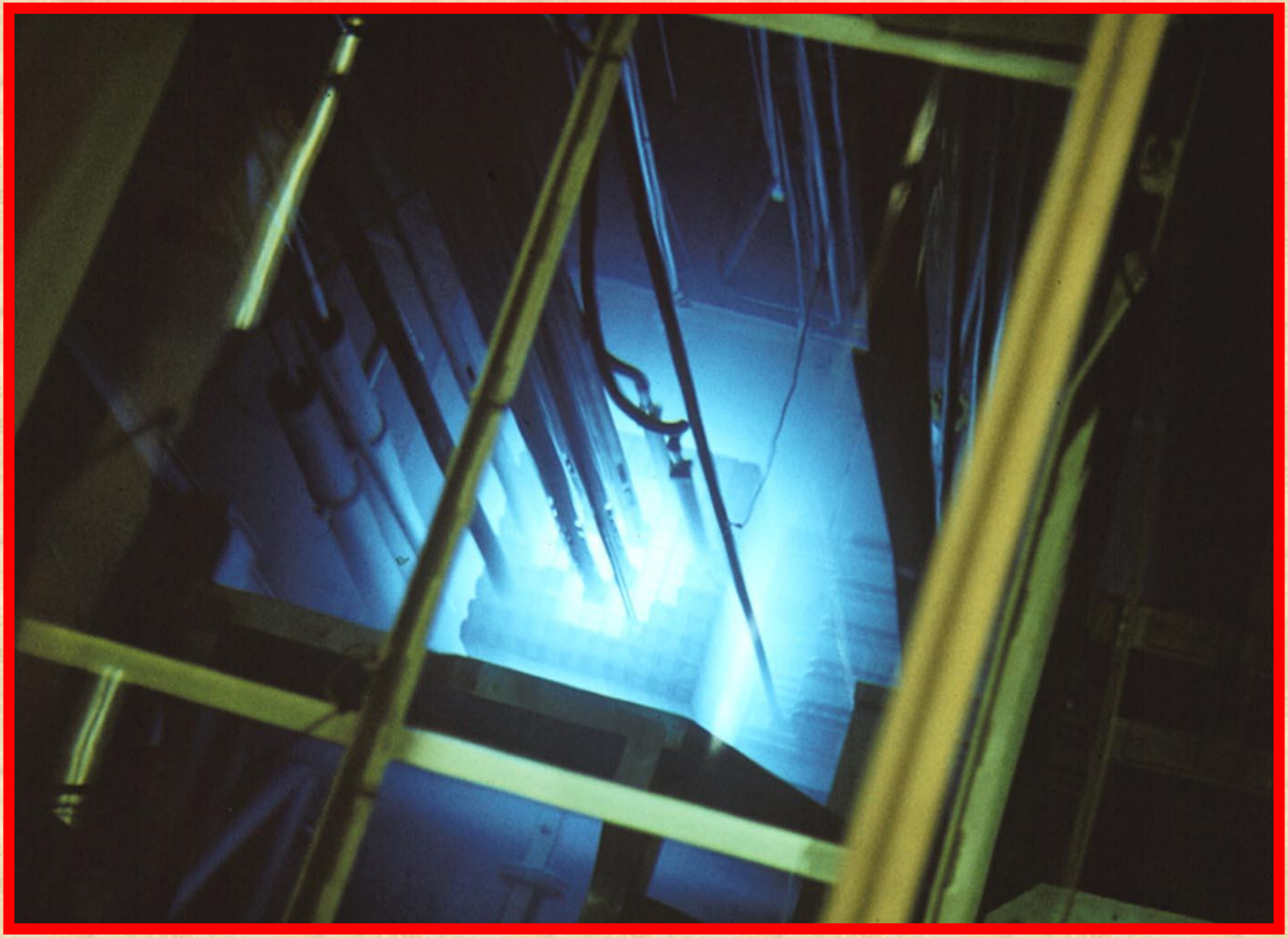






1946 Dec.25, first graphite miler in Moscow

Note: first A-Bomb 1945/1949, first atomic E-power station 1954



10 MW swimming pool reactor, Geesthacht (D)

Foto: G.Beyer, 1973

CONSTANTS and DIMENSIONS (1)

Radioactivity **1 Bq = 1 decay / sec**

old dimension *1 Ci = 3.7 10^{10} Bq*

1 kBq	=	10^3 Bq	= 27 nCi	1 nCi	=	37 Bq	=	1 ng ^{226}Ra
1 MBQ	=	10^6 Bq	= 27 µCi	1 µCi	=	37 kBq	=	1 µg ^{226}Ra
1 GBq	=	10^9 Bq	= 27 mCi	1 mCi	=	37 MBq	=	1 mg ^{226}Ra
1 TBq	=	10^{12}Bq	= 27 Ci	1 Ci	=	37 GBq	=	1 g ^{226}Ra

Atom **d ~ 10^{-10} m**

Nucleus **d ~ 10^{-14} m**

e-charge **e = 1.6021 10^{-19} C**

Cross section **1 barn (b) = 10^{-28} m^2**

CONSTANTS and DIMENSIONS
(2)

Specific Radioactivity =

Radioactivity / mass unit

[Bk / kg] or [Bq / Mol]

Radioactivity Concentration =

Radioactivity / volume unit

[Bk / cm^3]

CONSTANTS and DIMENSIONS (3)

DOSE = delivered Ion charges per mass unit

symbol: *J or X*

	1 C / kg	**=**	**1 A s / kg**
old:	1 R (Röntgen)	=	$0.258 * 10^{-3}$ C/ kg

Energy Dose (equivalent dose) symbol: D

	1 Gy (Grey)	**=**	**1 J / kg = 1 m^2 s^{-2}**
old:	1 Rad or Rem	~	0.01 Gy

Biological Dose (energy dose)

1 Sv (Sievert)	**~**	**0.01 R**
Dose Rate	**=**	**Dose per time unit**
1 mSv/h	**~**	**100 mR / h**

Radioactivity: Decay Law

$$A = \left(\frac{dN}{dt}\right)$$

(radio)activity = desintegrations per s

1 Bq = 1 desintergration/sec

$$A_o = \lambda N_o$$

$$N_t = N_o \cdot e^{-\lambda t}$$

$$A_t = A_o \cdot e^{-\lambda t}$$

$$\lambda = \ln 2 / t_{½}$$

N_o number of atoms at t = 0

N_t number of atoms at t

$t_{½}$ decay half time

A_o radioactivity in [Bq] at t = 0

A_t radioactivity in [Bq] at t

λ decay constant

Mother – Daughter Ratio

^{99}Mo (66 h) → ^{99m}Tc (6 h)

$N_1 \xrightarrow{\lambda_1 = 2.9\ 10^{-6}\ s^{-1}} N_2 \xrightarrow{\lambda_2 = 3.2\ 10^{-5}\ s^{-1}} N_{stab}$

if $\lambda_1 \ll \lambda_2$ than $A1 = A2$

(λ_1: t_1, $\ll$: $>>$, λ_2: t_2)

if $\lambda_1 <\sim \lambda_2$ than $A_2 = \frac{\lambda_1}{\lambda_2 - \lambda_1} \cdot A_1$

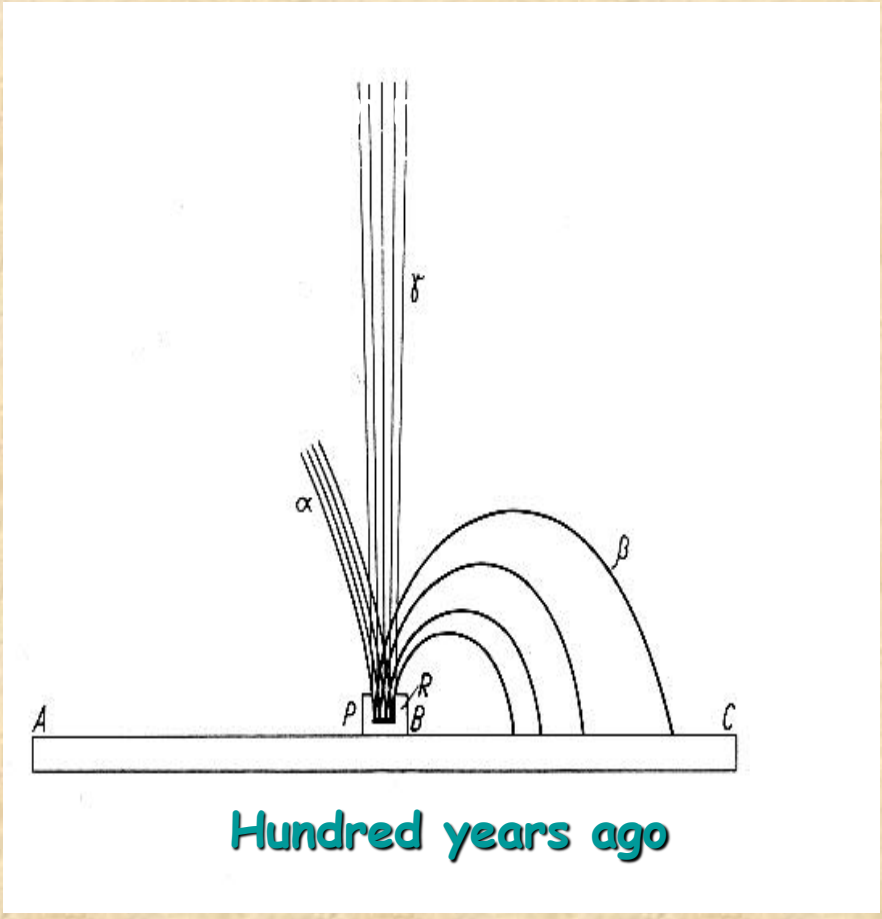
NOTE: In radioactive equilibrium: ^{99m}Tc is 10 % higher than ^{99}Mo!

But the ^{99}Mo decay goes only with 93 % into the ^{99m}Tc

RADIOACTIVITY

Marie Curie (1867 – 1934)

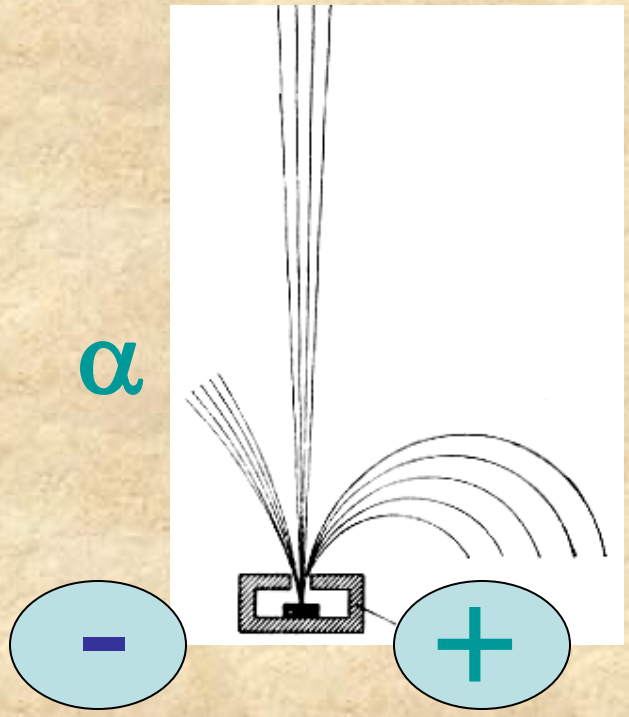
Pierre Curie (1859 – 1906)

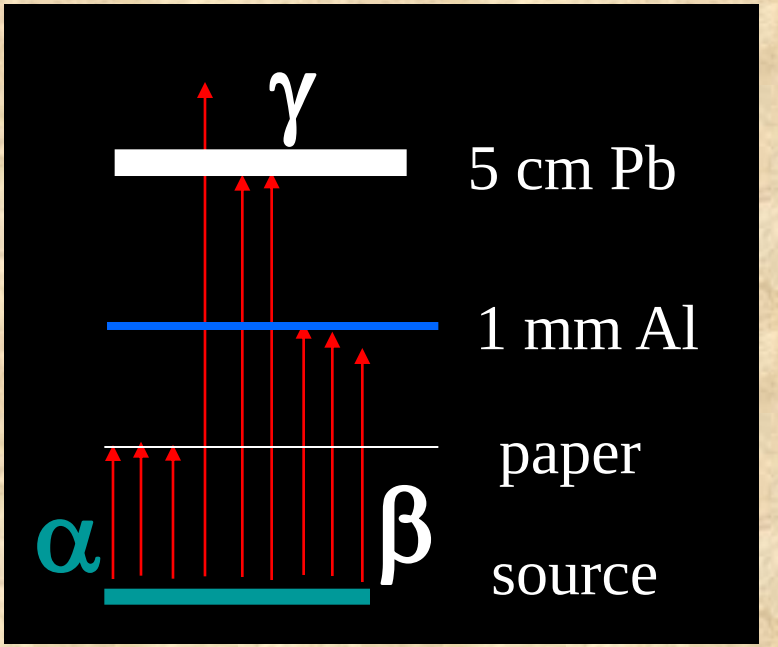


Hundred years ago

RADIOACTIVITY

The radiation characteristics of an isotope determines where and how it can be used in medicine





DECAY MODES

		Energy	Range in water / Pb	
ß$^-$, ß$^+$		~ 0.2 – 4 MeV	~ 1 cm	
EC, X-ray	f(Z)	Fe: 7 keV	$d_{1/2}$ ~ 1 mm	
		Ra: 100 keV	$d_{1/2}$ ~ 4 cm	
α		4 - 8 MeV	28 – 80 µm	
γ		50 keV	$d_{1/2}$ ~ 3 cm	0.01 mm
		140 keV	**$d_{1/2}$ ~ 5 cm**	**0.4 mm**
		1 000 keV	$d_{1/2}$ ~ 10 cm	1 cm
		2 000 keV	$d_{1/2}$ ~ 15 cm	1.5 cm
conversion electrons		Eγ - Ee	~ mm range	
Auger electrons			~ µm range	
IT		like γ		

exotic decay modes, spontaneous fission

1946, June 14

Nuclear Medicine's modern era began

Availability of Radioactive Isotopes,

Announcement from Headquarters, Manhatten Project, Washington D.C.:

Production of tracer and therapeutic radioisotopes has been heralded as one of the greatest peacetime contributions of the uranium chain-pile. This use of the uranium pile will unquestionably be rich in scientific, medical, and technological application.

On 1.Aug.1946 the Atomic Energy Act
passed the congress,
releasing radioisotopes from military control.

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Imaging with Radiotracers

Gerd-Jürgen BEYER
Prof.Dr.rer.nat.habil.
Cyclotron Unit, University Hospital of Geneva, Switzerland
GSG-Int. GmbH, Switzerland
gerd.beyer@cern.ch
gerd.beyer@gsg-int.com

Lecture
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Joint University Accelerator School
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ISOTOPES IN MEDICINE

DIAGNOSIS

in vitro

^{14}C

^{3}H

^{125}I

others

in vivo

^{99}Mo-^{99m}Tc

^{201}Tl

^{123}I

^{111}In

^{67}Ga

^{81}Rb-^{81m}Kr

others

ß$^{+}$ emitters for PET

^{18}F, ^{11}C, ^{13}N, ^{15}O

^{86}Y, ^{124}I, ^{64}Cu

^{68}Ge - ^{68}Ga

^{82}Sr - ^{82}Rb

^{44}Ti - ^{44}Sc

THERAPY

internal

systemic

^{131}I, ^{90}Y

^{153}Sm, ^{186}Re

^{188}W-^{188}Re

^{166}Ho, ^{177}Lu, others

α-emitters:

^{225}Ac-^{213}Bi

^{211}At, ^{223}Ra

^{149}Tb

e^{-}-emitters:

^{125}I

sources

sealed sources

^{192}Ir, ^{182}Ta, ^{137}Cs

many others

needles for brachytherapy:

(^{103}Pd), ^{125}I

many others

stands

^{32}P and others

seeds

^{90}Sr or ^{90}Y, others

applicators

^{137}Cs, others

external

tele radio

^{60}Co

gamma knife

^{137}Cs

blood cell irradi-ation

G.J.BEYER, Geneva, 2011

THE TRACER PRINCIPLE 1923

G.V.Hevesy:
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Biochem.J. **17**, 439 (1923)

Measurements of the tracer's Radioactivity provided thousand fold increases in sensitivity and accuracy over existing chemical assays. The foundation and basic rationale of much of Hevesy visualized that **a radioactive atom might be used as a "representative" tracer of stable atoms of the same element** whenever and wherever it accompanied them in biological systems.

1943 Nobel Prize Chemistry

the father of Nuclear Medicine

NUCLEAR MEDICINE = in vivo APPLICATION of RADIOTRACERS

1923 First tracer study with $^{210}Pb/^{210}Bi$ G.Hevesy

1925 ^{214}Bi arm-to-arm circulation time, H.Blumgart

1935 ^{32}P renewal of mineral constituents of bone, O.Chieivitz & G.Hevesy

1937 dynamics of sodium transport in vivo, J.G.Hamilton

1937 ^{128}I, thyroid physiology, R.Hertzs, A.Roberts, R.Evans

1938 ^{131}I discovered by G.T.Seeborg, 1939 first diagnostic use J.G.Hamilton et al.

1947 ^{131}I –Fluorescine, 1950 ^{131}I –HSA, 1955 ^{131}I-rose bengale & hippurane, …

1957 ^{99}Mo-^{99m}Tc generator (1960 first sale), ^{133}Xe for lung ventilation

1969 ^{67}Ga accumulation in cancer, C.L.Edwards

1970 Instant KIT's for ^{99m}Tc

1973 ^{201}Tl, ^{123}I, ^{111}In, many other isotopes and tracer compounds

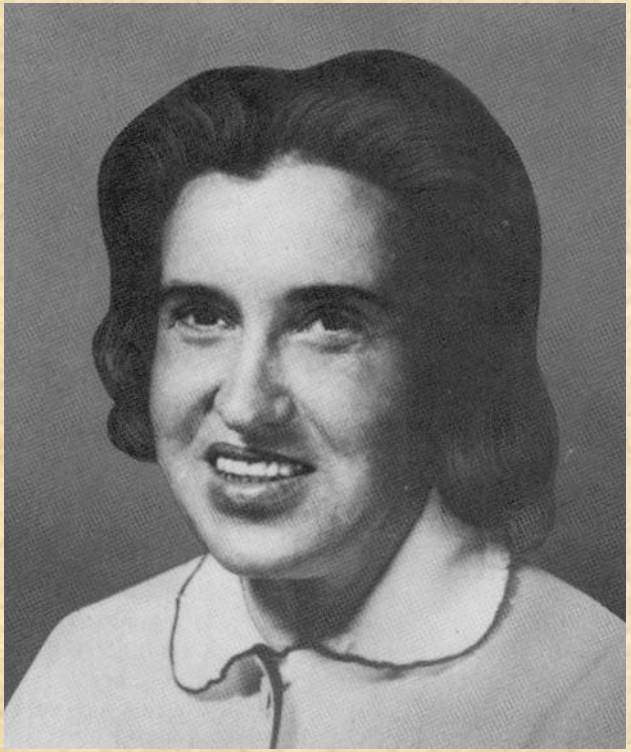
1978 first ^{18}FDG PET scan

> 30 million individuals receive every year a radiotracer for diagnosis

ISOTOPES in MEDICINE

Application	Requirement	Isotope
DIAGNOSIS in vitro	**$T_{½}$ = long biogenic behavior**	**^{3}H, ^{14}C ^{125}I**
DIAGNOSIS In vivo SPECT	single photons no particles biogenic behavior $T_{½}$ = moderate	^{99m}Tc, ^{123}I, ^{111}In, ^{201}Tl,
DIAGNOSIS in vivo PET	$ß^{+}$-decay mode biogenic elements $T_{½}$ = short	^{11}C, ^{13}N, ^{15}O, ^{18}F

Diagnostic in vitro RIA



Rosalyn S.YALOW **S.A.BERSON**

Nobel Prize 1977

Introduced the radioimmunoassay (RIA)

assay for insulin based on the principle of competitive binding by antibody of natural and radioactive labeled hormone)

ISOTOPES in MEDICINE

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DIAGNOSIS **in vivo** **PET**	$ß^{+}$-decay mode biogenic elements $T_{½}$ = short	**^{11}C, ^{13}N, ^{15}O, ^{18}F**

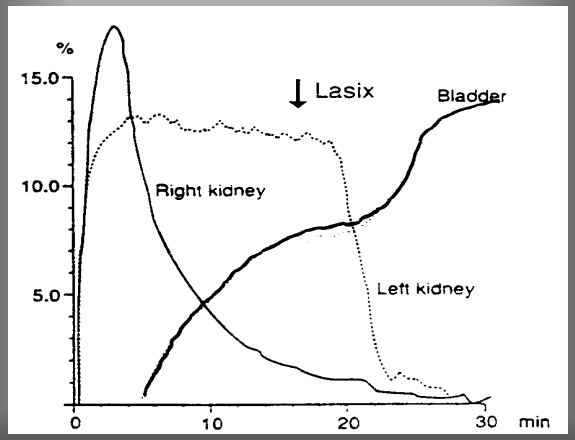
Photo published 1942

J.G.Hamilton, M.H.Soley:

"Studies of **iodine** metabolism by thyroid in situ"

1940, Am.J.Physiol. **131**, 135

Kidney Isotope Nephrogram



How it began – the detection systems

1951

1958

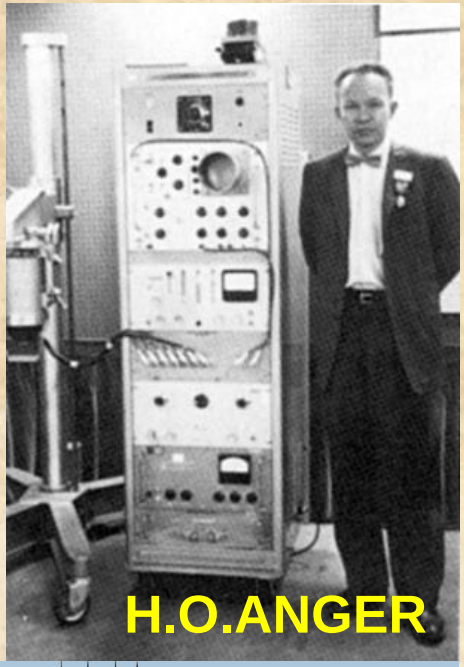
1951: SCANNER

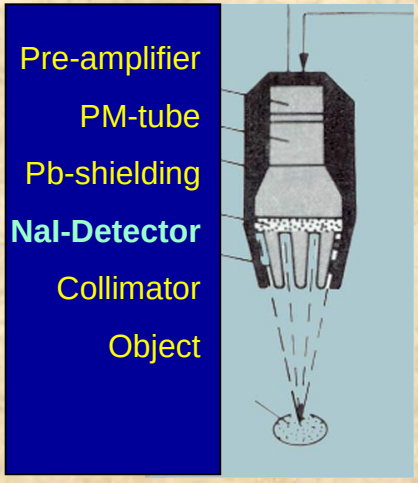
The scanner was designed for 131-I

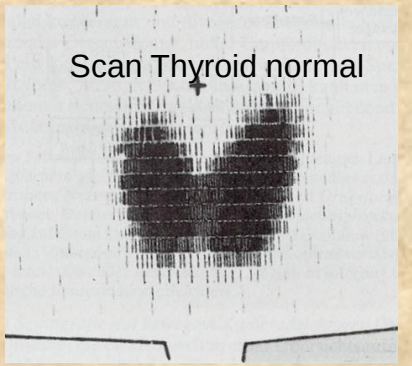
1958: GAMMA CAMERA

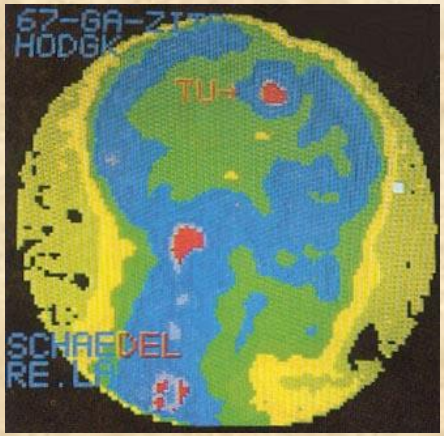
The camera is „taylor-made“ for 99m-Tc

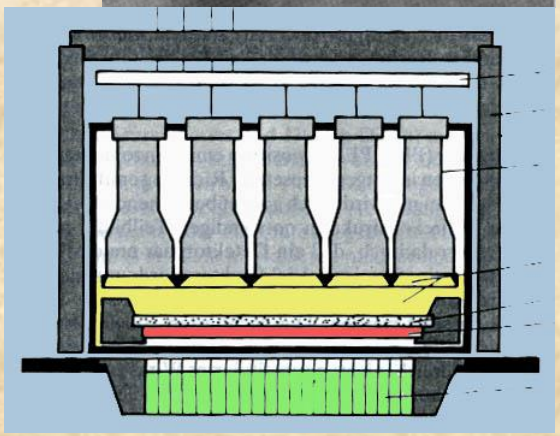
The basic concept of the gamma camera remained without major changes and represents today the basic principles for all SPECT instrumentation.





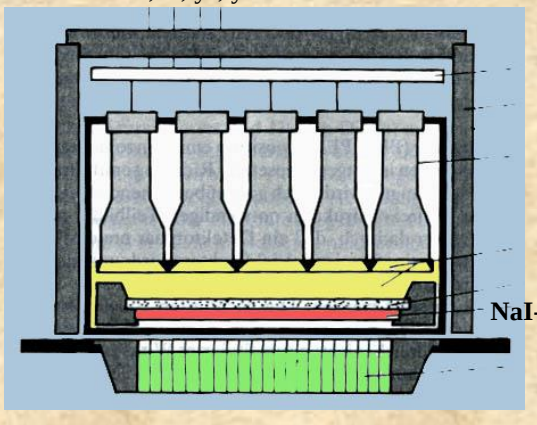




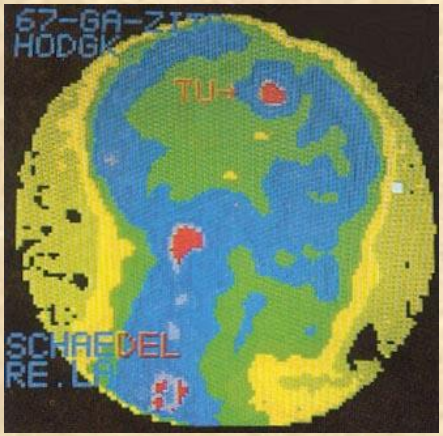


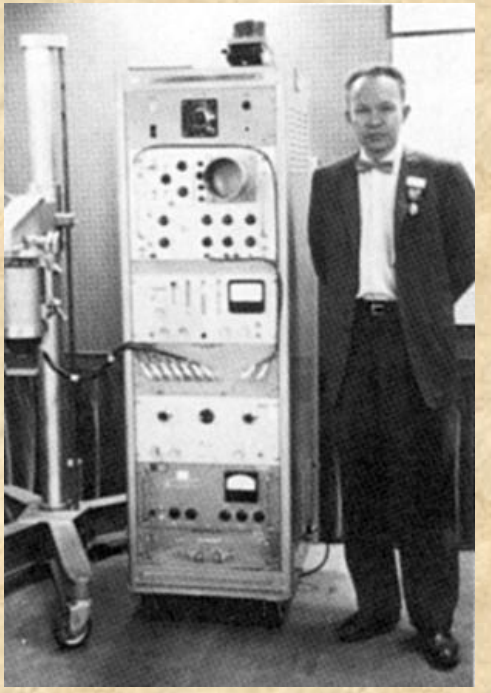
GAMMA CAMERA

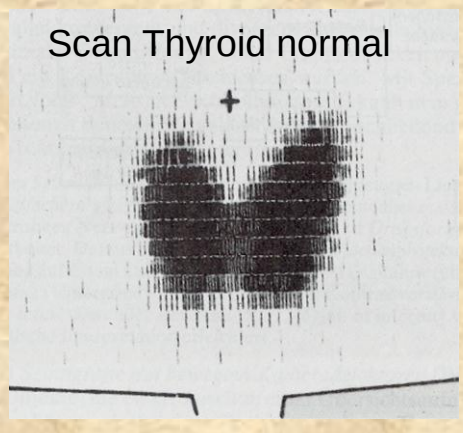
H.O.ANGER



1958 Planar scintigram

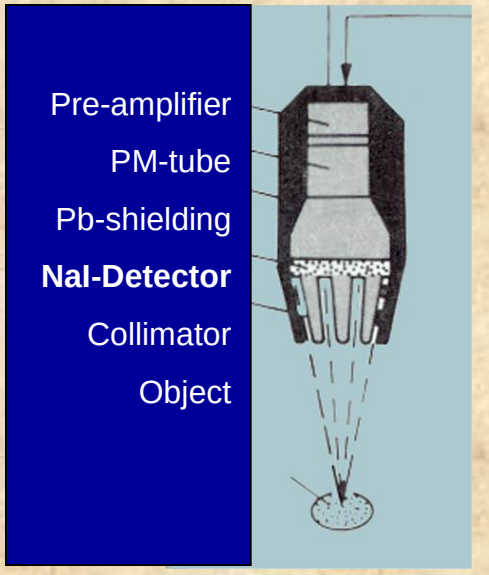






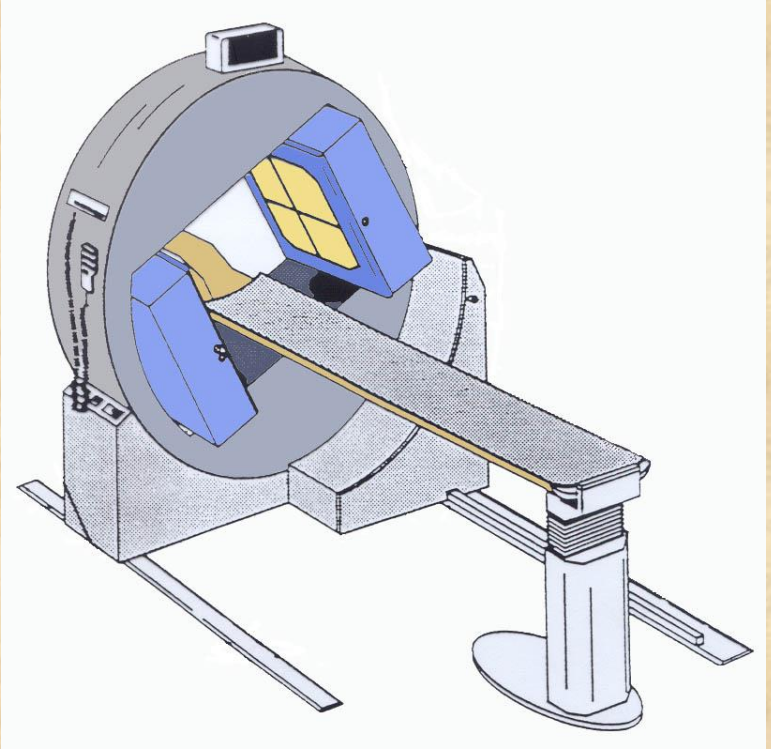
B.CASSEN

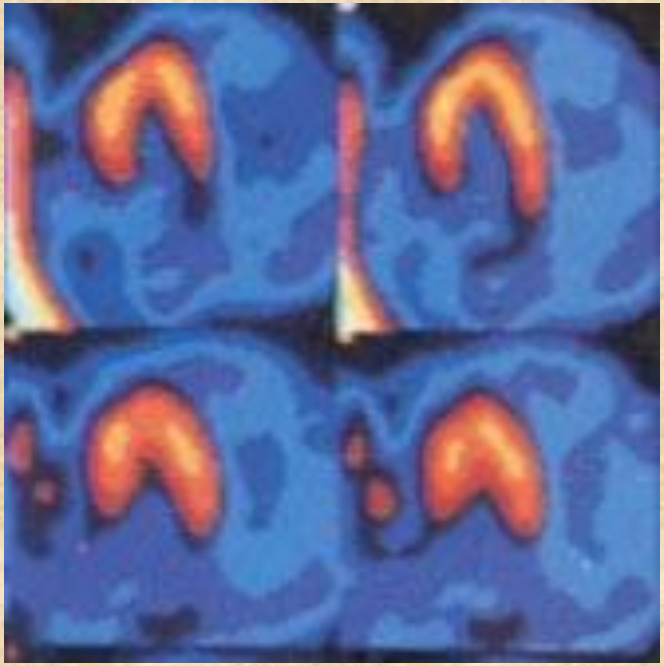
SCANNER



SPECT

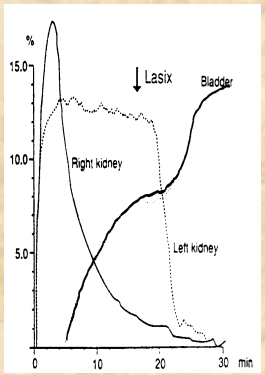
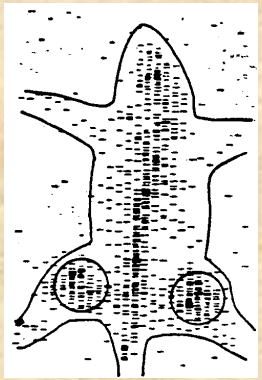
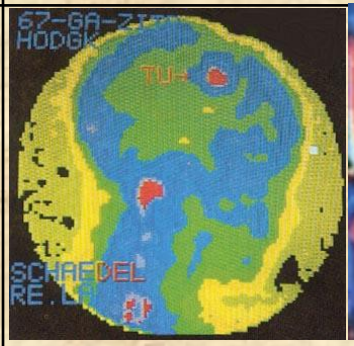
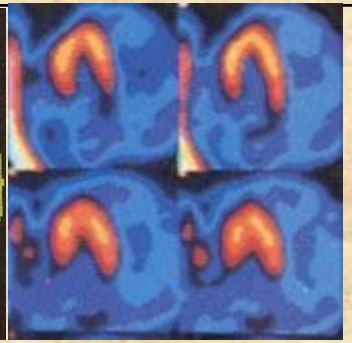
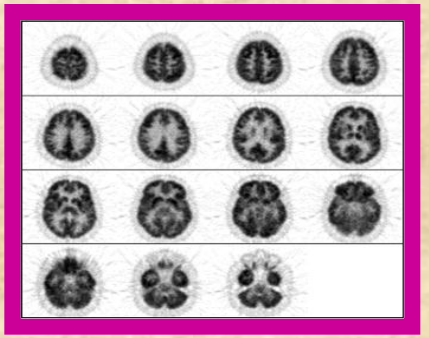
Single Photon Emission Computed Tomography

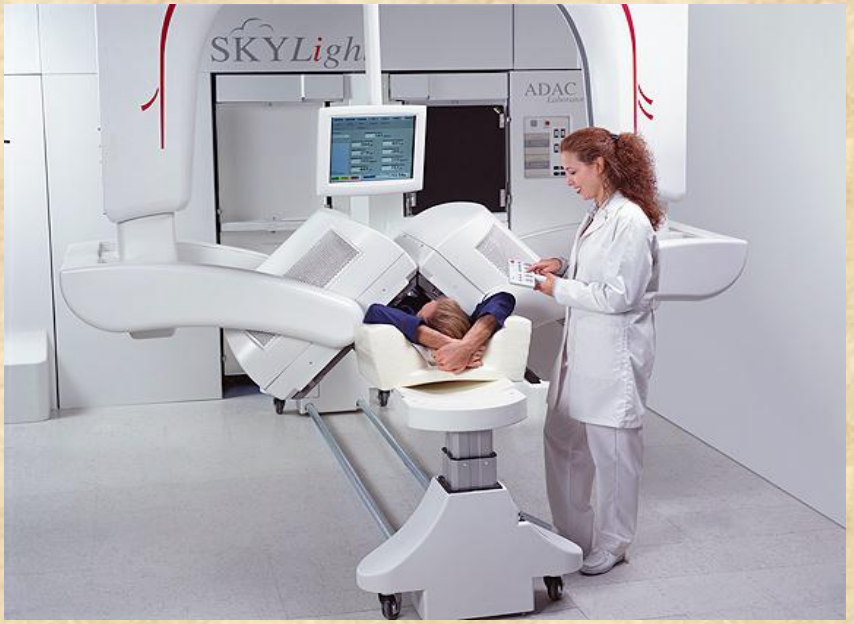




1984 **^{99m}Tc DMPE**

Nuclear Medicine Instrumentation

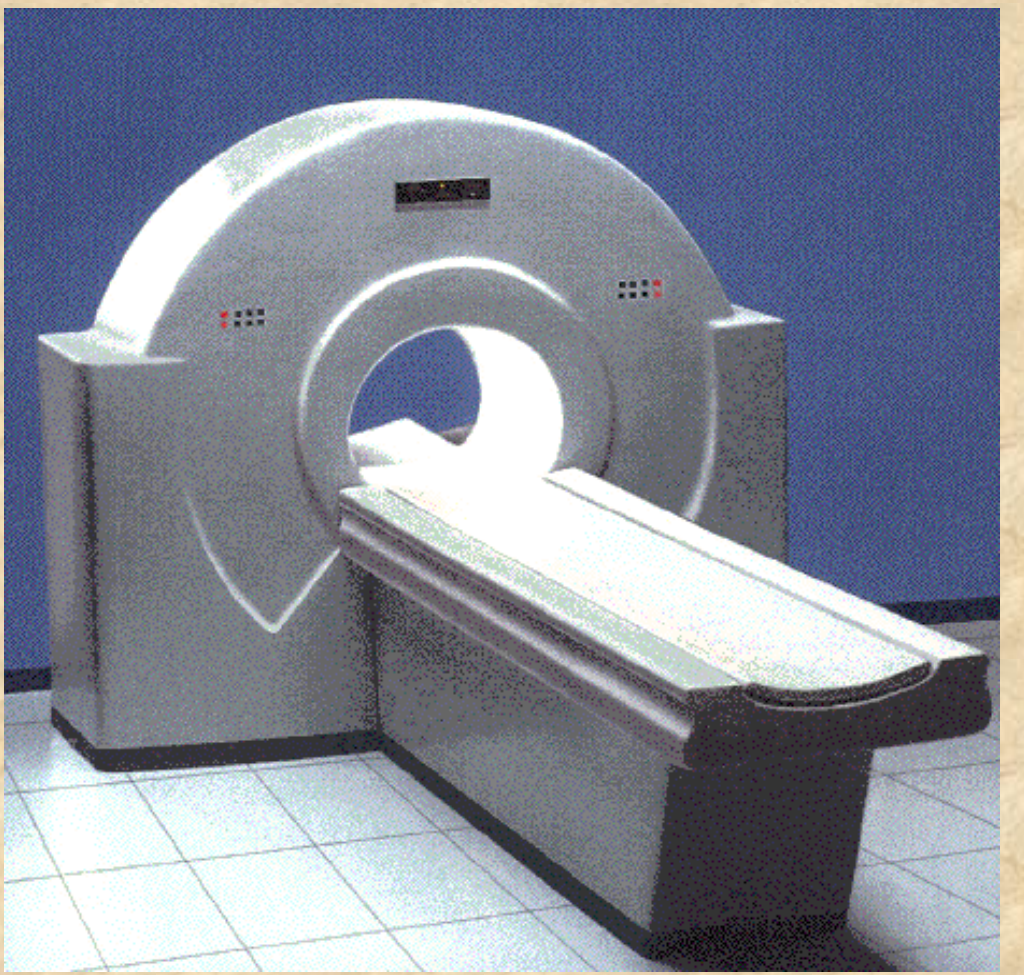
Point sensitive	**DETECTOR's are**	combined
stationary moving	Place sensitive	
Point collimator	stationary moving	with / without septa
	multi-hole collimatuers	
single detector	NaI + many PM's	Multi-ring systems
GM / NaI -PM NaI-PM	single head 1-3 heads	Block detectors BGO
Probe Scanner	**γ-Camera SPECT**	**PET**
 	 	
	^{67}GaCIT ^{99m}Tc DMPE	
1 D dynamic **2 D static**	**2 D dynamic** **3 D dynamic**	**2 D and 3 D dyn.& quantitative**

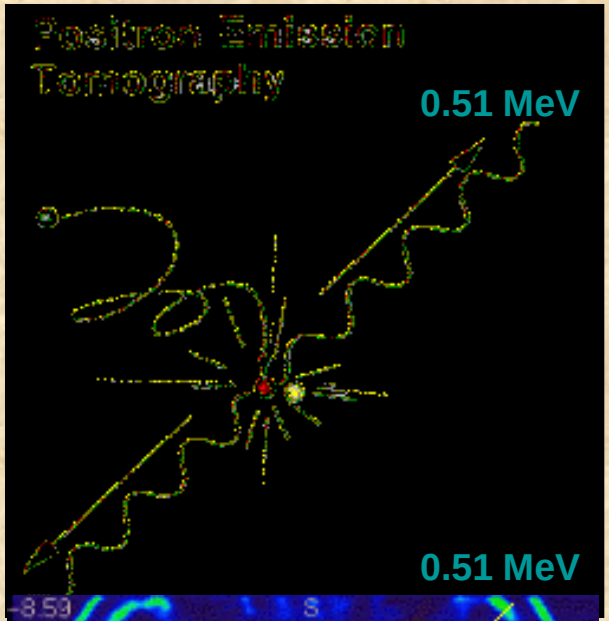


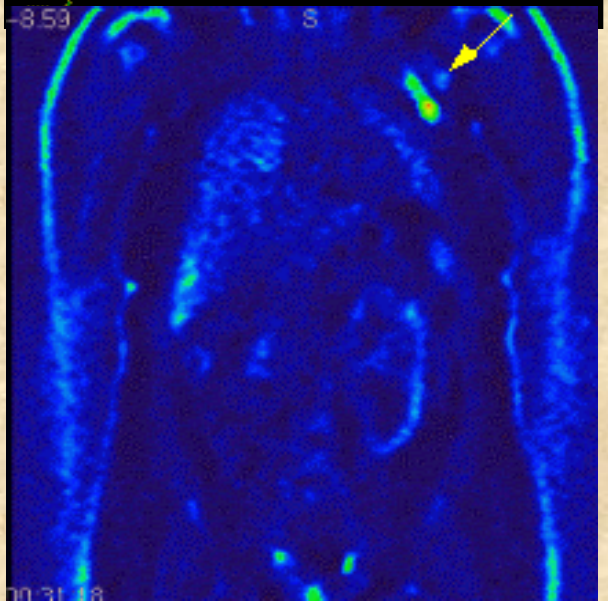
Modern SPET Cameras

(GE Medical Systems)

PET = Positron Emission Tomography







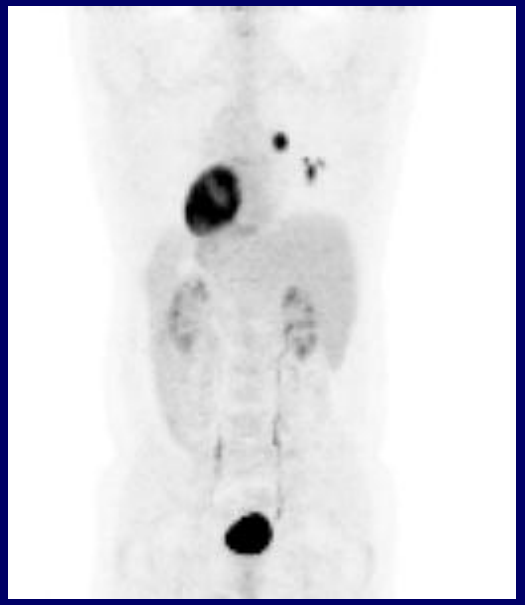
The Power Behind PET.

SIEMENS

3D whole-body PET

ECAT HR+

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



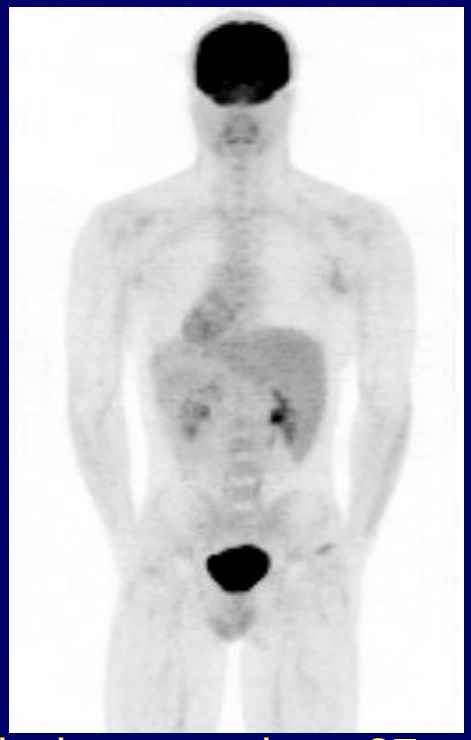
Emission scan time: 54 min
Transmission scan time: 18 min

Data courtesy of
Kettering Memorial Hospital, Kettering, USA

year 2000

ECAT ACCEL

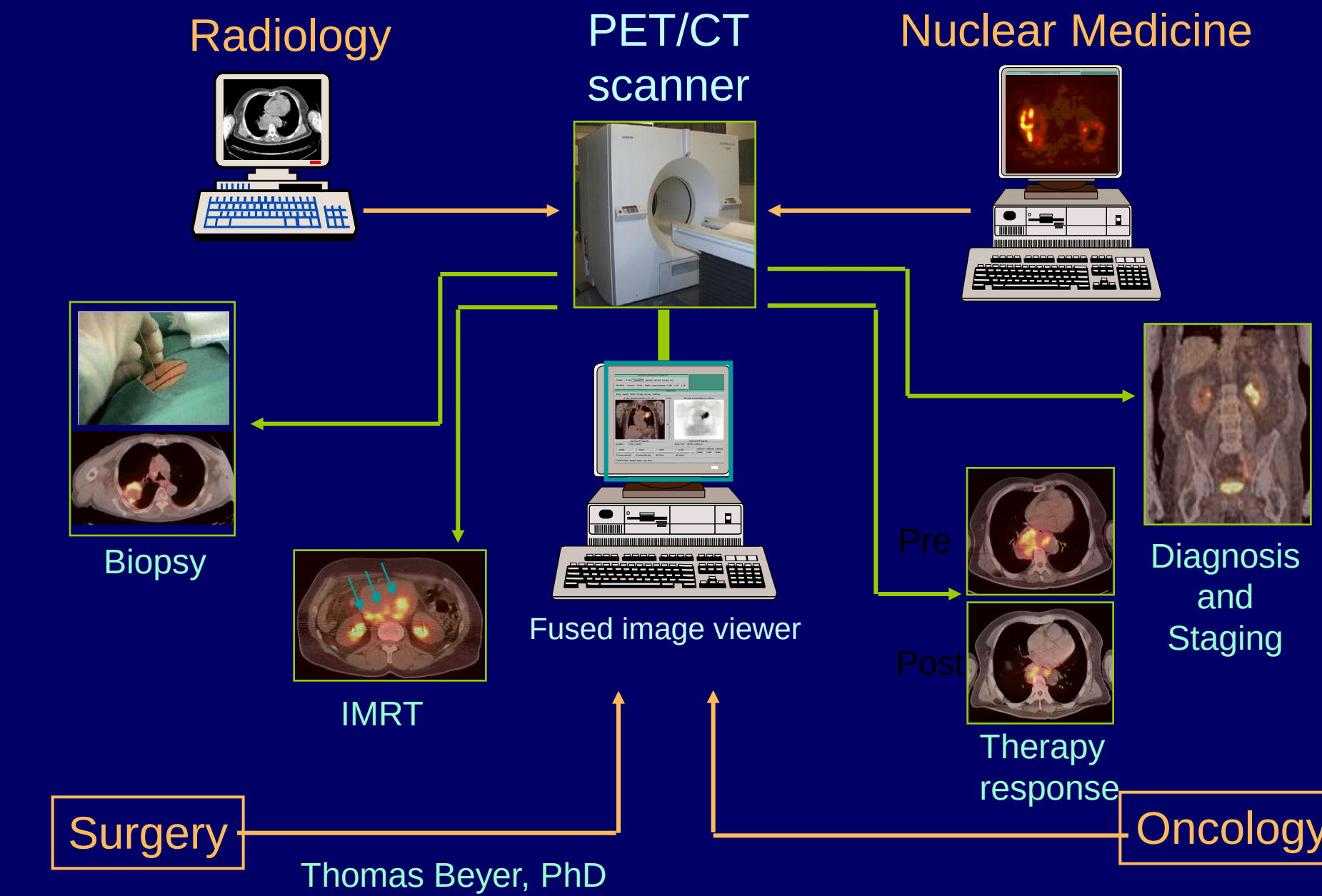
50 year-old male with colon CA
91 kg, 183 cm, 720 MBq FDG, 162 min p.i.



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

Data courtesy of
NC PET Imaging Center, Sacramento, USA

Fused Image Tomography



Thomas Beyer, PhD

PET/CT concepts 1998-2000


RSNA 1999


SNM 2000


RSNA 2000

RSNA 2000

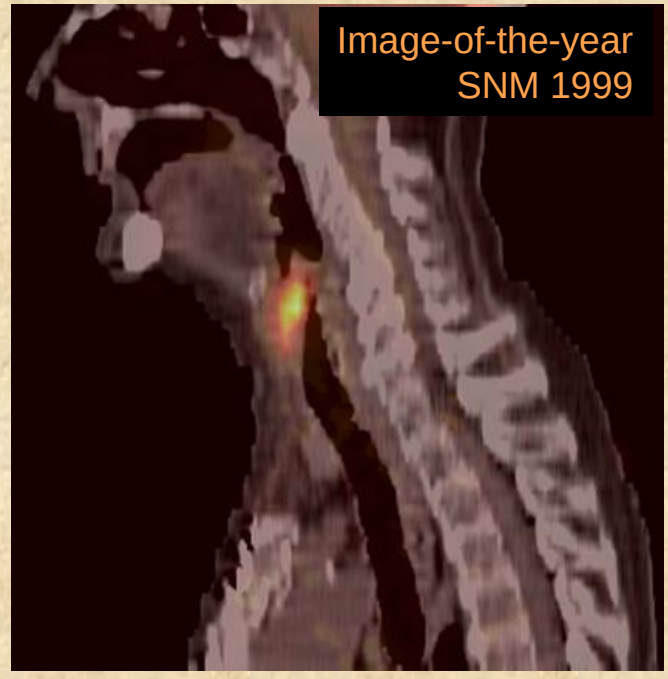
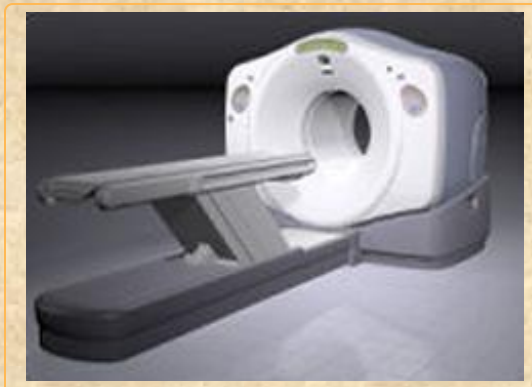


Image-of-the-year
SNM 1999

^{18}FDG-PET/CT of a patient w/ ENT

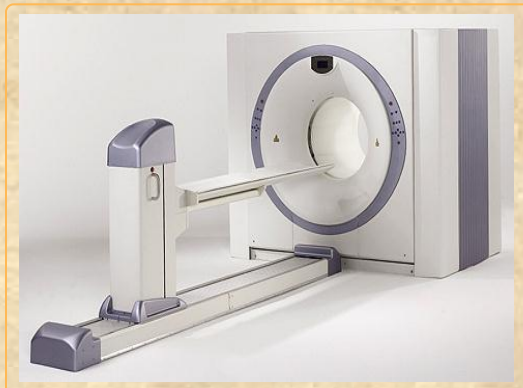
TIME, 04-Dec-2000

PET/CT today

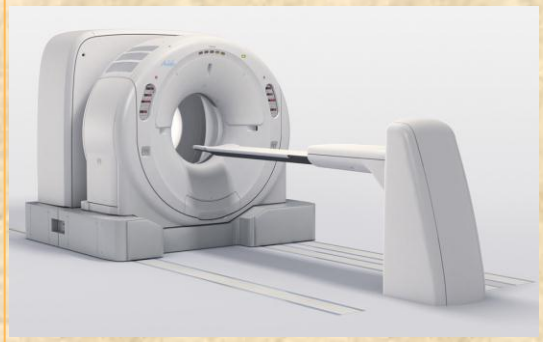


Discovery ST, STE, RX

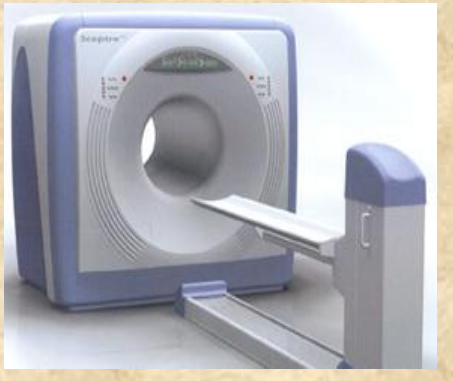
Gemini GXL, TF



Biograph HiRez, TruV



Aquiduo



Sceptre P3

AnyScan PC

Trend: New PET components in combination w/ high-performance CT

PET/CT 2009: routine application

Oncology

35 y/o M w/ malignancy in mandibula

Feb: ^{18}FDG-PET/CT identified disease

Mar: right mandibulectomy and maxillectomy

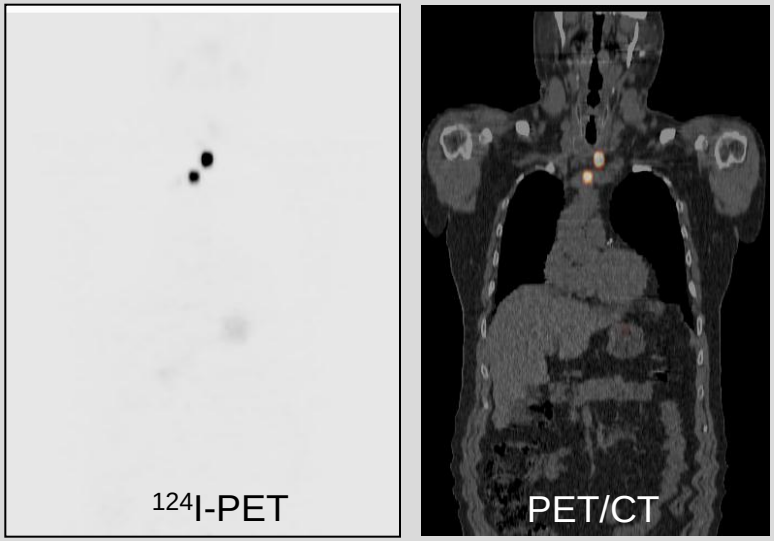
Jun: PET/CT identified recurrent disease

Jun: Extensive surgery

Oct: PET/CT showed recurrent disease

UPMC, Pittsburgh

Oncology - Specific tracer



45 y/o M w/ papillary thryorid CA (pT4)

^{124}I-PET/CT

→ mediastinal LN metastasis w/o CT correlate

UH Essen-Duisburg

Anatomy
CT-based AC

Anatomy
CT-based AC

Structure without function is a corpse,
… function without structure is a ghost.

Stephen Wainwright, Duke Dept Biology

RADIOISOTOPES in MEDICINE:

Requirements - Production - Application and Perspectives

3

Medical Isotope Production

Gerd-Jürgen BEYER
Prof.Dr.rer.nat.habil.
Cyclotron Unit, University Hospital of Geneva, Switzerland
GSG-Int. GmbH, Switzerland
gerd.beyer@cern.ch
gerd.beyer@gsg-int.com

Lecture
JUAS
Joint University Accelerator School
Archamps (France) March 08, 2012

NUCLEAR MEDICINE 2009

DIAGNOSIS

SPECT (SINGLE PHOTON EMISSION TOMOGRAPHY)

- → ^{99m}Tc still working horse
- → Increase of diagnostic value
- → New radiopharmaceuticals
- → New instrumentation & quantification

PET became a clinical tool

- → [^{18}F] FDG is the working horse
- → **ONCOLOGY (80 %)**
- → Neurology
- → Cardiology

PET is a powerfull R&D tool

- → clinical research
- → Drug development
- → invivo biochemistry

Multi-Modality Imaging

- → SPECT - PET
- → PET – CT, SPECT - CT
- → PET – MRI
- → Animal PET-CT, SPECT-CT, PET-MRI

Molecular Imaging

THERAPY (RIT)

New Approaches in Radionuclide Therapy

- → free chelates (EDTMP, others)
- → bio-selective antibody conjugates (mab)
- → bio-specidfic peptide conjugates
- → Lyposomes
- → Nanoparticles
- → others

New Radionuclides for Therapy:

- → Beta-Emitters with different energies
- → Alpha emitters
- → Auger electron emitters
- → Research isotopes

PET for individual invivo dosimetry

- → Quest for metallic positron emitters
- → longer lived positron emitters
- → PET imaging with „durt“ isotopes
- → Simmulatne Multi-tracer studies

G.BEYER (ITD, Geneva, 2010)

ISOTOPES IN MEDICINE

DIAGNOSIS

in vitro

^{14}C

^{3}H

^{125}I

others

in vivo

^{99}Mo-^{99m}Tc

^{201}Tl

^{123}I

^{111}In

^{67}Ga

^{81}Rb-^{81m}Kr

others

ß$^{+}$ emitters for PET

^{18}F, ^{11}C, ^{13}N, ^{15}O

^{86}Y, ^{124}I, ^{64}Cu

^{68}Ge - ^{68}Ga

^{82}Sr - ^{82}Rb

^{44}Ti - ^{44}Sc

THERAPY

internal

systemic

^{131}I, ^{90}Y

^{153}Sm, ^{186}Re

^{188}W-^{188}Re

^{166}Ho, ^{177}Lu, others

α-emitters:

^{225}Ac-^{213}Bi

^{211}At, ^{223}Ra

^{149}Tb

e^{-}-emitters:

^{125}I

sources

sealed sources

^{192}Ir, ^{182}Ta, ^{137}Cs

many others

needles for brachytherapy:

(^{103}Pd), ^{125}I

many others

stands

^{32}P and others

seeds

^{90}Sr or ^{90}Y, others

applicators

^{137}Cs, others

external

tele radio

^{60}Co

gamma knife

^{137}Cs

blood cell irradi-ation

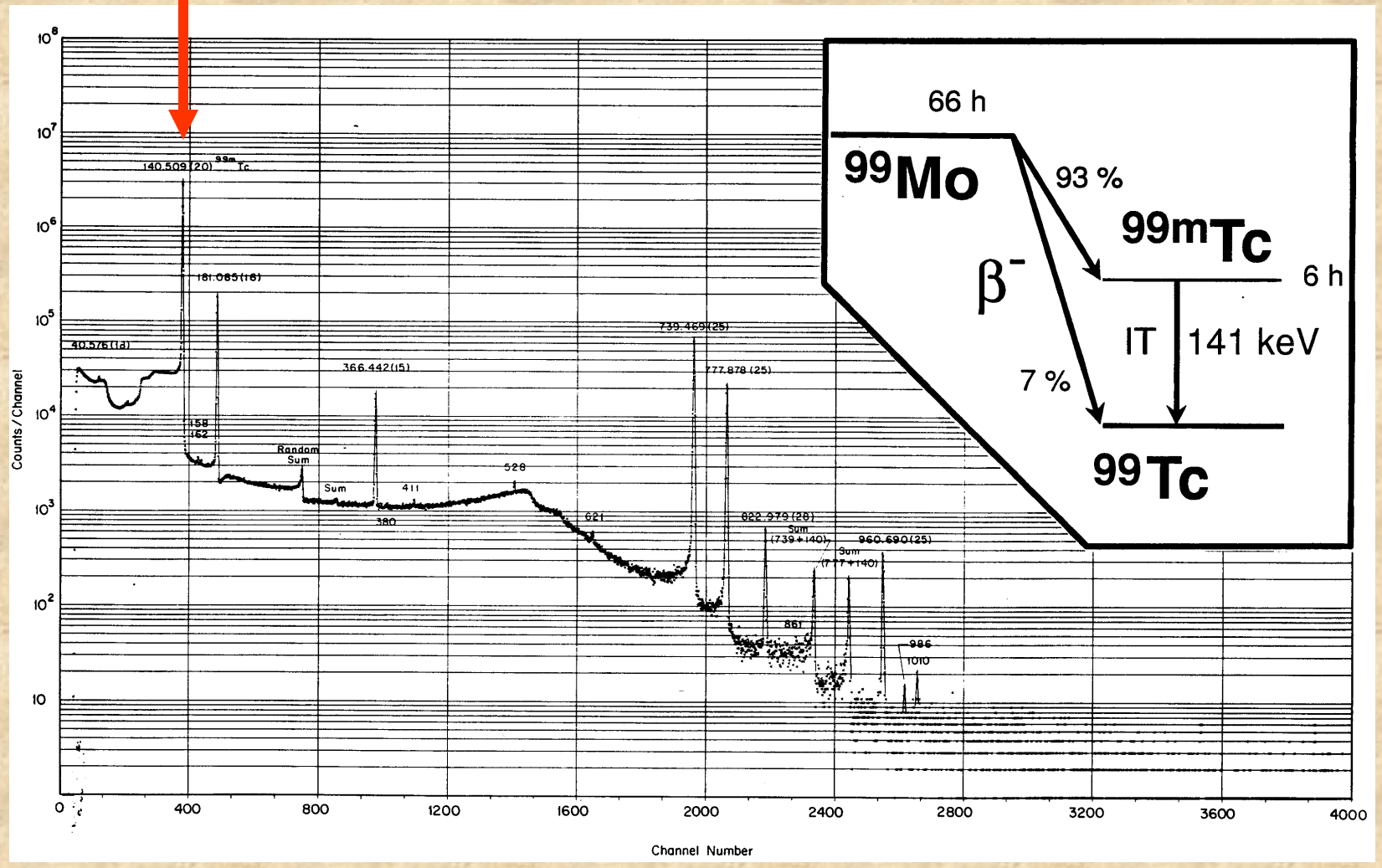
G.J.BEYER, Geneva, 2011

Why 99m-Tc

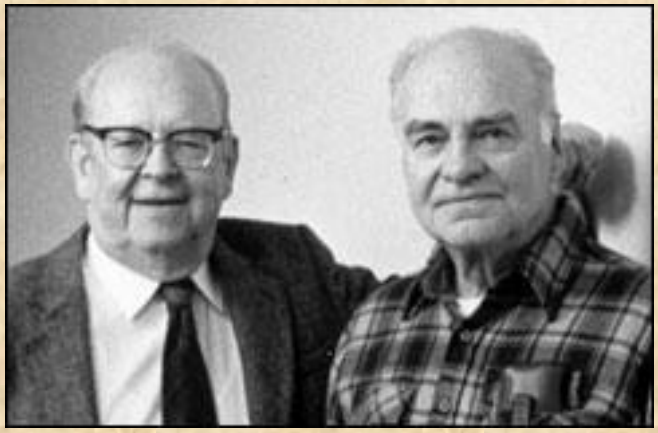
Three Aspects:

1. Nuclear properties
2. Generator principle (availability)
3. Sn(II) as reducing agent opened the door for KIT Technology

141 keV photons - the strength of ^{99m}Tc



Discovery of ^{99m}Tc generator in 1957 in BNL



^{99m}Tc detected while refining ^{132}I from ^{132}Te → ^{99}Mo-^{99m}Tc generator → Stang, Tucker, Greene,

Richards

BNL declined to file a patent for this device - ^{99m}Tc generator!

BNL memo in 1958:

"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."

Slide from Ramamoorthy, IAEA Vienna

Sn(II) as reducing agent

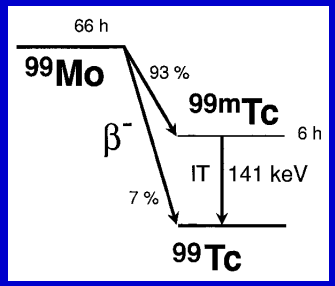
1962: The 99-Mo / 99m-Tc Generator introduced into clincal practice:
Harper P.V., G.Autors, K.A.Latrhrop, W siemens, L Weiss:
Technetium-99m as a biological tracer, J.Nucl.Med. **3** (1962) 209

1969: **Introduction of Sn(II) as reducing agent:**

Dreyer R. & Muenze R. (Dresden, Germany);
Markierung von Human Serum Albominw with 99m-Tc
Wiss.Z.K-Marx Uni Leipzig Nat.Wiss.R. **18** (1969) 629-633
Zur Tc-99m-Markierung von Serumalbumin; Isotopenpraxis **5** (1969) 296

2009: **Eckelmann W.C.:** JACC cardiovascular Imaging **2**, (2009) 364-368:

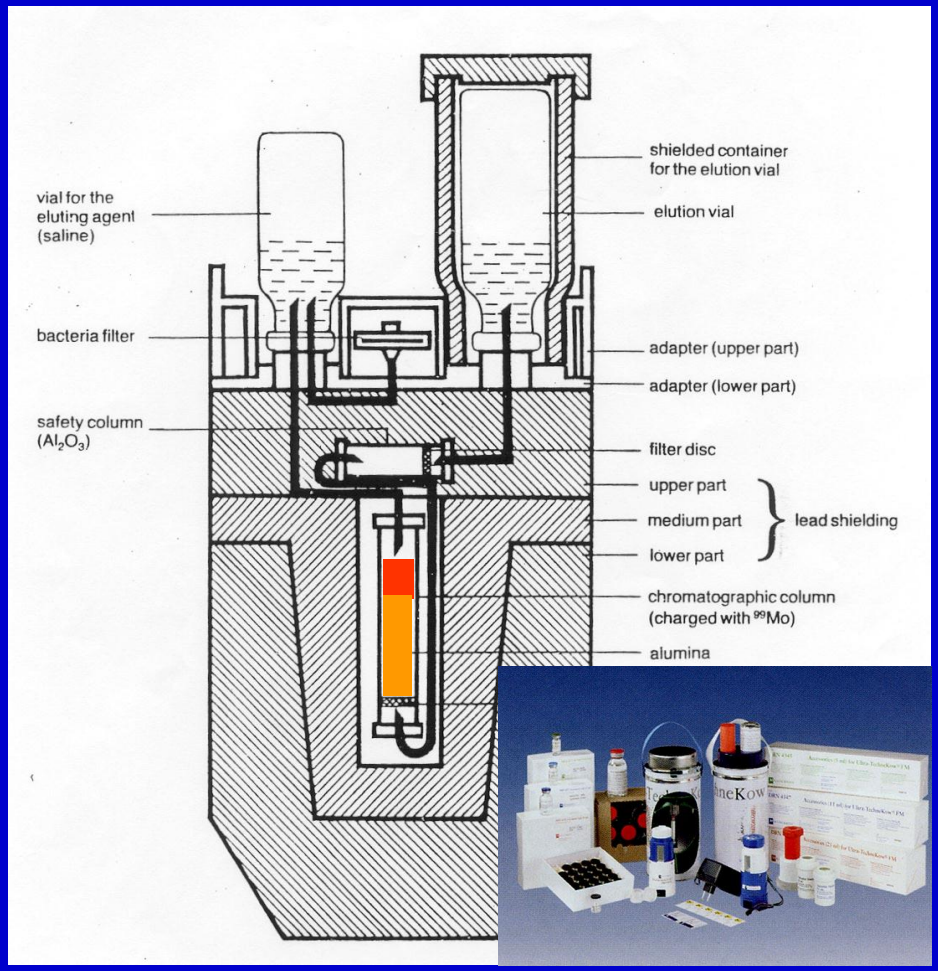
"…On a practical level, the use of stannous ion was a key development and current radiopharmaceutical kits employ the stannous reduction technique. With the advent of the Mo-99/Tc-99m generator in the 1960s followed by the development of "instant" kits, the use of Tc-99m–labeled compounds expanded rapidly"



$^{99m}TcO_4^-$

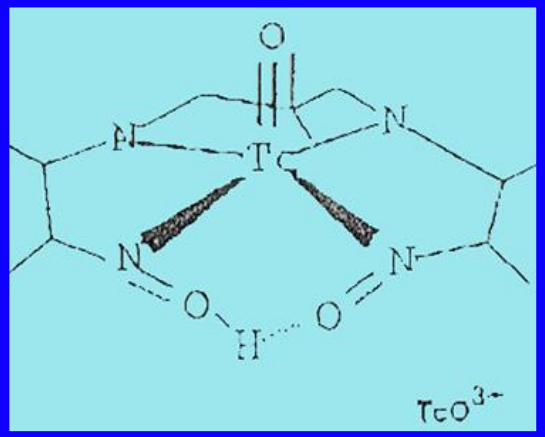
0.9 % NaCl solution

+

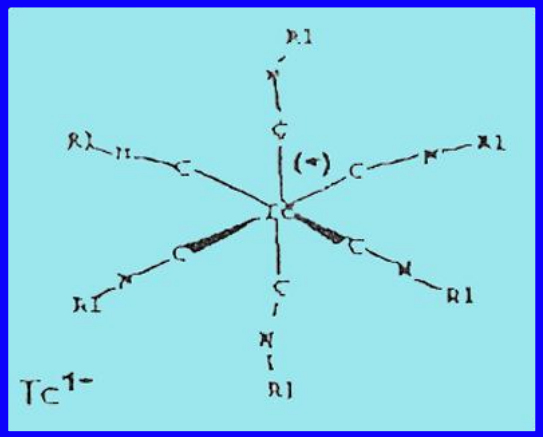


many different ^{99m}Tc-tracer for imaging of many different organ and tissue functions

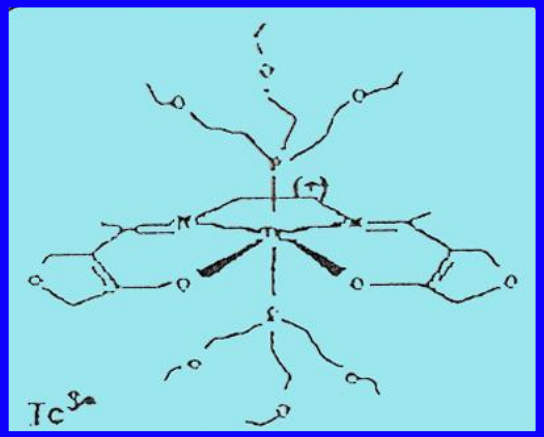
^{99m}Tc Perfusion Tracers



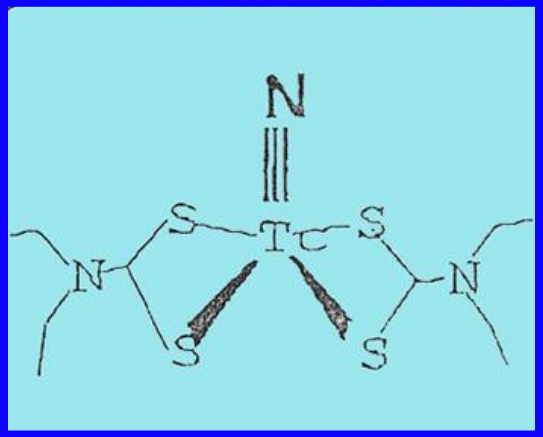
Tc-HMPAO



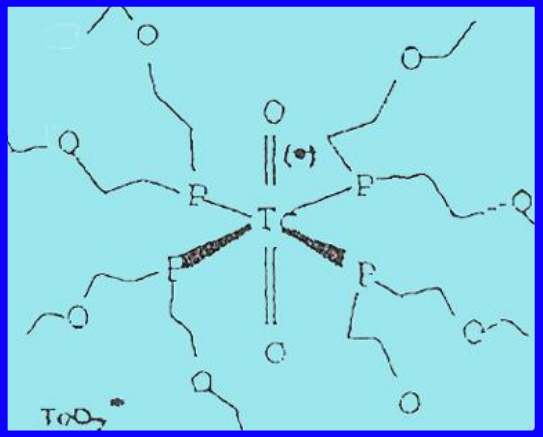
Tc-MIBI



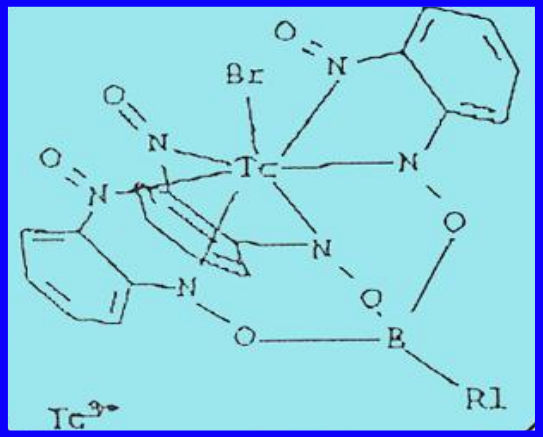
Tc-O12



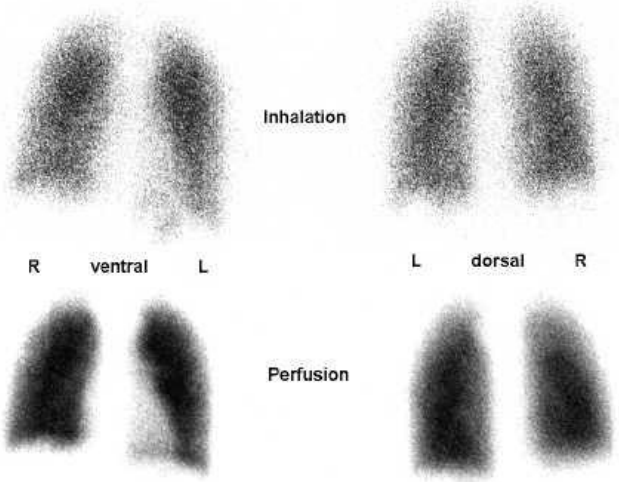
Tc-NOEt



Tc-P53



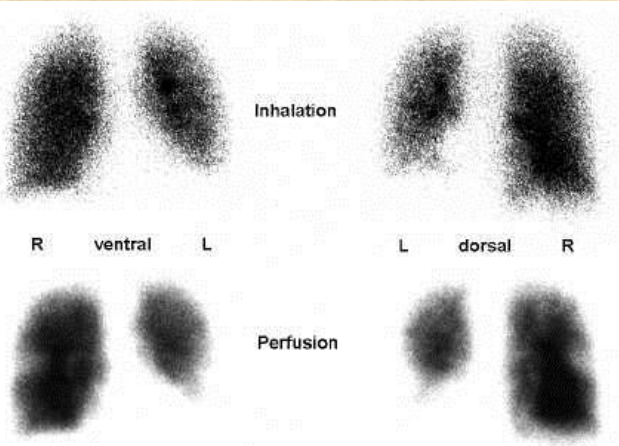
Tc-BATO



Ventilation study

LUNG Function

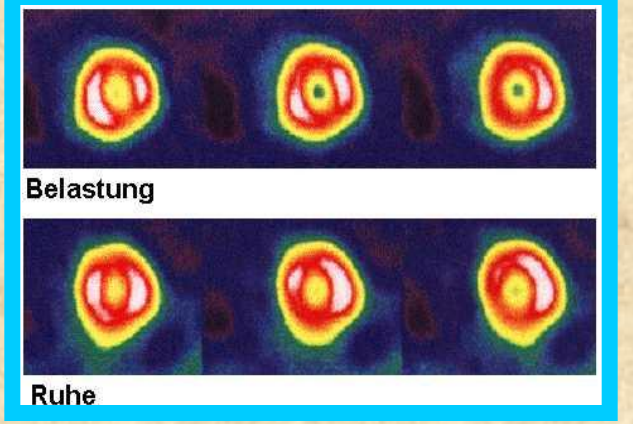
Perfusion Study



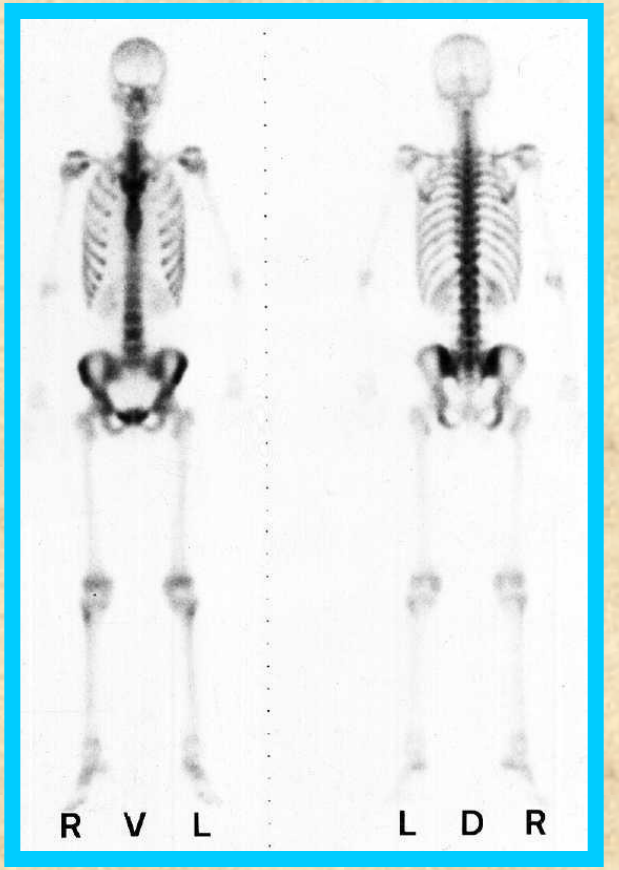
^{99m}Tc TRACER

Examples

HEART Perfusion



BONE metabolic activity



The FIRST FDG SYNTHESIZER

J. Fowler, BNL

SYNTHESIS OF [^{18}F]FDG

Preparation

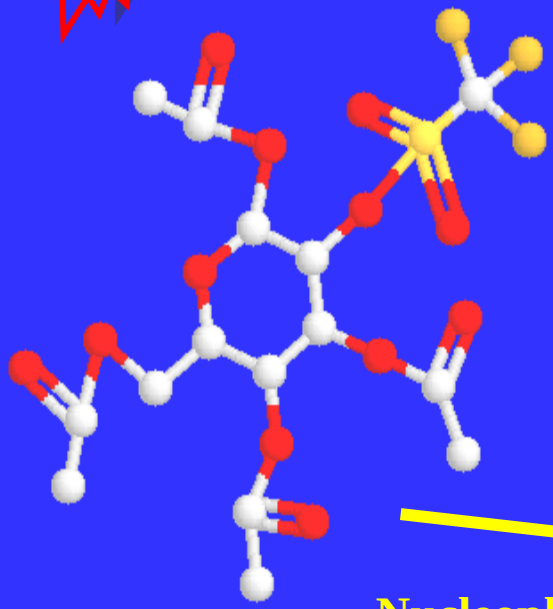
$^{18}F^-$

"NAKED" FLUORIDE

Nuclear Interface

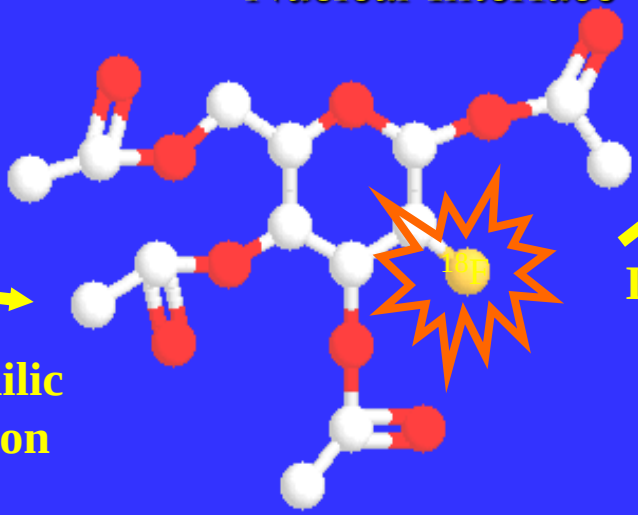
PRODUCT

Cleaning



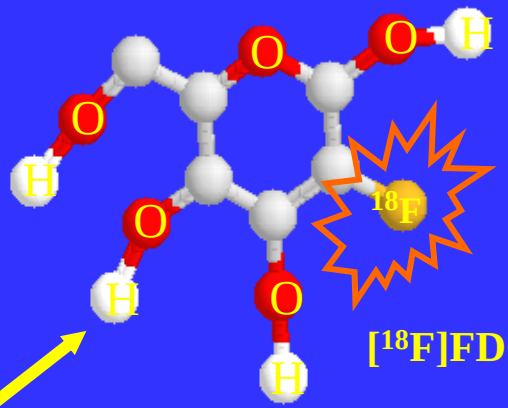
PRECURSOR

Nucleophilic substitution



INTERMEDIATE

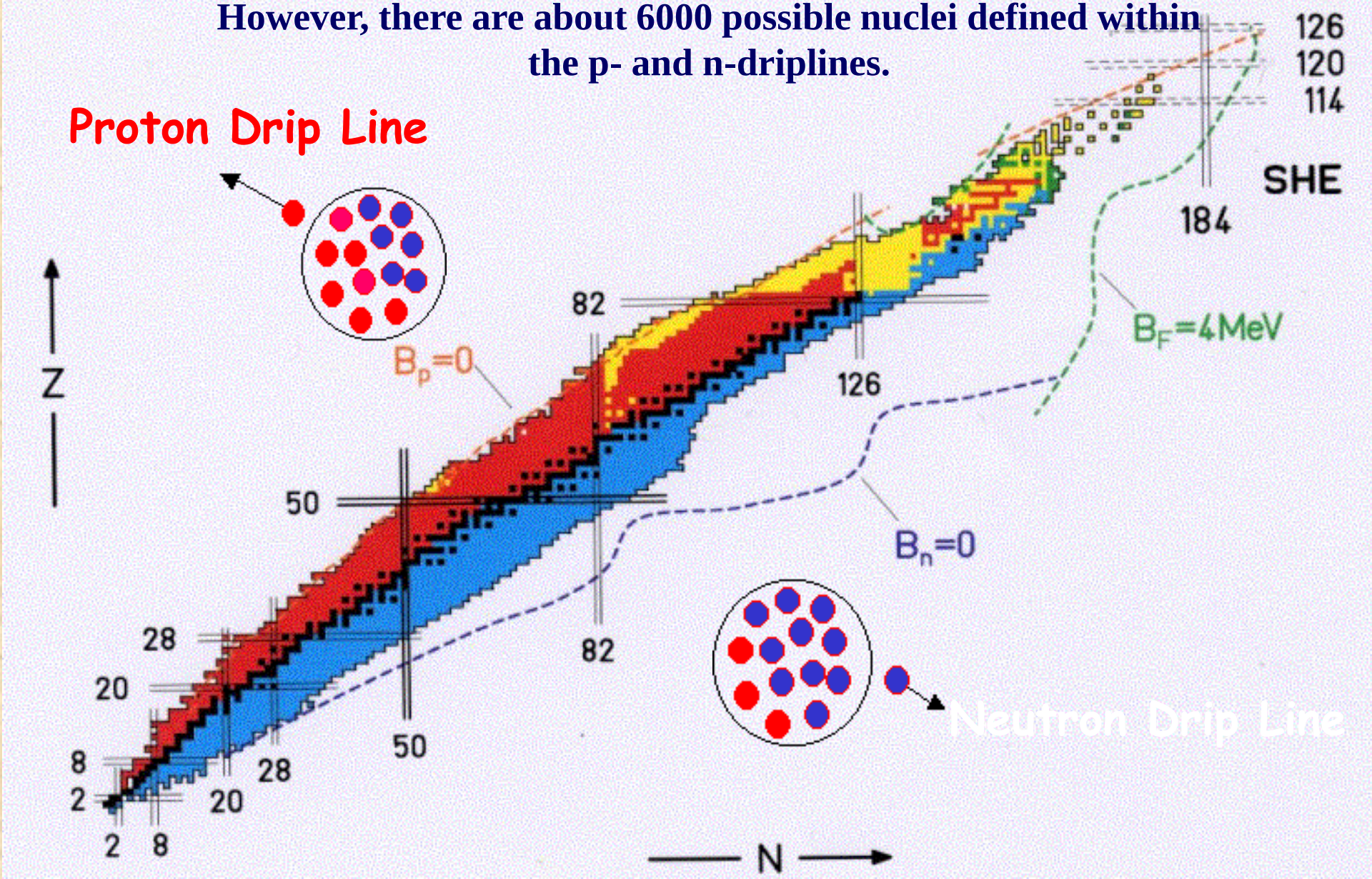
De-protection



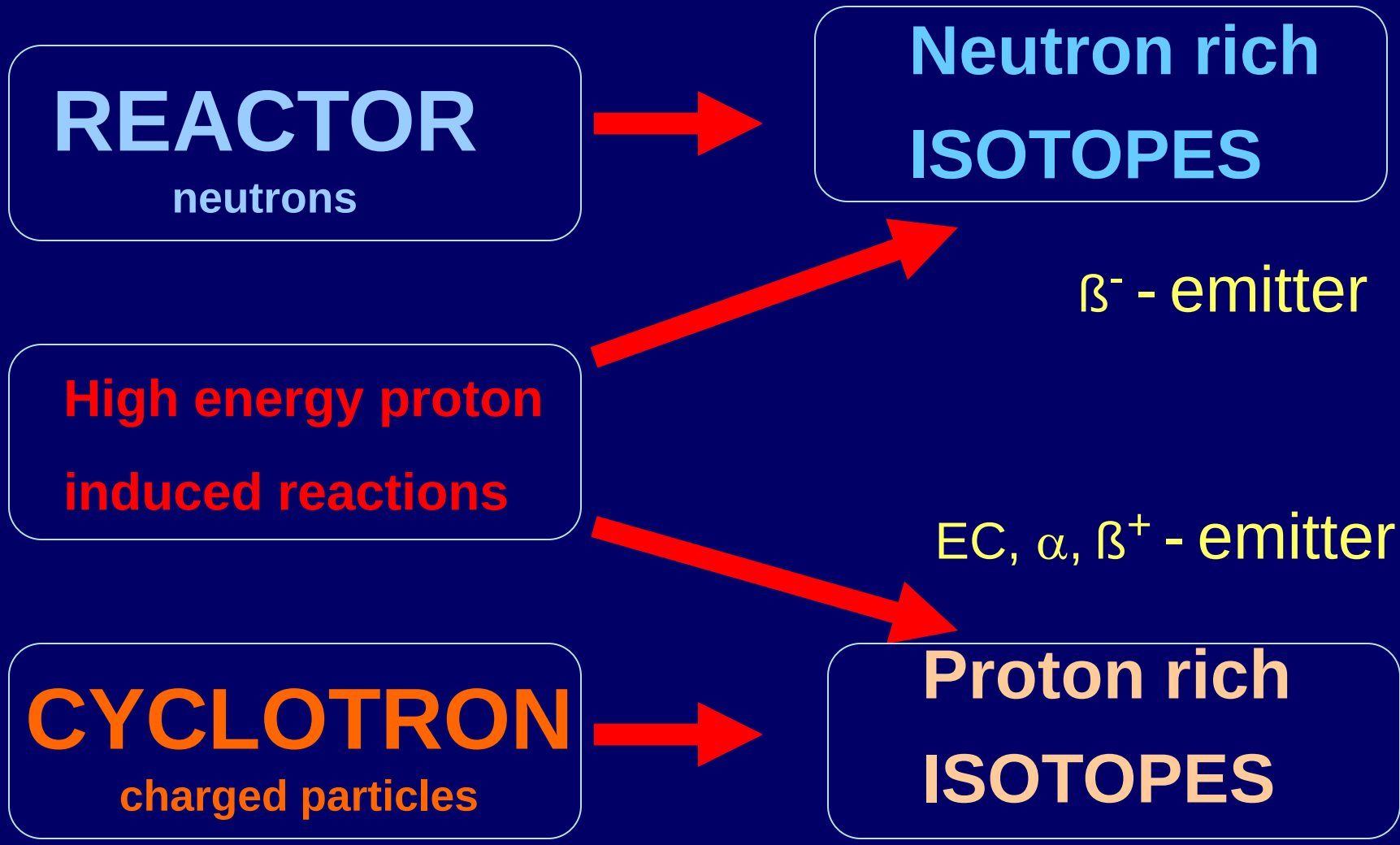
[^{18}F]FDG

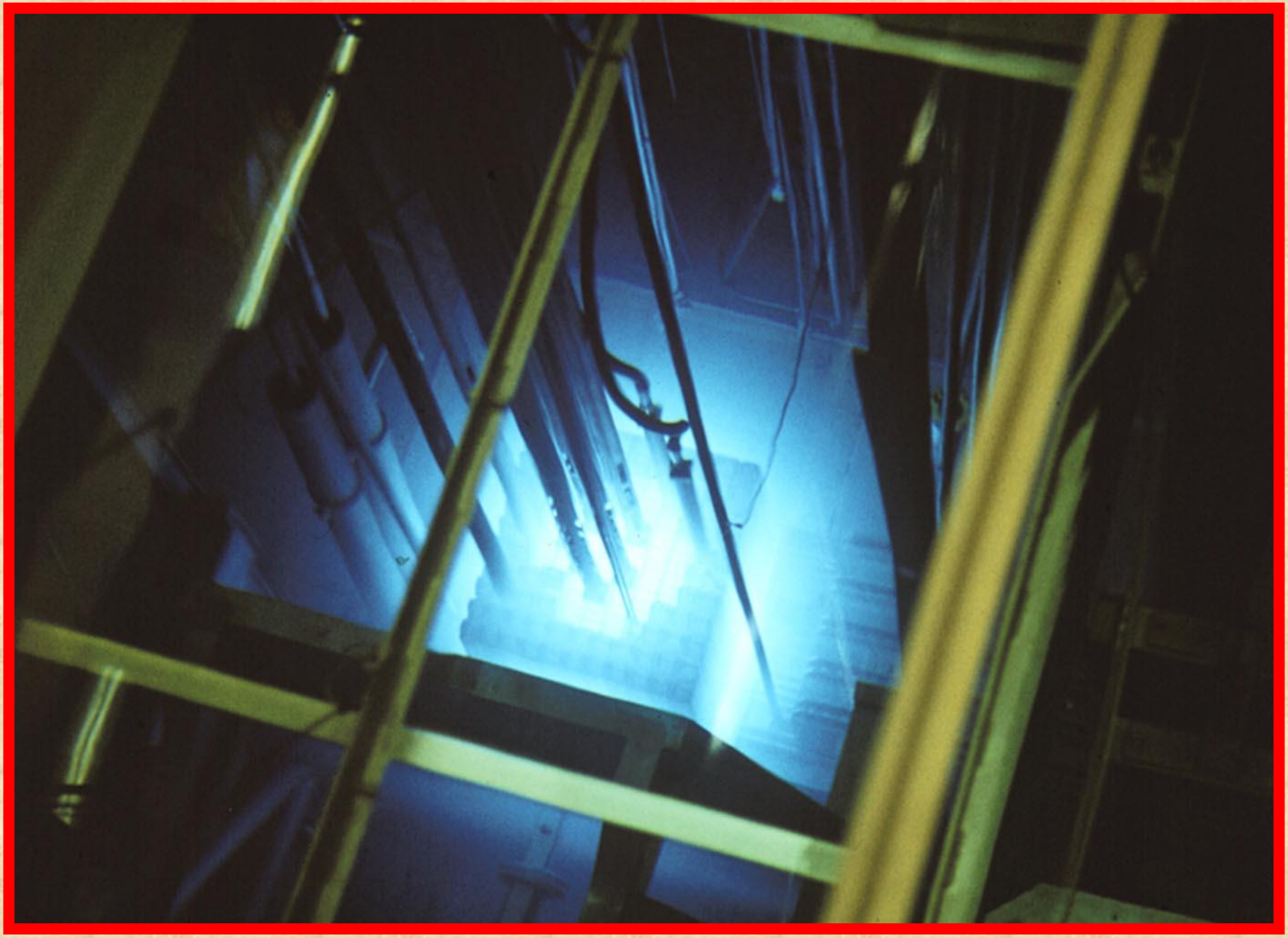
Naturally found on our planet are 265 stable plus 60 radioactive nuclei
About 3000 isotopes are synthesised in laboratories

However, there are about 6000 possible nuclei defined within the p- and n-driplines.



ISOTOPE PRODUCTION





10 MW swimming pool reactor, Geesthacht (D)

Foto: G.Beyer, 1973

Reactor: Activation Equation

$$A = \frac{\Phi \sigma m h}{A_t m_u} [1 - \exp(-\lambda t)]$$

A	activity of the generated radioisotope at end of irradiation in [Bq]
A_s	saturation activity
Φ	neutron flux density in [cm^{-2} s^{-1}]
σ	reaction cross section in barn (1 b = 10^{-28} m^2)
m	target mass in [kg]
h	relative branching of the target isotope
A_t	atomic mass number
m_u	1.6606 10^{-27} kg
λ	decay constant ($\lambda = \ln 2 / t_{1/2}$)
t	irradiation time in [sec]

$$A_s = \frac{\Phi \sigma m h}{A_t m_u} = N_t \sigma \Phi$$

REACTOR: Problems of RI Production

- Radiation dose — targets: elements, oxides, carbonates only, no organic compounds, material requirements for capsules
- Temperature — research reactors usually 60 ^{o}C, reactors in power stations useful for special activations only (^{60}Co)
- Heat production — nuclear reaction energy heats up the targets, fission energy, large target masses – low heat transfer
- Burn out — losses of product and generation of impurities, significant, when σ > 1000 b
- N-depression — must be considered when σ > 10 b, lower yield
- Side reactions — impurities with high σ, other reactions
- Irradiation time — can be long
- Targets — large

^{99}Mo: PRODUCTION ROUTES

^{98}Mo (n, γ) ^{99}Mo

σ = 0.130 b

1 g ^{98} Mo, Φ_{nth} = 1 * 10^{13} $cm^{-2}s^{-1}$

8 GBq ^{99}Mo/g ^{98}Mo (**low specific activity**)

^{235}U (n; f) ^{99}Mo

σ = 586 b

^{99}Mo - fission yield = 6.15 %

1 g ^{235} U, Φ_{nth} = 1 * 10^{13} cm^{-2}

914 GBq ^{99}Mo/ mg Mo(**high specific activity**)

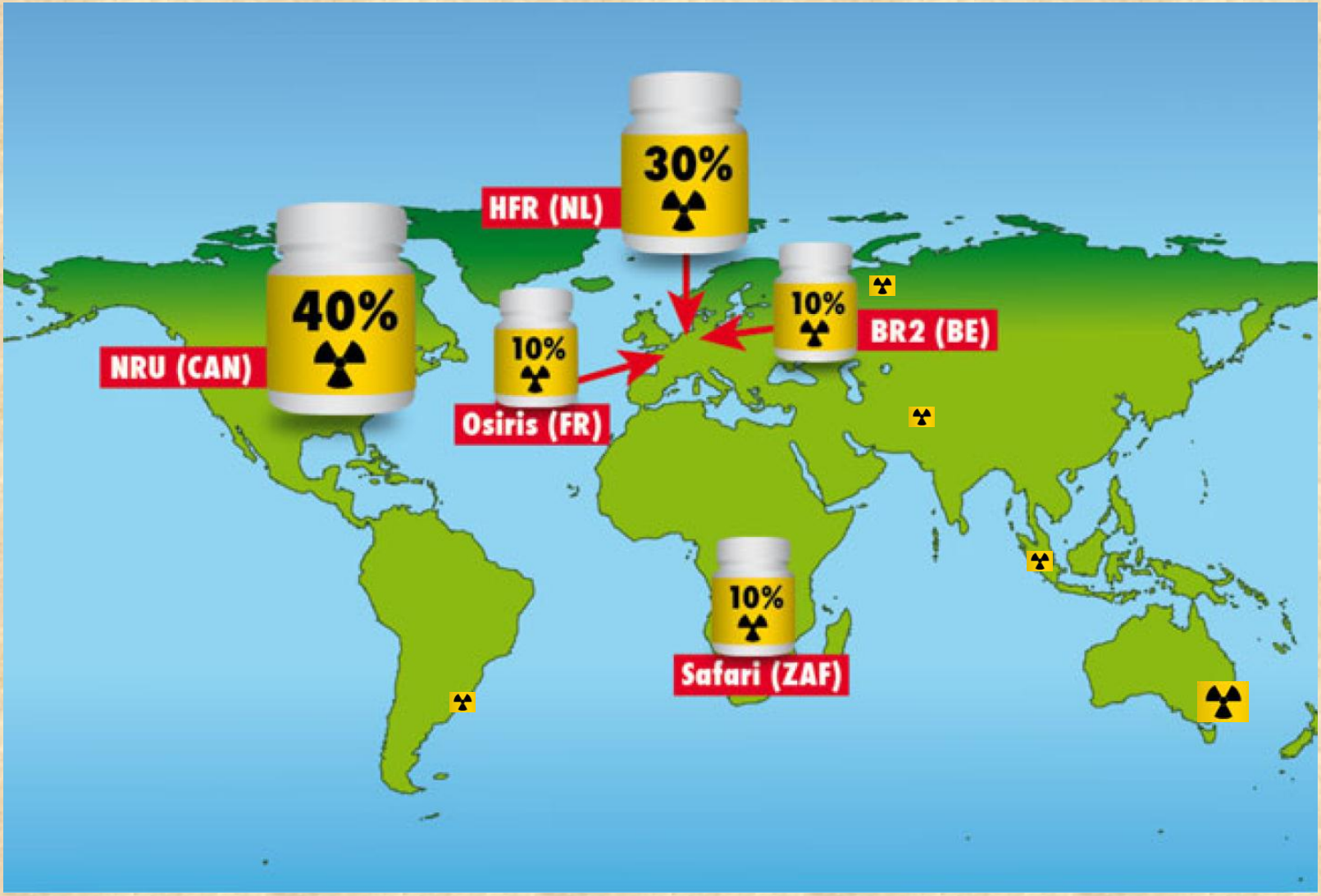
NRU Reactor, Canada

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

HFR Petten, NL

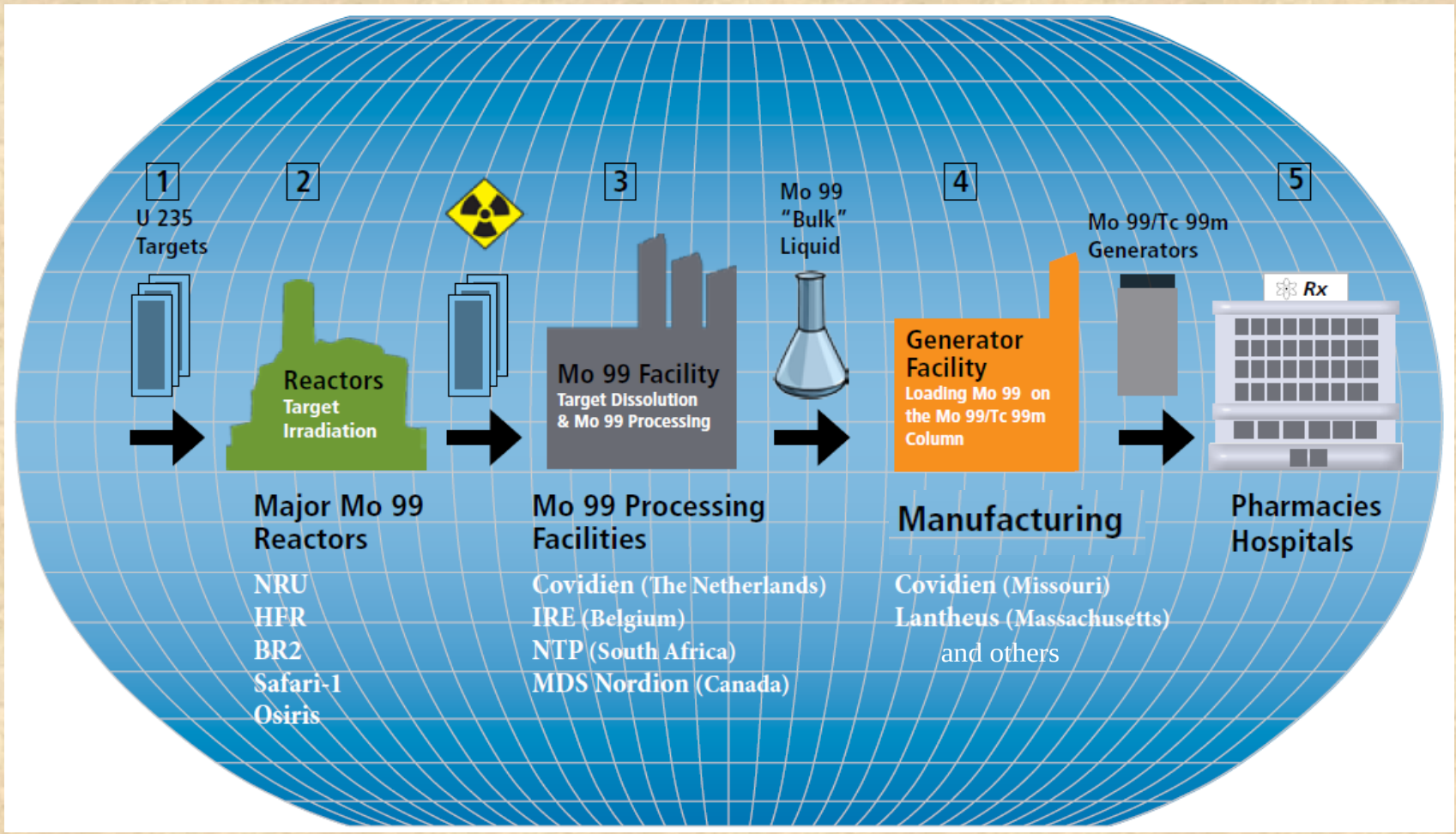
- extended maintenance stop from 19 February 2010

Main ^{99}Mo-Production Sites

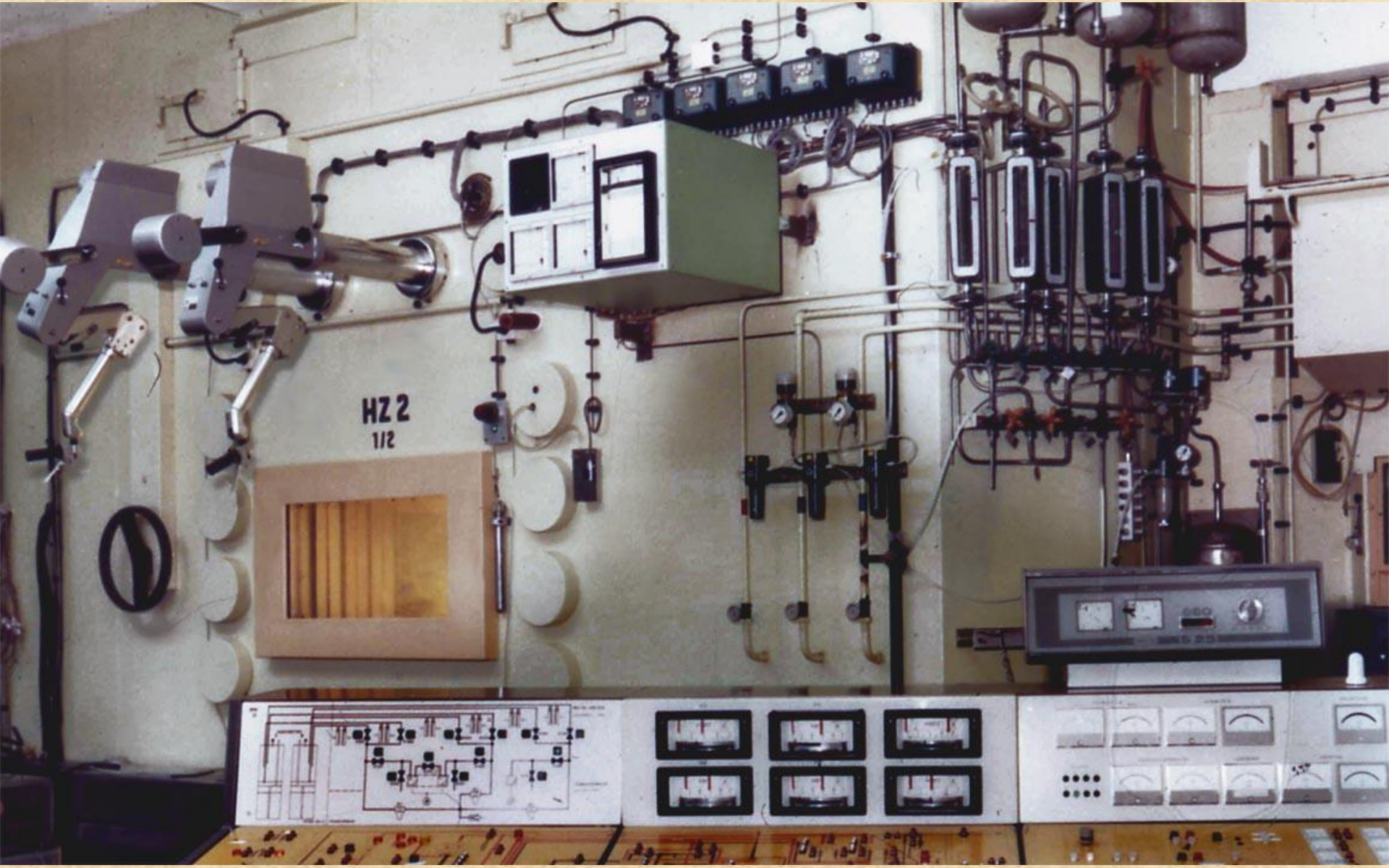


Complex Supply-Utilisation Chain of ^{99}Mo

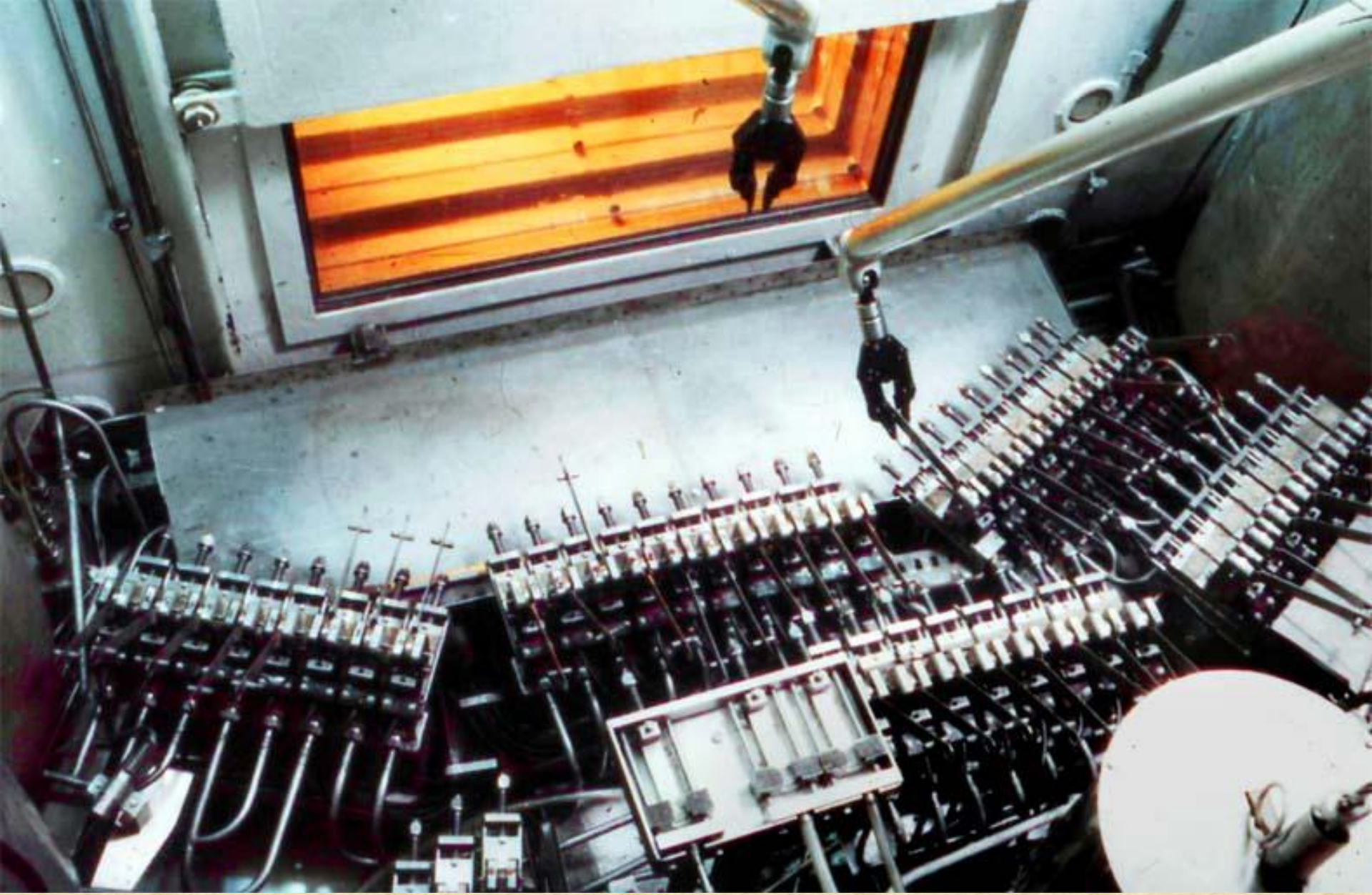
(source: from Covidien web site; modified to show generator producers)



Slide from Ramamoorthy, IAEA Vienna



Fission ^{99}Mo Process Rossendorf (AMOR) 1988



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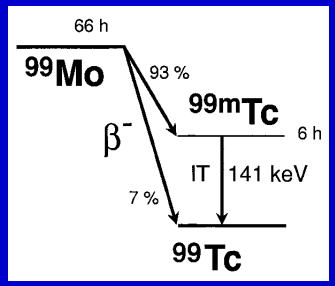
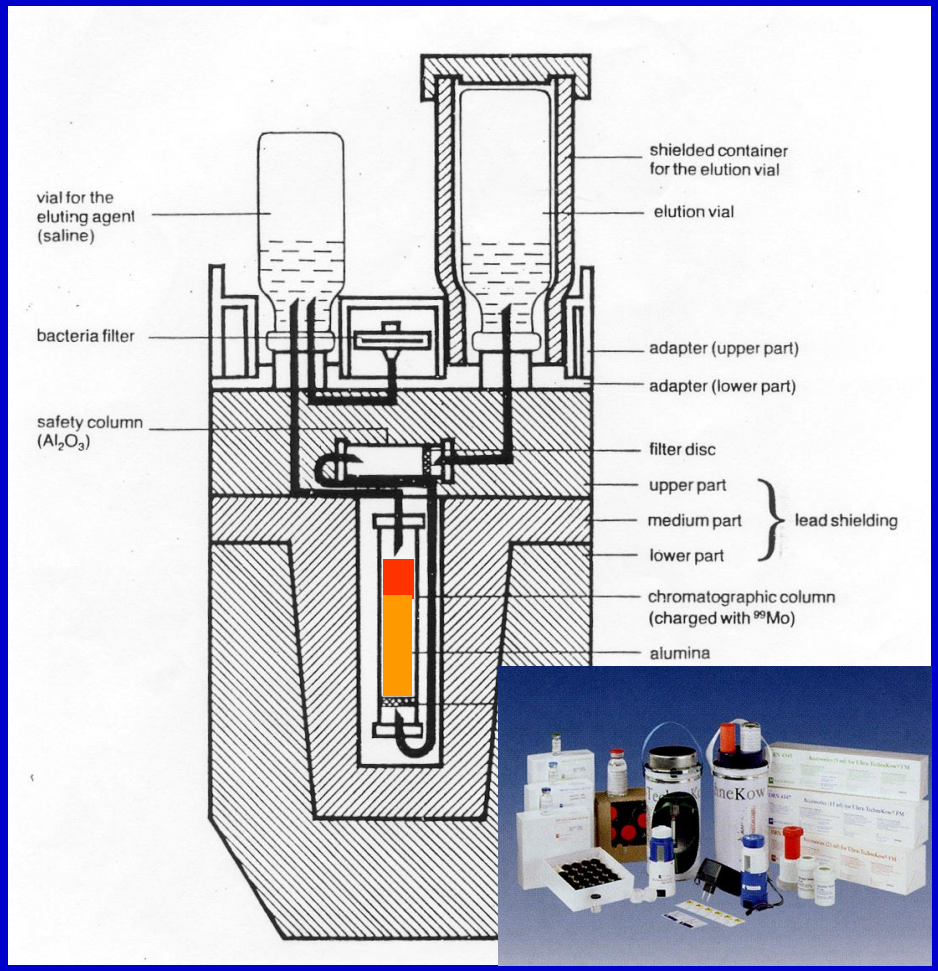


$^{99m}TcO_4^-$

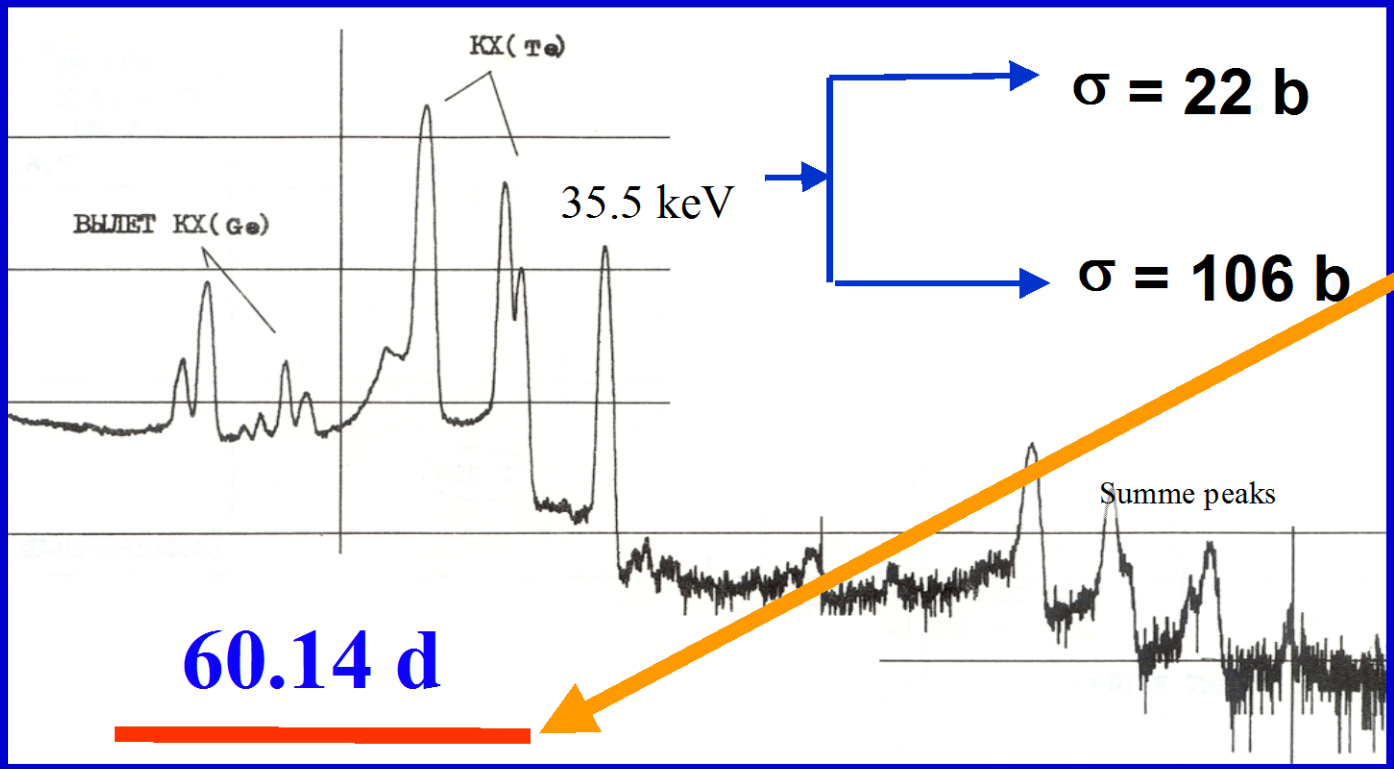
0.9 % NaCl solution

+



many different ^{99m}Tc-tracer for imaging of many different organ and tissue functions

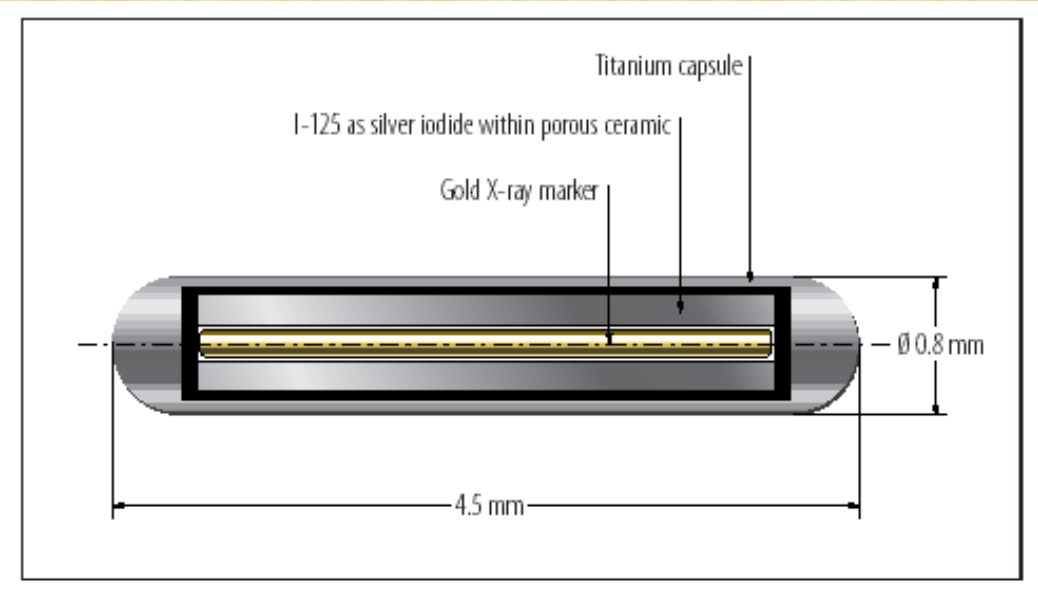
$^{124}Xe\ (n,\gamma)\ ^{125}Xe \xrightarrow{EC} {}^{125}I$

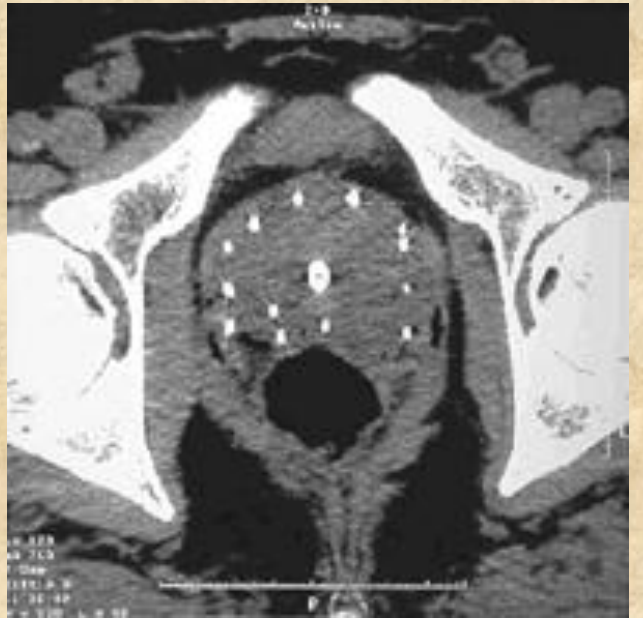


$^{125}I \xrightarrow{(n,\gamma)\ \sigma = 894\ b} {}^{126}I$ (13.6 d)

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.

$^{130}Te\ (n,\gamma)\ ^{131}Te \xrightarrow{\beta^-} {}^{131}I$

$\sigma = 0.02$ b

$\sigma = 0.27$ b

182 keV

IT

22 %

30 h

25 min

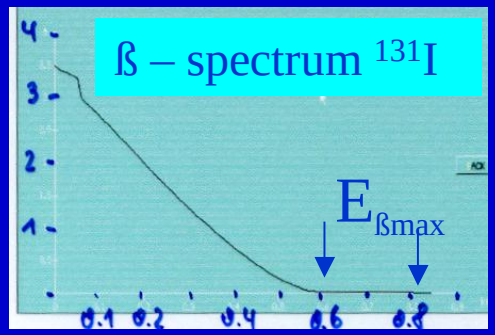
22 %

78 %

8.04 d

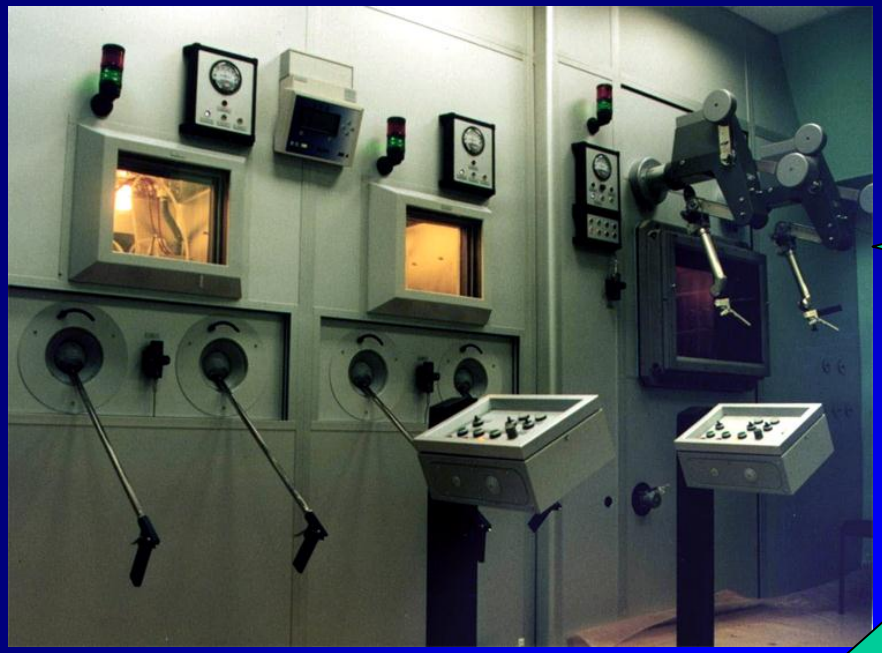
β^-

^{131}I



Simplified scheme for ^{131}I-production via thermal neutron irradiation of natural TeO_2

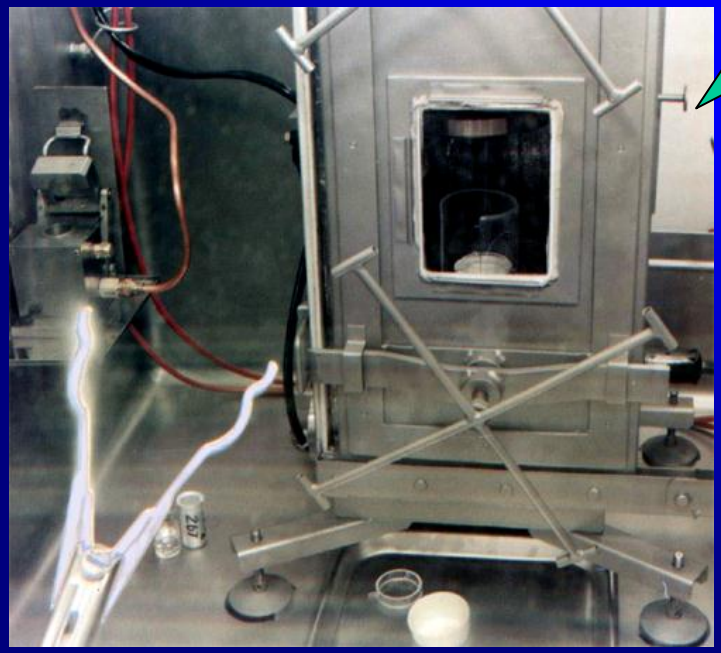
^{131}I Production Technology

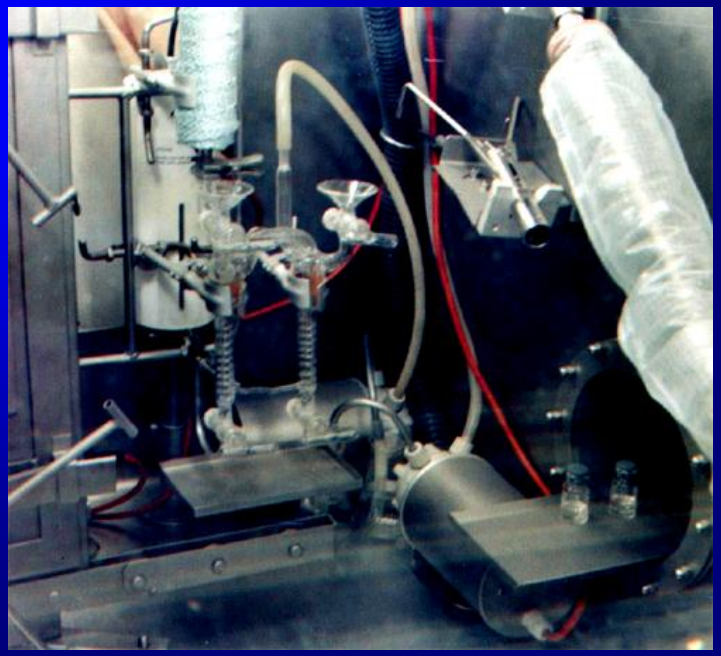


Hot Cell Facility

Target Processing

Iodine Trapping





Problems of medical RI Production with CYCLOTRONS

- **Short range of the particle beam**

  Range: 30 MeV p about 1 mm
  15 MeV d about 0.3 mm
  30 MeV a about 0.1 mm

  small target - high thermic energy deposition!

- **Small cross sections**

  Low productivuity

- **Limited and expensive target material**

  enriched isotopes

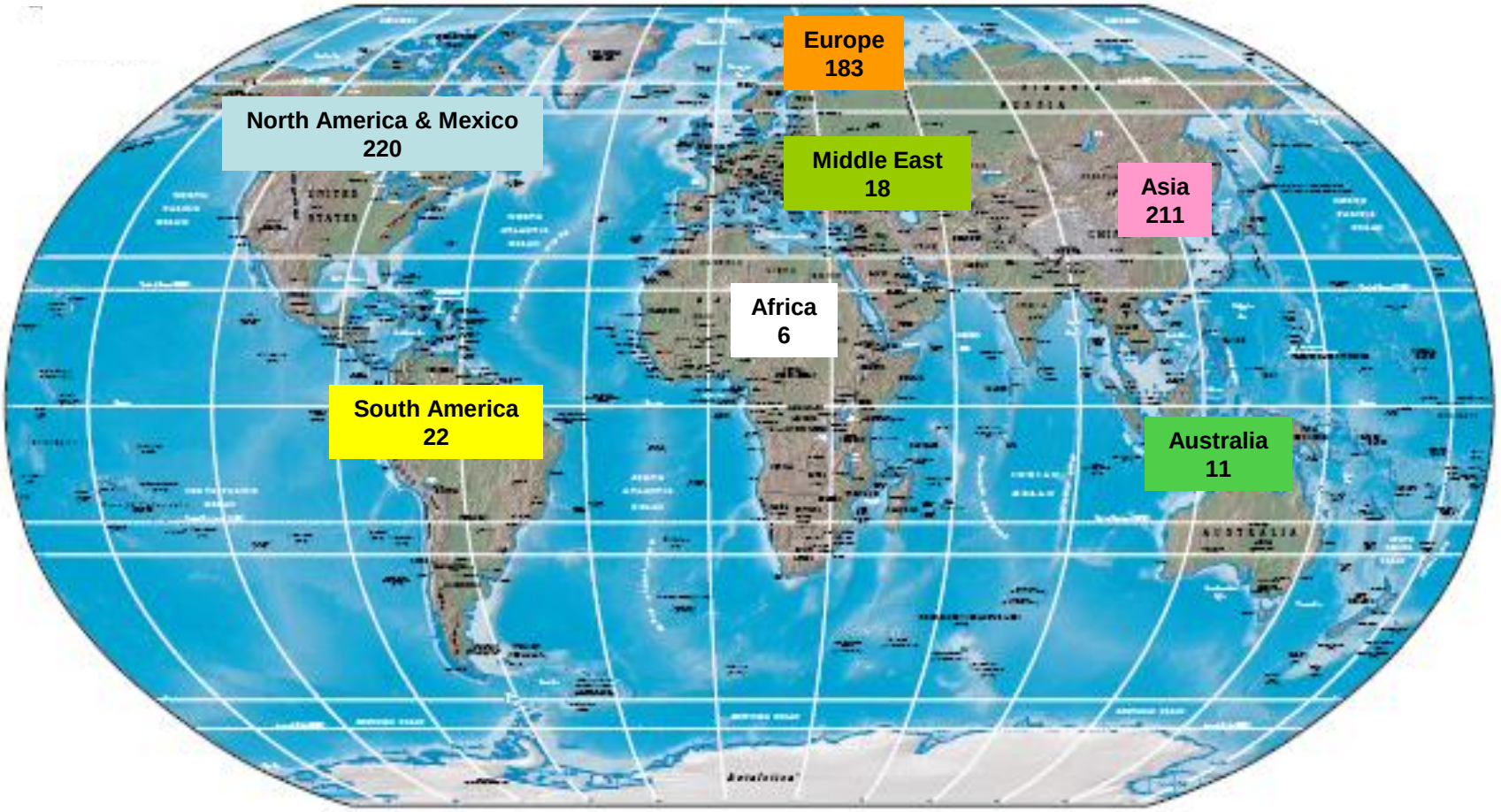
- **Vacuum**

  Target window problems, sensitive target material

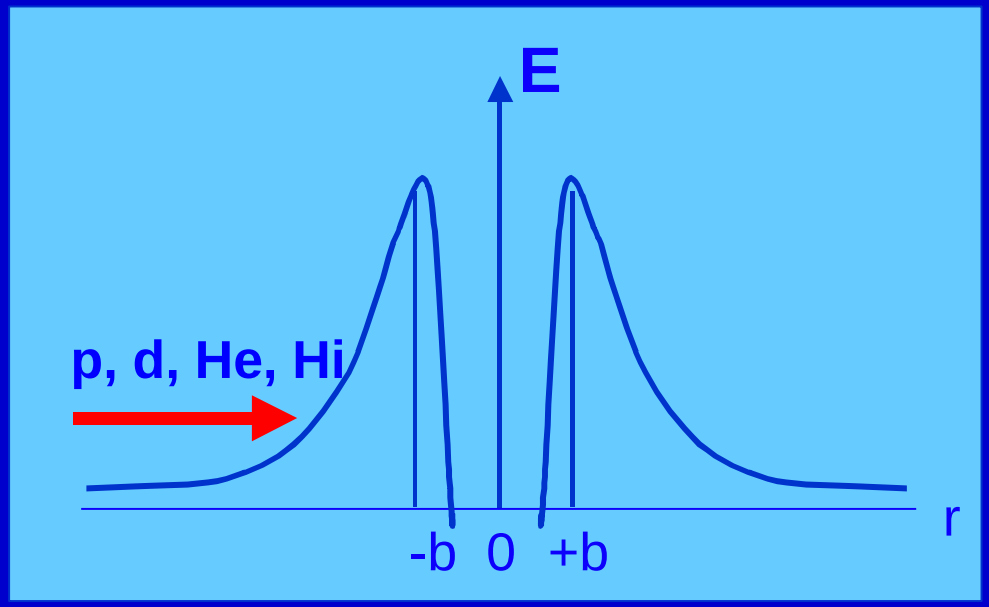
- **Single target – one isotope**

Distribution of cyclotrons for production of PET tracers (2008)

(source: D. Schlyer, BNL/USA, based on inputs of 4 major manufacturers)

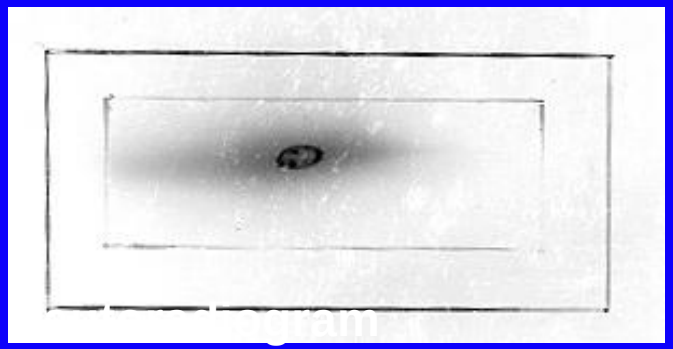


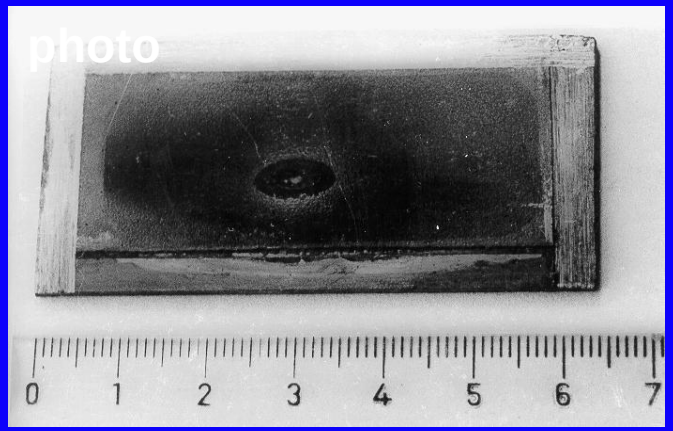
Particle Beam Energy



Ep	=	30 MeV,
Ip	=	100 µA
E_{th}	=	3 kW
Area	=	1 cm
Range	=	1 mm

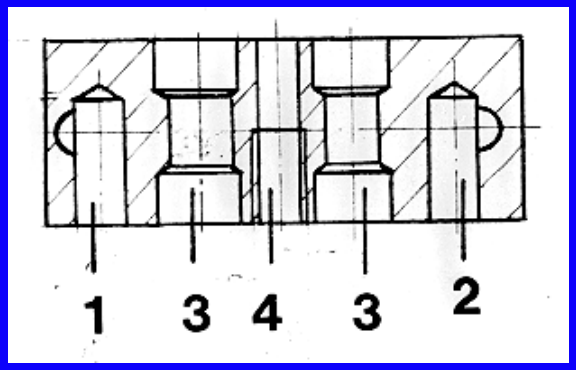
- at “b” strong nuclear force
- only one particle out of 10^4……10^7 reacts in reality
- full particle beam is stopped inside the target material
- the whole particle energy is transformed into thermic energy (heat)





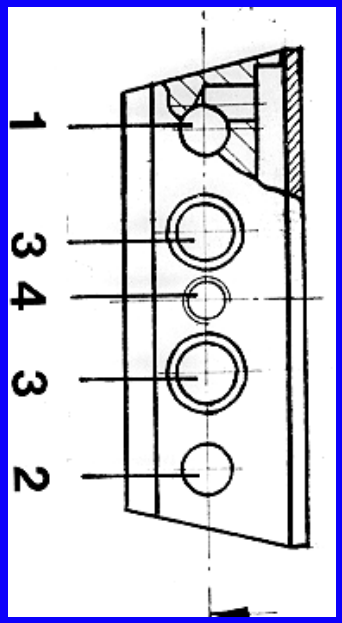
Zn on Cu Backing

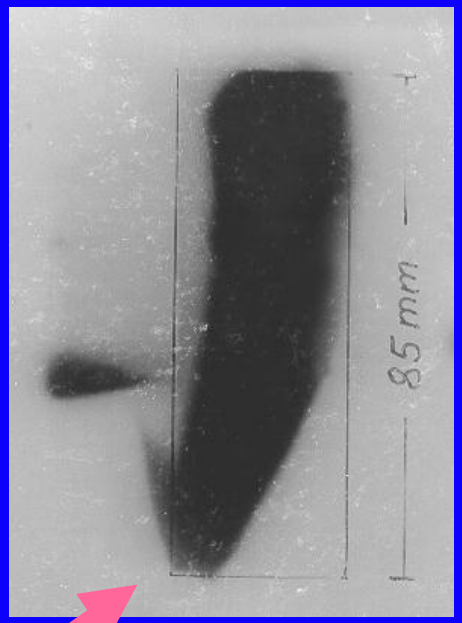
14 MeV d, 50 µA
U-120 Cyclotron Rossendorf
1979

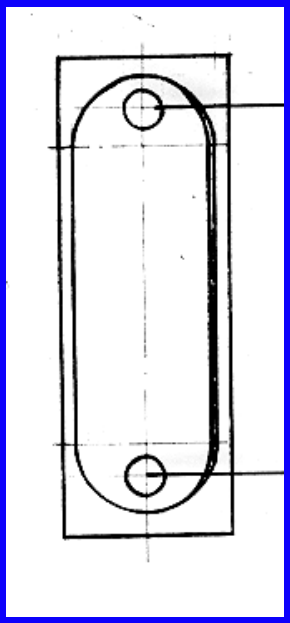


1 water in
2 water out
3 openings
4 winding A8

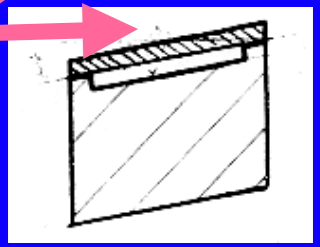
autoradiogram

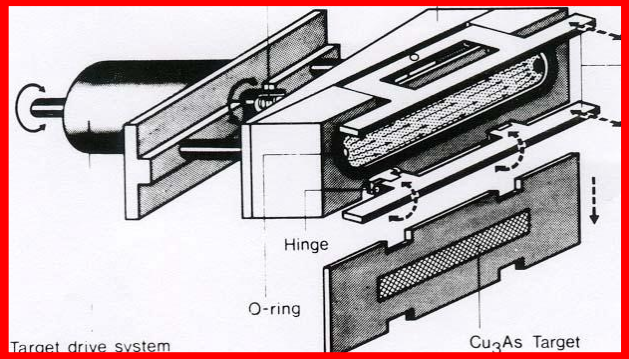






BEAM





Target system

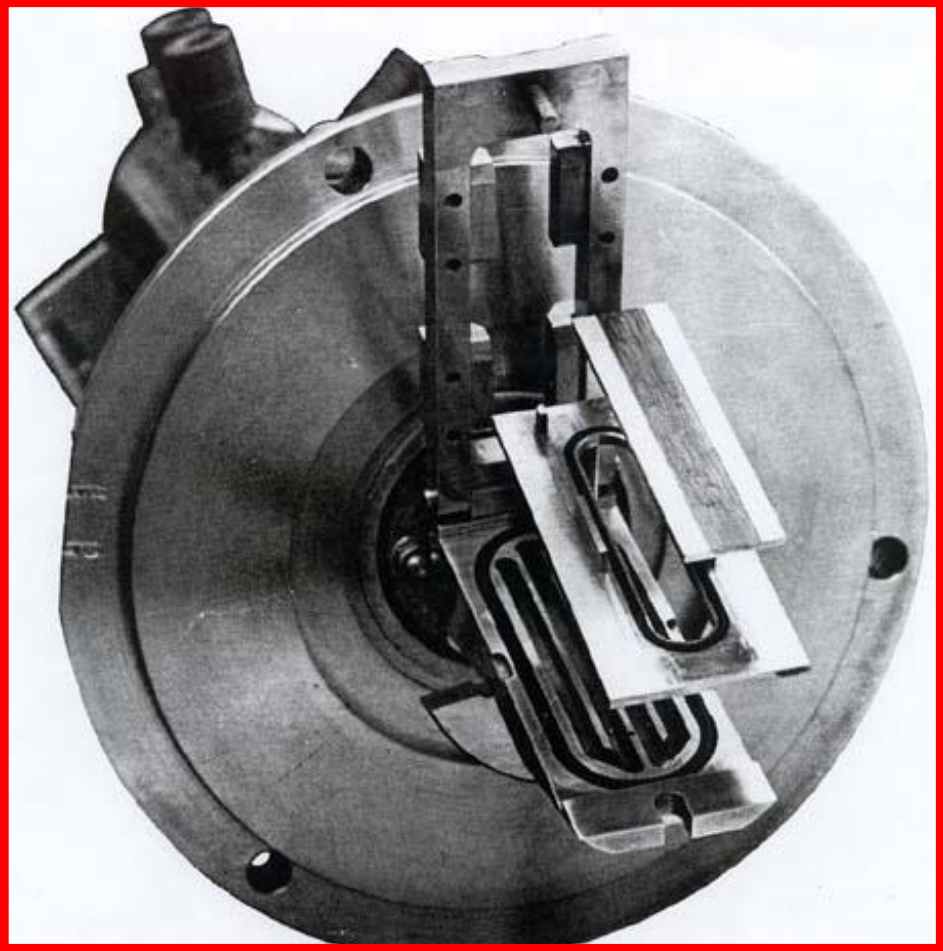
for irradiation of

Sensitive target materials

inside the

vacuum chamber of a

cyclotron



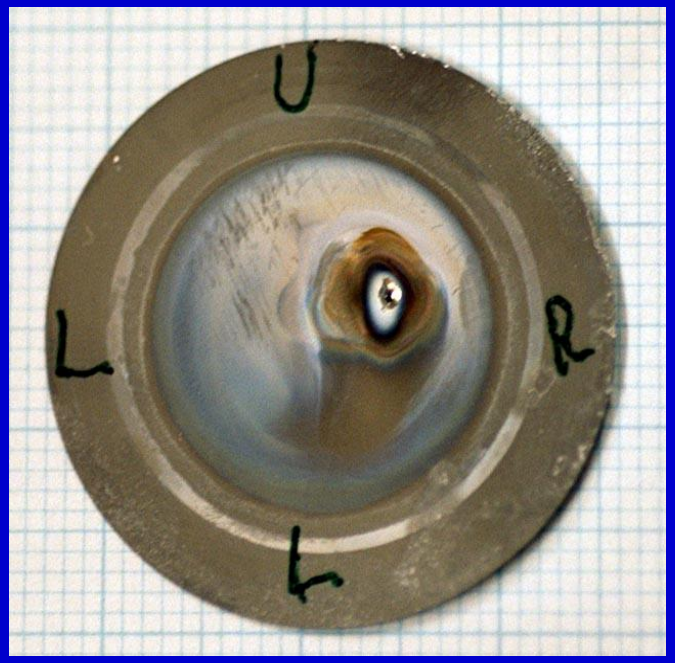
Cu_3AS-alloy as Target for the ^{77}Br production

FZ Jülich, 1983

Qaim & Stöcklin

IBA Cyclone 18/9, Cyclotron in Geneva
9 MeV Deuteron beam spot
on the Havar Window foil
of the Ne(F_2) [^{18}F]F_2 target

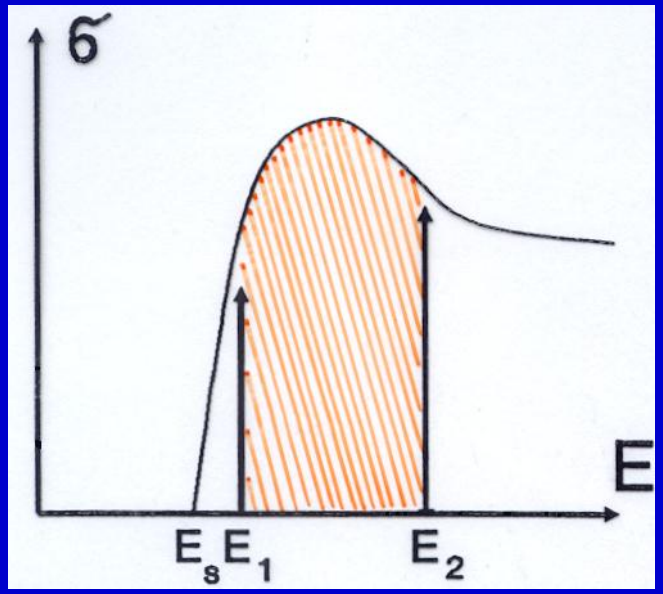
E_d = 9 MeV, I_d = 18 µA, area few mm^2



inside **the target chamber** **outside**

ACTIVATION EQUATION

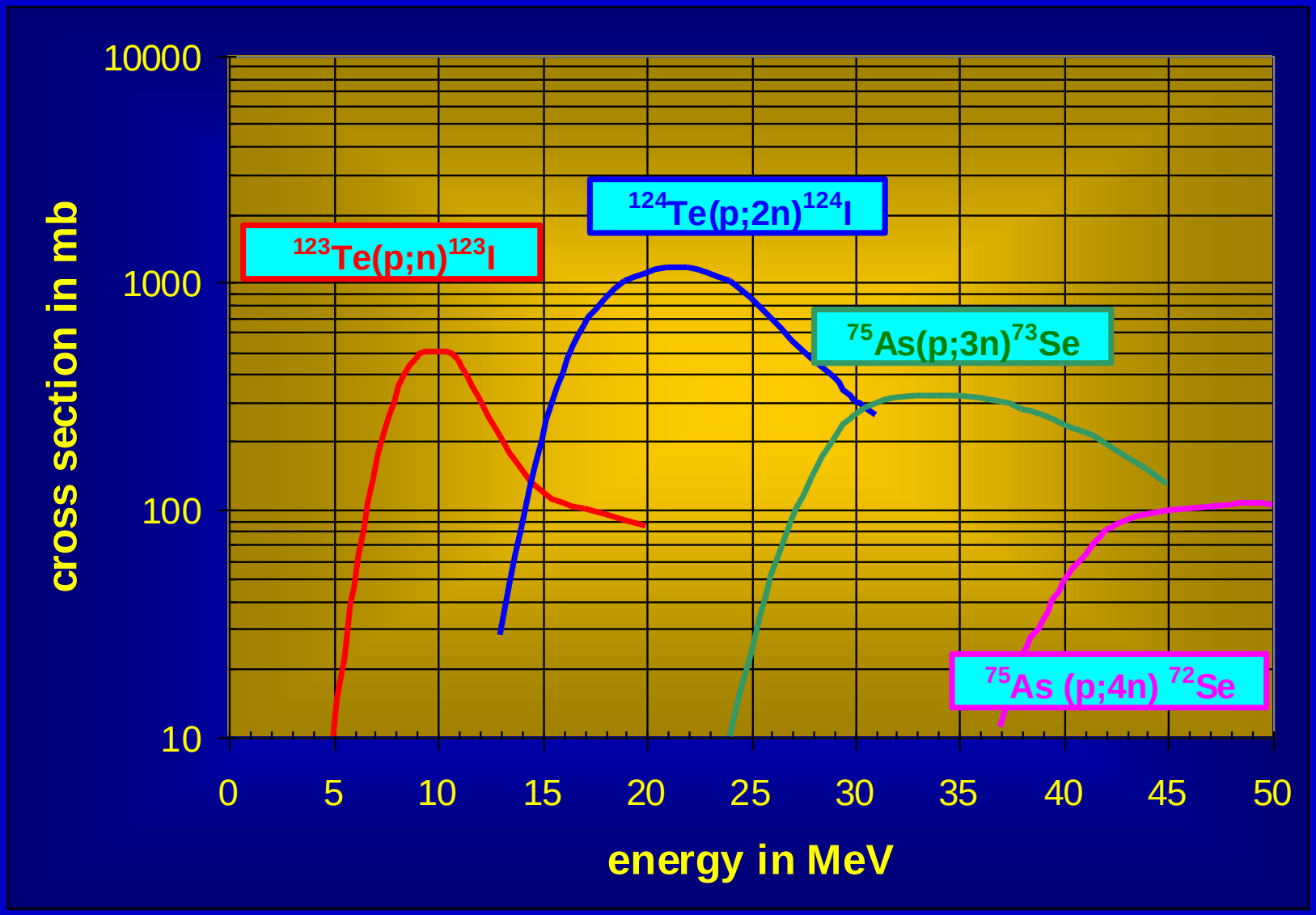
$$Ai = \frac{N_A h_i \rho_i I}{A_t} \times \left(1 - \exp \frac{\left(-t_A \ln 2\right)}{T_{1/2}}\right) \times \int_{E_1}^{E_2} \frac{\sigma(E)}{-\left(\frac{dE}{dx}\right)} \times dE$$



EXCITATION FUNCTION

Ai	activity of isotope I at end of activation
N_A	Avogadro number
h_i	relative branching of target isotope
σ_i	density of the target material
A_t	atomic mass number of target isotope
I	particle beam intensity
$\sigma_{i(E)}$	cross section
E_s	threshold energy of the reaction
E_1 or E_2	defined energy of the reacting particles
(-dE/dx)	stopping power, energy dependent
t_A	time of activation
$T_{1/2}$	radioactive decay half time

Excitation function for proton induced reactions



123-IODINE PRODUCTION ROUTES

1985 Karlsruhe, Canada	1980 Würenlingen PSI	1975 Many places
^{124}Xe (p,2n)	^{127}I (p,5n)	^{124}Te (p,2n)
20 – 30 MeV p	75 MeV p	22 – 28 MeV
^{125}I < 10-3 %	^{125}I < 1 %	^{124}I = 1 %

ALTERNATIVES:

local ^{123} I production using PET cyclotrons

^{123}Te (p,n) ^{123} I

15 MeV p, 150 MBq/µAh

Fast, easy, reliable, clean product, suitable for direct labeling,

30 MeV CYCLOTRON

201-Tl

203-Tl (p,3n) 201-Pb

Irradiated Tl-Target
Dissolution in 6M HNO_3
Fe3+ carrier

Hydroxide presipitation
$Fe(OH)_3$ collects ^{201}Pb

→ **Tl**

Dissolution in 6 M HNO_3
Hydroxide presipitation

→ **Tl**

Dissolution in 6M HNO_3
$Fe(OH)_3$ collects ^{201}Pb

→ **Tl**

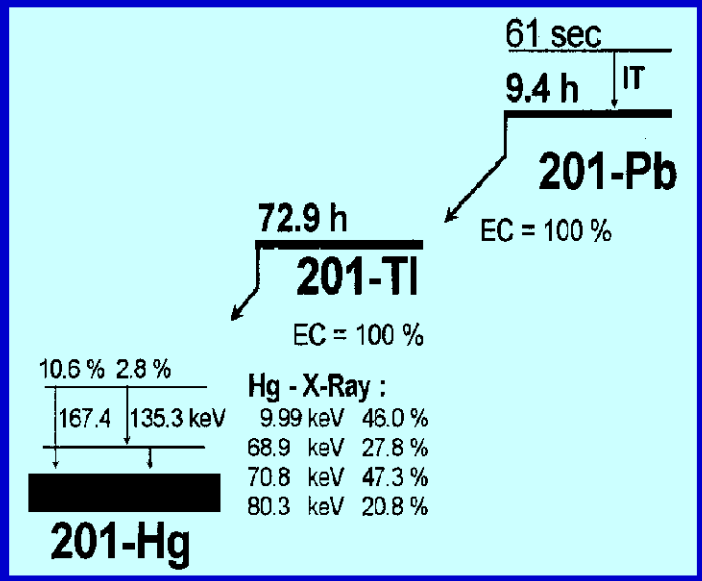
DOWEX 1x8 column
Elution with 6 M HCl

→ **Fe**

Decay of ^{201}Pb,
formation of ^{201}Tl
Decay period 30 h

Reduction of Tl^{3+} to Tl^{1+}
Elution with 3 M HCl

→ **^{201}Tl**



Target 1 – 3 g enriched ^{203}Tl

Irradiation with 30 MeV protons

Complete separation of Tl from ^{201}Pb

Decay of ^{201}Pb into ^{201}Tl

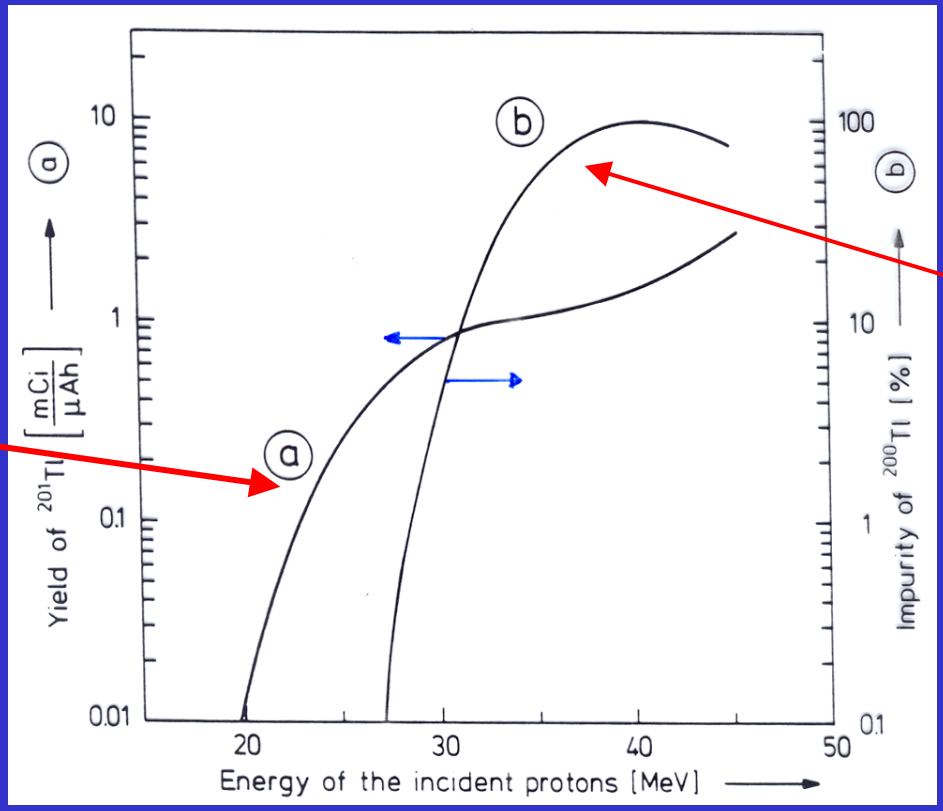
Separation of ^{201}Tl from ^{201}Pb

Why not use higher proton energy for ^{201}Tl production?

Higher p-energy

a

higher ^{201}Tl yield



Higher p-energy

b

higher ^{200}Tl impurity

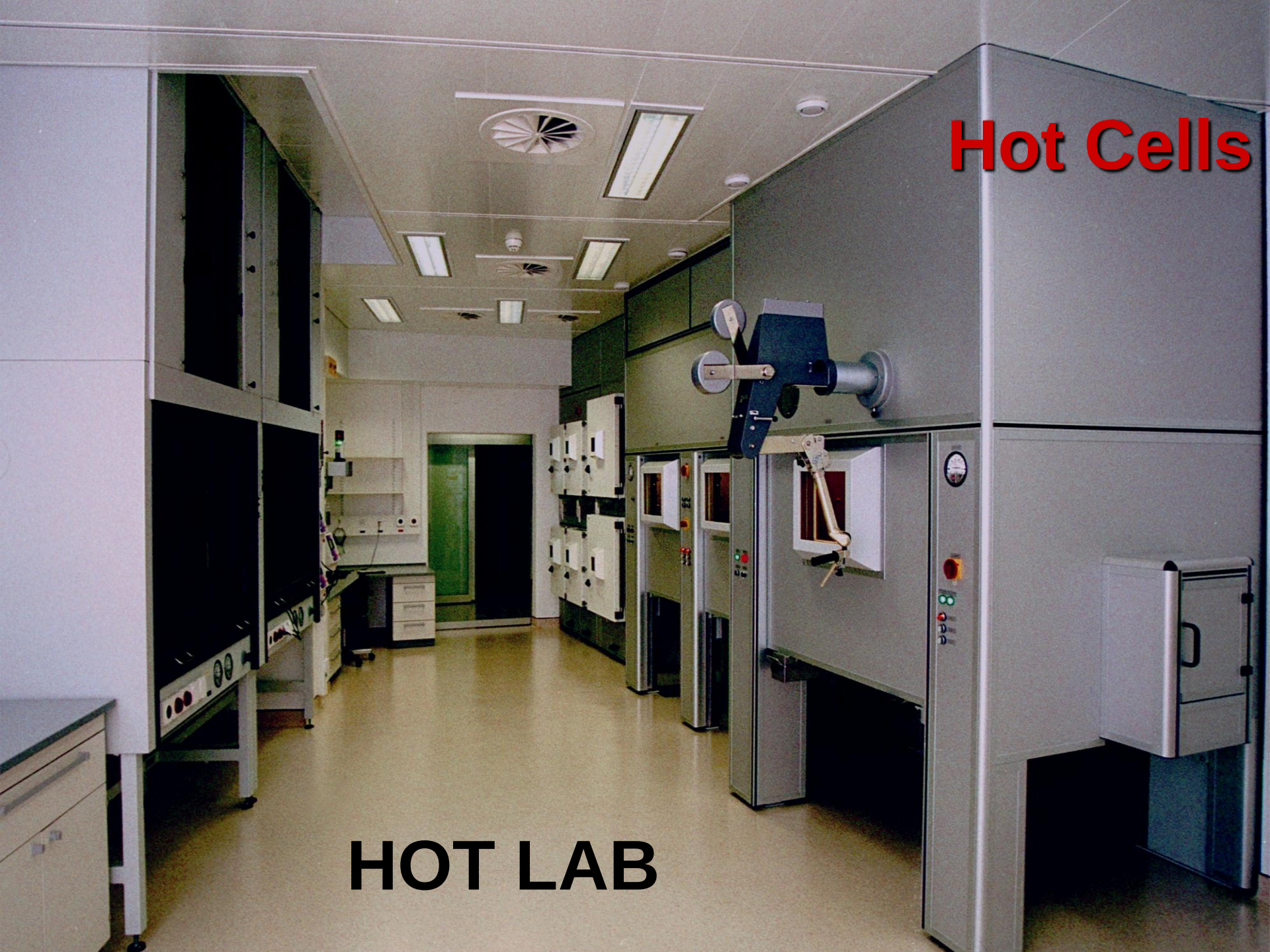
^{203}Tl (p,3n) ^{201}Pb —EC, 9.4 h→ ^{201}Tl (73.1 h)

^{203}Tl (p,4n) ^{200}Pb —EC, 21.5 h→ ^{200}Tl (26.1 h) impurity

ISOTOPES for Tracer Synthesis

ISOTOPE	$T_{1/2}$	Reaction	Target	Product
^{11}C	**20 min**	**^{14}N (p,α) ^{11}C**	**N_2**	**unlimited**
^{13}N	10 min	^{16}O (p,α) ^{13}N	**H_2O**	**[^{13}N]**NH_3
^{15}O	**2 min**	**^{14}N (d,n) ^{15}O**	**H_2O**	**[^{15}O]H_2O**
^{18}F	110 min	^{18}O (p,n) ^{18}F ^{20}Ne (d, α) ^{18}F	**[^{18}O]H_2O** **^{20}Ne**	**[^{18}F]FDG** **[^{18}F]FDOPA**


July.2000


Hot Cells
HOT LAB

TRENDS

- **Therapy** — fast growing demand
  mab, peptides, oligonucleaotides, nanoparticles, seeds
- **PET** — cost effective use of [^{18}F] FDG
  new tracer molecules,
  diagnostic support of therapy
- **^{99}Mo/^{99m}Tc** — remains working horse in Nucl.Med.
  growing demand, presently shortage in supply
- **Brachytherapy** — growing demand
  seeds (^{125}I) spheres (^{90}Y)

RADIOISOTOPES in MEDICINE:

Requirements - Production - Application and Perspectives

4

Isotopes for future Nuclear Medicine

Gerd-Jürgen BEYER
Prof.Dr.rer.nat.habil.
Cyclotron Unit, University Hospital of Geneva, Switzerland
GSG-Int. GmbH, Switzerland
gerd.beyer@cern.ch
gerd.beyer@gsg-int.com

Lecture
JUAS
Joint University Accelerator School
Archamps (France) March 08, 2012

NUCLEAR MEDICINE 2009

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

PET AS CLINICAL TOOL

* Oncology
  Reimbursement of FDG-studies
* Neurology
* Cardiology

Multi - modality Imaging

* combined SPECT -PET
* Function and morphology
  (PET – CT , MRI - PET)

THERAPIE

NEW APPROACHES IN RADIONUCLIDE THERAPY

* bio-selective antibodies
  (mab = monoclonal antibodies)
* bio-specific peptides
  (Octreotides, others)
* gene therapy
* free chelators like EDTMP
* Lyposomes
* Nanoparticles

NEW RADIONUCLIDES for THERAPY

* β - emitters
* α-emitters

α-THERAPY & AUGER THERAPY

PET FOR IN VIVO DOSIMETRY

* metallic positron emitters
* labelled drugs
* dose localization

CANCER

~ 1 300 000 new cancer cases per year in EU
58 % local disease, 42 % generalized

45 % cured (5 year survival)

22 % surgery alone
12 % radiation therapy
6 % combination surgery + radiation
5 % chemo-therapy
just beginning of systemic radionuclide therapy

HOW: expose cancer cells or cancer tissue with sufficient radiation doses?

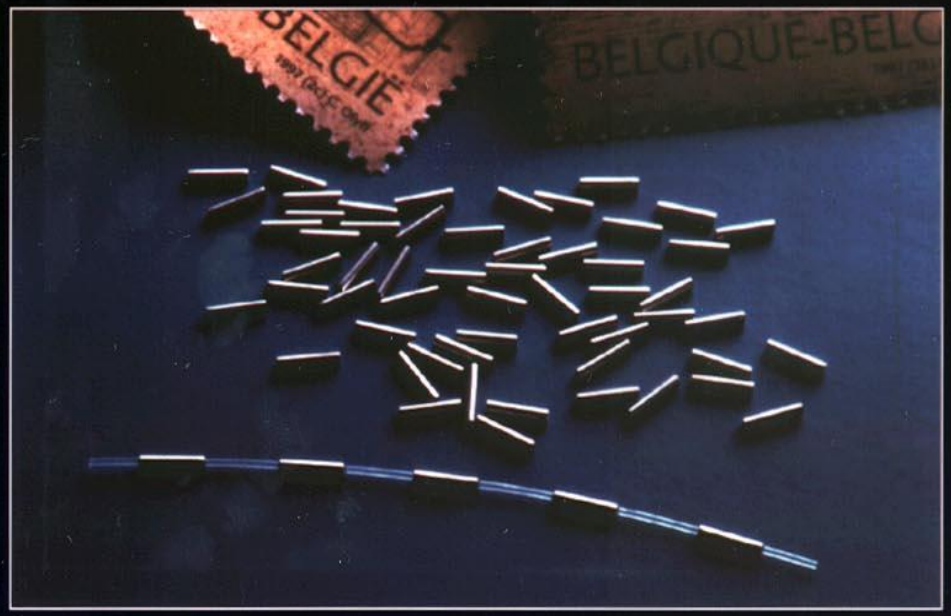
ISOTOPES in Therapy =
surgery with radiation

	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, $^{223,224}Ra$ E_{α} 4–8 MeV	^{125}I ^{165}Er E_{e} few eV
Range	about 1 cm	30 – 80 µm	10 nm
	ß-Knife	α-Knife	Auger Knife

IBA

Brachytherapy

Local Eradication
of a Tumor
by Radioactive Implants



Theragenics

IBt

RIT = RADIOISOTOPE THERAPY

or RADIOIMMUNO THERAPY

or systemic radionuclide therapy

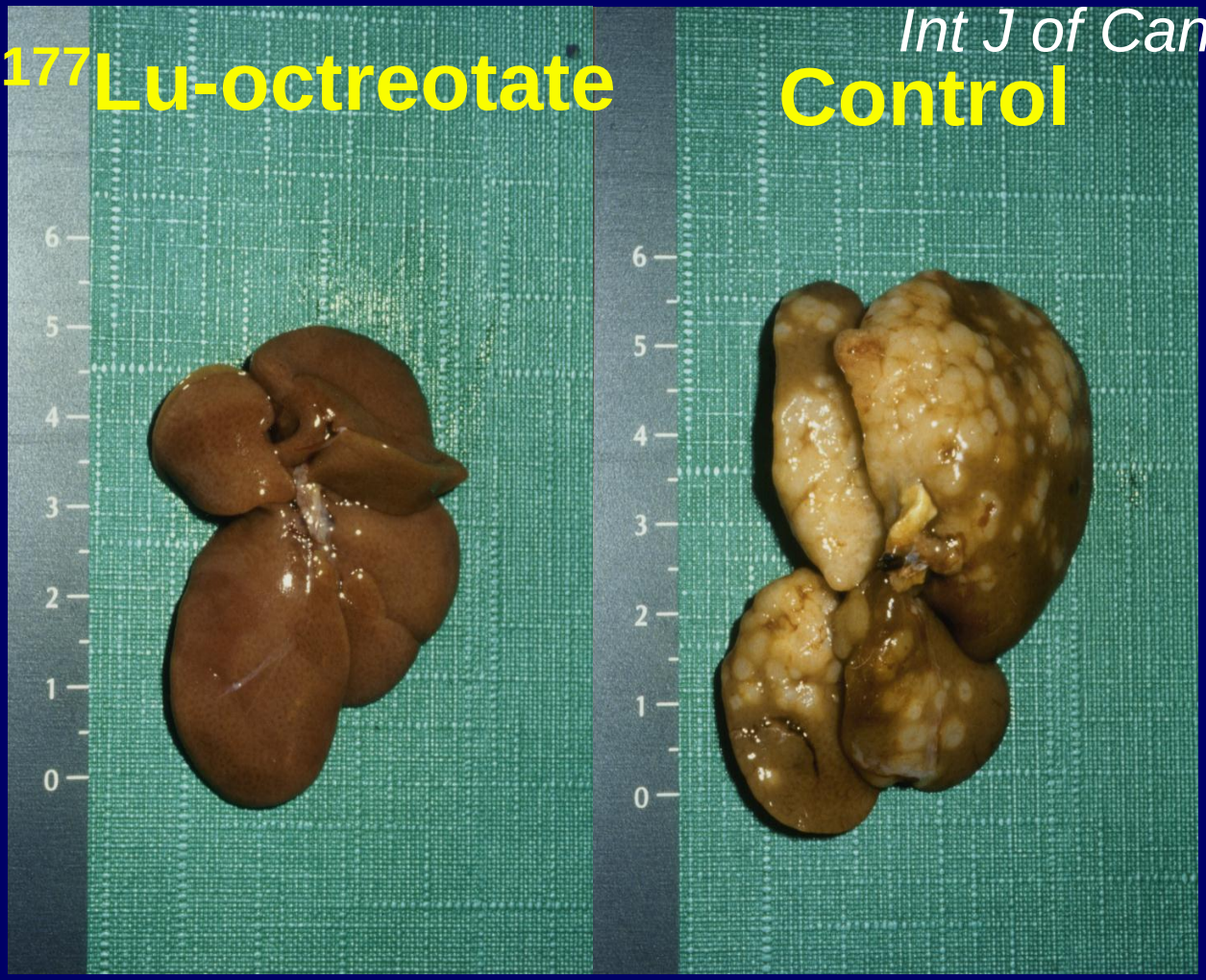
1936 ^{32}P against leukemia, J.H.Lawrence
1939 ^{89}Sr uptake in bone metastases, C.Pecher
1946 ^{131}I treatment of thyroid cancer, S.M.Seilin et al.
1963 Radioactive colloides, B.Ansell et al
1976 ^{89}Sr against pain from bone metastases, N.Firusian
1978 Radiolabelled mab, D.Goldenberg
1982 Treatment with ^{131}I labelled mab, S.Larson et al.
1990 Somatostatine receptor binding tracers, E.Krenning
1993 ^{89}Sr, FDA approval
2000 FDA approval of ^{131}I-CD20 against Lymphoma ?

Development of therpeuticals delayed

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

(PRRT = Peptide Receptor Radionuclide Therapy)

Int J of Cancer 2003



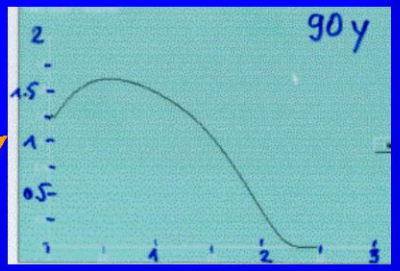
Questions to be answered:

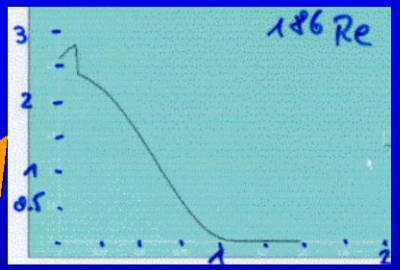
- Realtionship between radiation dose delivered to a leason and the therapeutic response
  - **In vivo dosimetry by quantitative PET imaging need for ß$^+$-emitting metallic radionuclides**
- Relationship between beta – energy and therapeutic response
  - **Variation of radionuclides with different ß-energy need for metallic ß$^-$-emitters with very different energy**

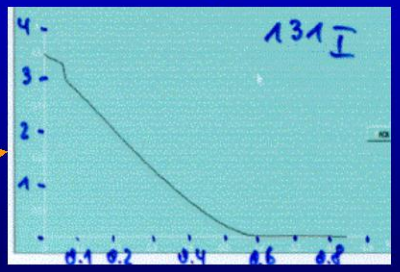
β^- emitter for therapy

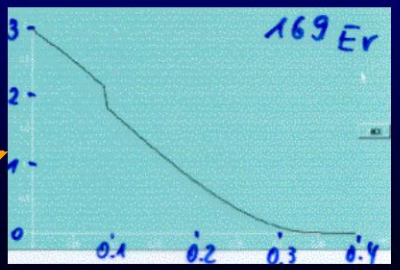
RIT = RADIOISOTOPE THERAPY
or RADIOIMMUNO THERAPY

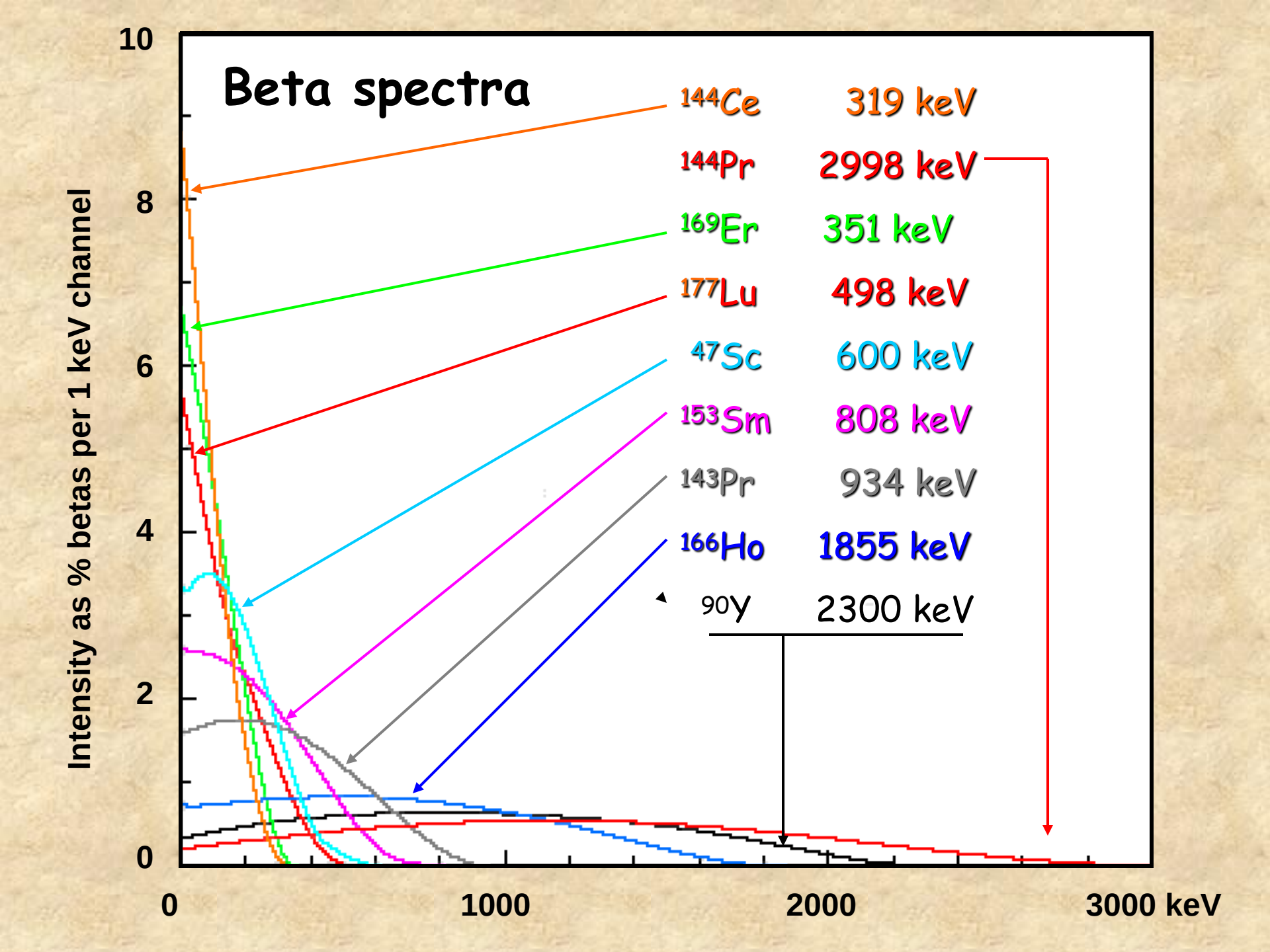
Nuclide	$E_{\beta max}$ [MeV]	Range [mm]	$T_{1/2}$	photons [keV]	comment
^{90}Y	**2.3**	4.2	64.1 h	no	Easy available
^{188}Re	**2.1**		17 h	155 keV	Difficult, generator
^{166}Ho	**1.9**	0.7	26.8 h	(81 keV)	difficult
^{89}Sr	**1.5**		50.5 d	no	Palliation only
^{186}Re	**1.1**		90.6 h	137	Carrier
^{153}Sm	**0.8**	0.269	46.8 h	103 keV	Easy, carrier
^{131}I	**0.8**		8.04 d	(364keV)	Most common
^{177}Lu	**0.5**	0.147	6.7 d	113/208	Not easy
^{67}Cu	**0.4/0.6**		61.9 h	185	Interesting
^{47}Sc	**0.4/0.6**		80.4 h	159	interesting
^{169}Er	**0.3**	0.1	9.4 d	no	soft










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

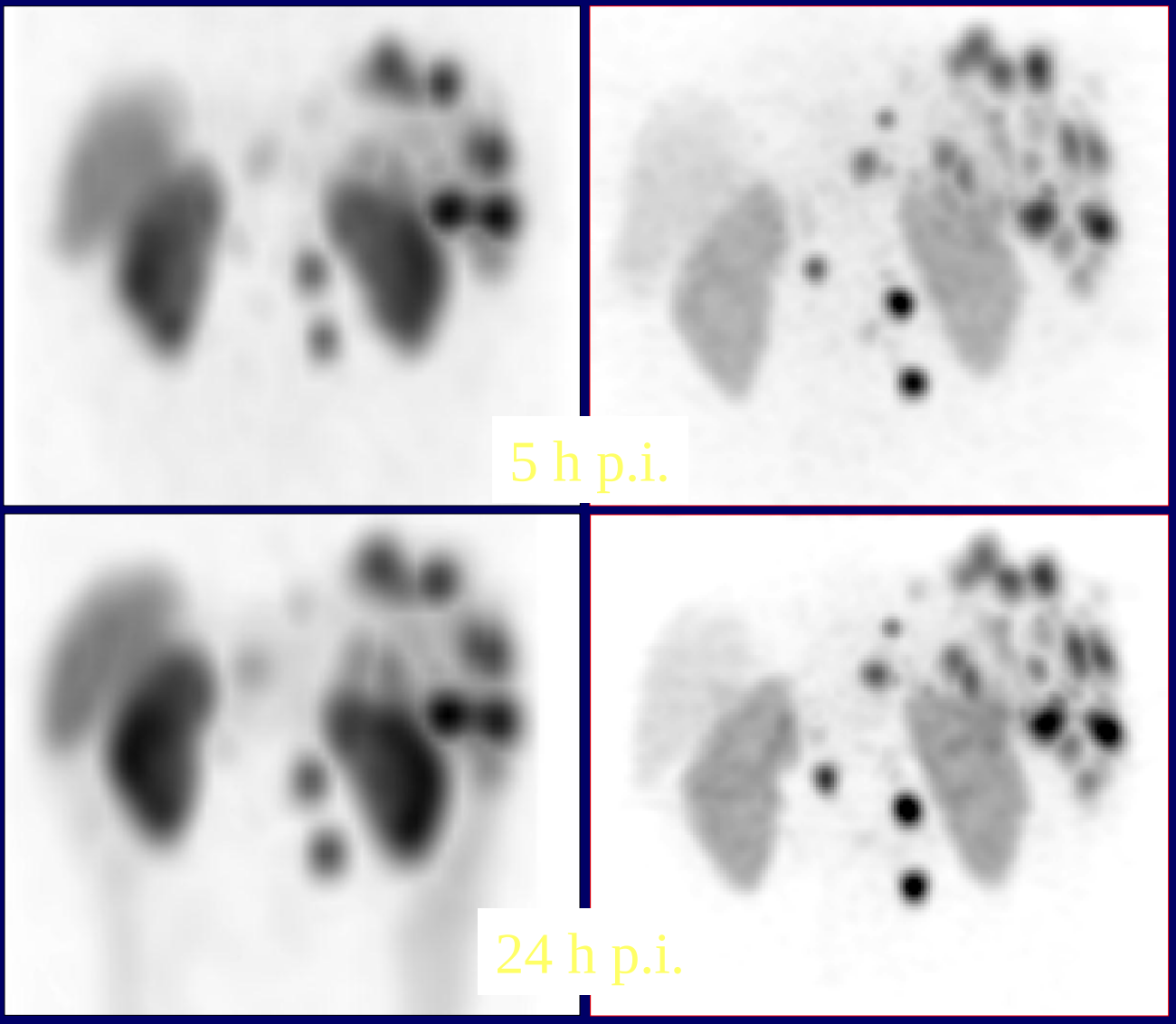
Why metallic radionuclides?

- ^{131}I cannot fulfill all requirements (weak in vivo stability)
- We learnt to make bio-conjugates, that contain chelating groups
- Universality: the chelated bio-conjugates can be labelled practically with any metallic radionuclide of group III and group IV elements
- The radiolabeled bio-conjugates are stable in vivo
- The bio-selective ligands are mainly monoclonal antibodies or peptides

β^+ emitters for in vivo dosimetry

[^{111}In]DTPA-octreotide SPECT

[^{86}Y]DOTA-$_{D}$Phe^{1}-Tyr^{3}-octreotide PET



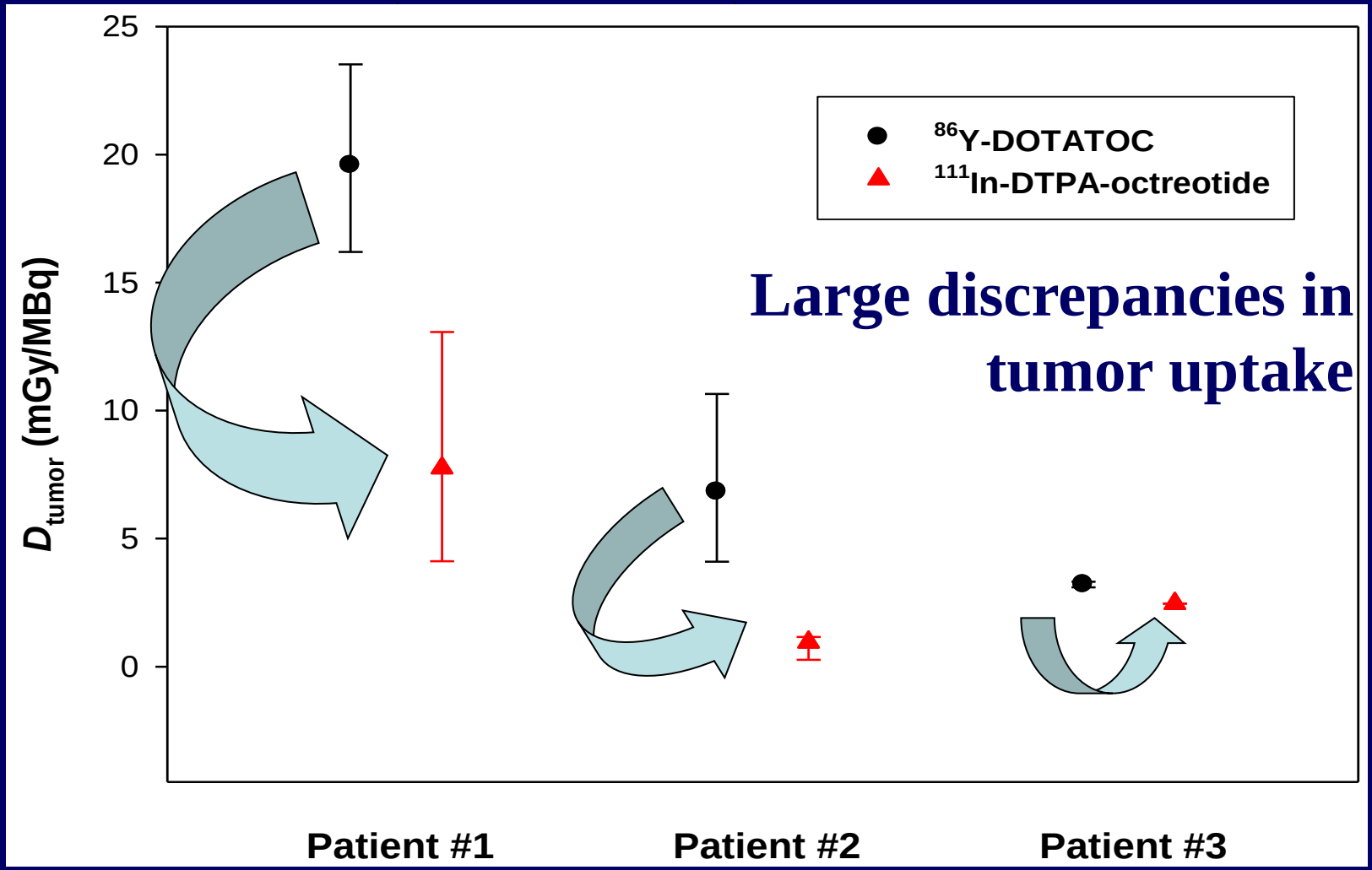
Scintigraphic abdominal images 5 & 24 h p.i. affected by carcinoid with extensive hepatic and paraaortal metastases.

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)



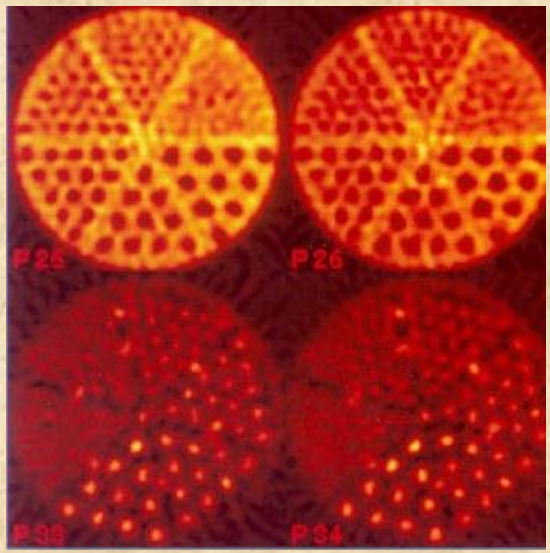
H.Wagner Jr: A diagnostic dosimetric imaging procedure will be unevoidable a part of the protocoll for the radioimmuno therapy (individual in vivo dosimetry).

F.Rösch et.al.

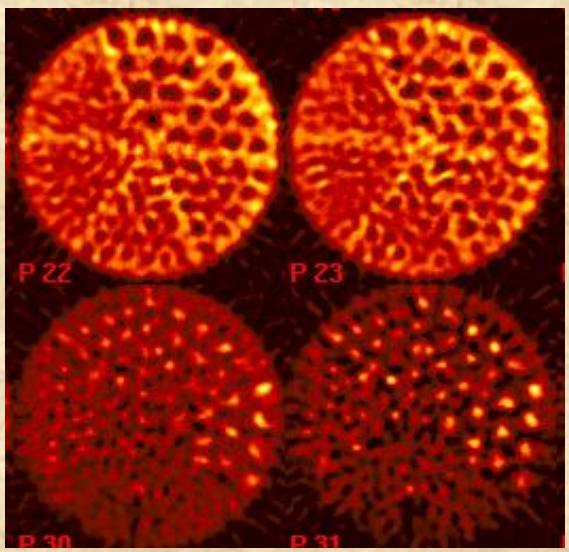
Rare Earth Elements: Positron Emitters

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

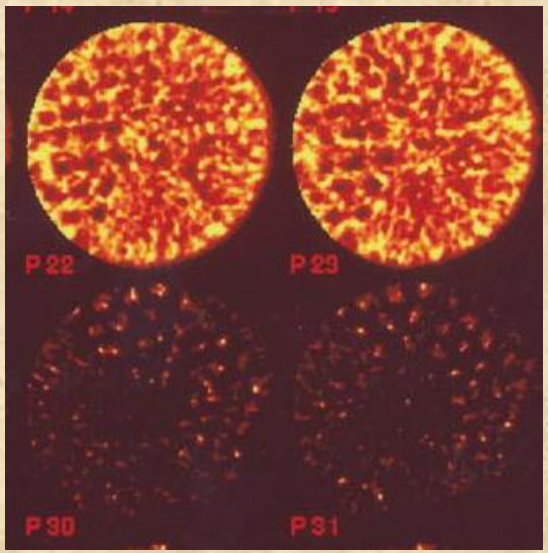
^{134}Ce/La



^{140}Nd/Pr



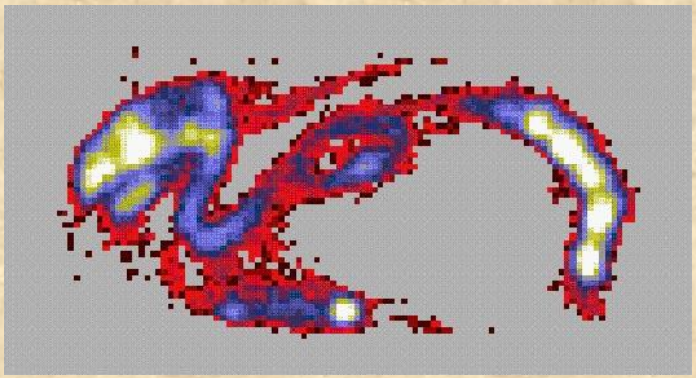
^{149}Tb

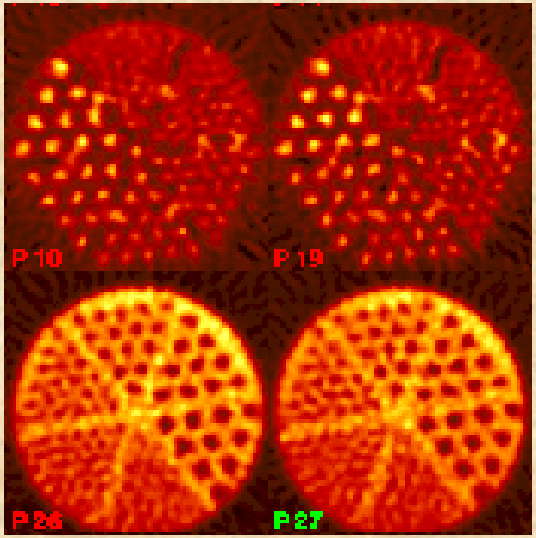


Positron emitting radiolanthanides

PET phantom studies

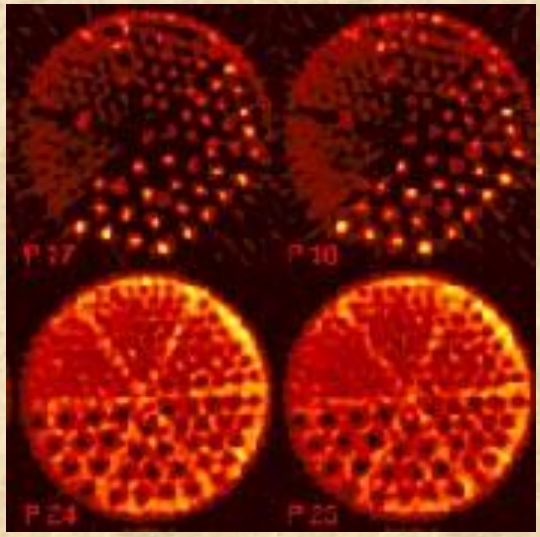
^{142}SmEDTMP in vivo study





^{138}Nd/Pr

^{142}Sm/Pm

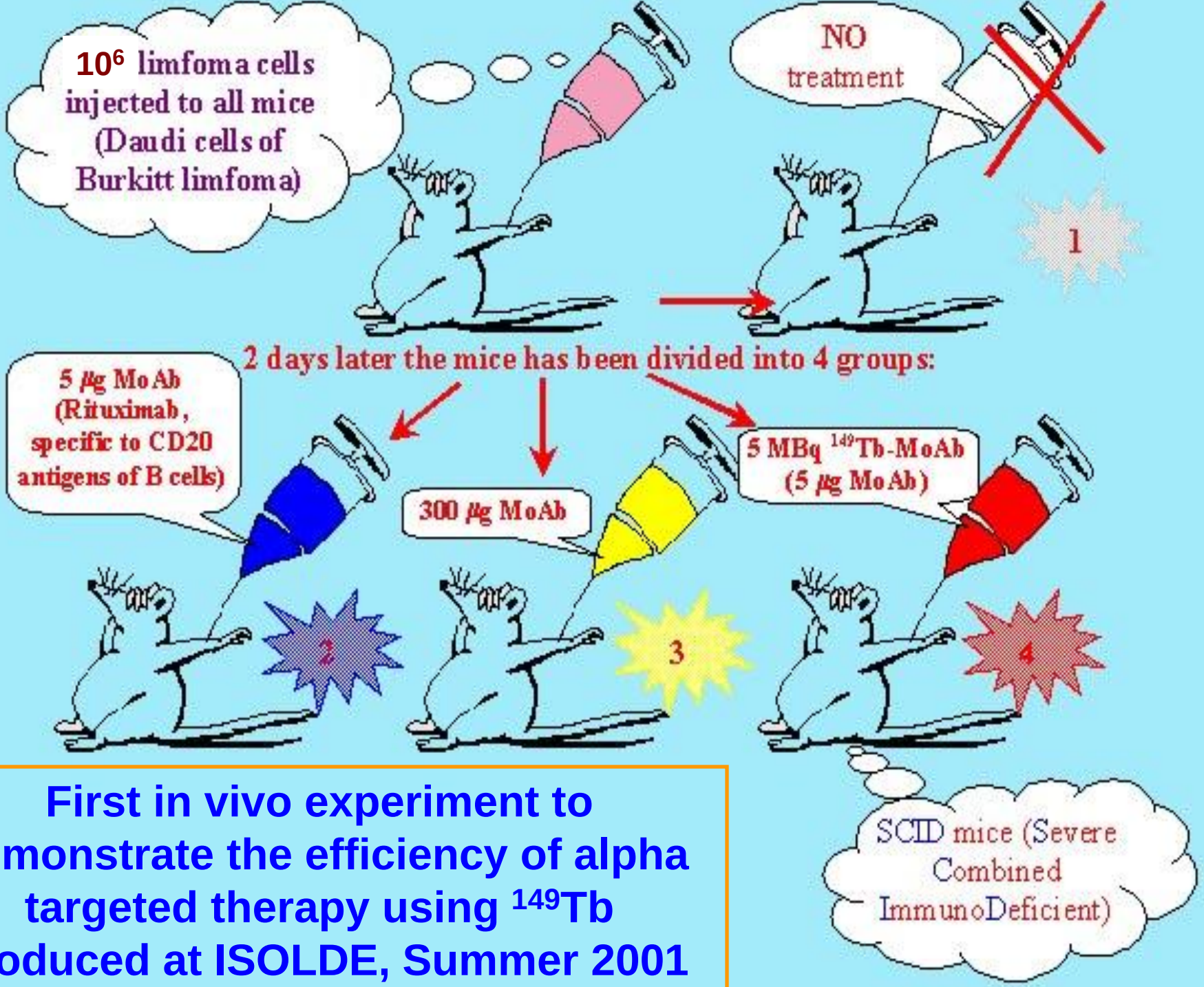


^{152}Tb

ISOTOPES in Therapy =
surgery with radiation

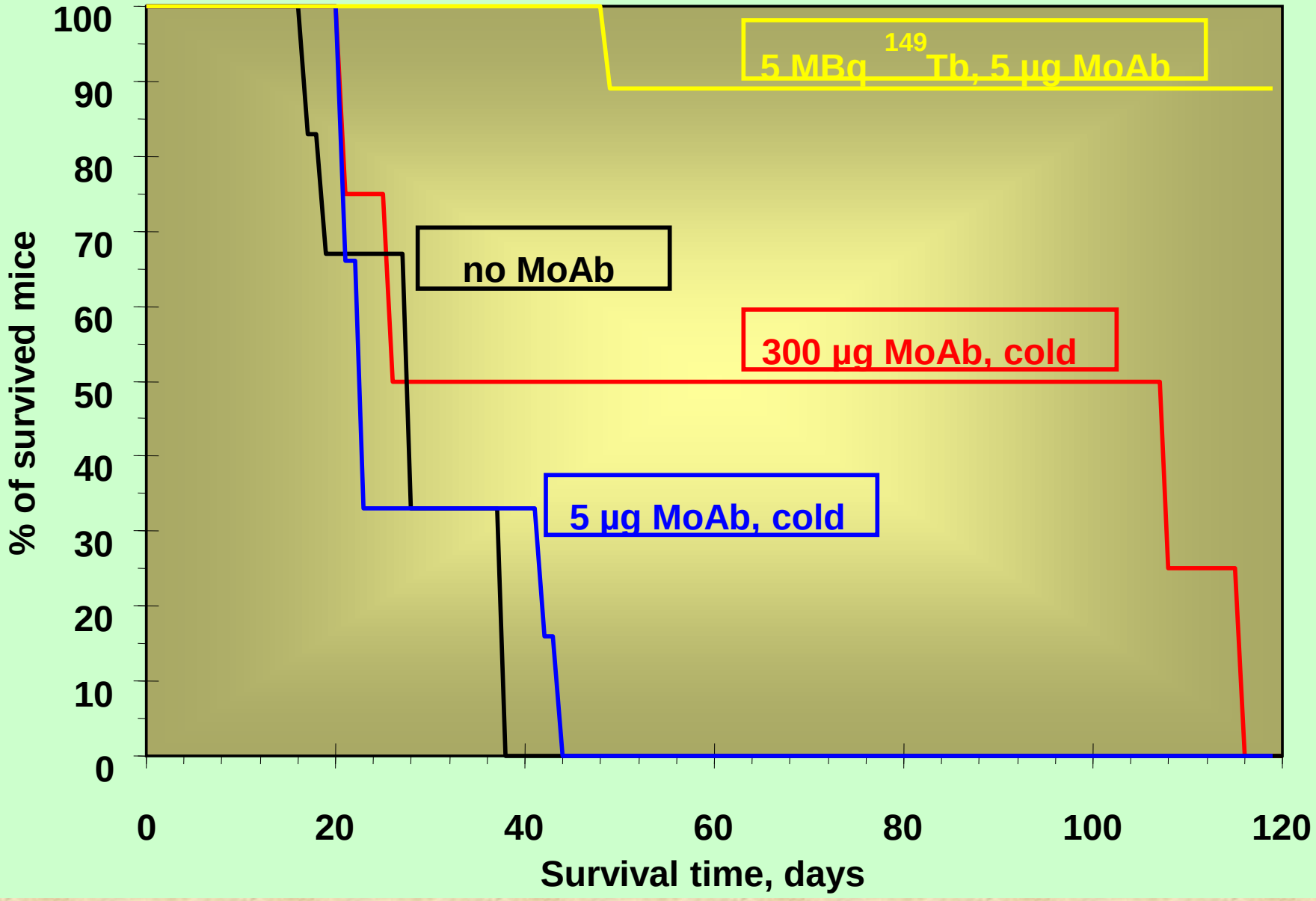
	Tissue surgery	Cell surgery	Molecular surgery
ISOTOPE	^{131}I, ^{90}Y, ^{153}Sm, ^{166}Ho, ^{177}Lu Others $E_{ß}$ 1 – 3 MeV	$^{212,213}Bi$, ^{211}At, ^{149}Tb, $^{223,224}Ra$ E_{α} 4–8 MeV	^{125}I ^{165}Er E_{e} few eV
Range	about 1 cm	30 – 80 µm	10 nm
	ß-Knife	α-Knife	Auger Knife

α-emitters for therapy



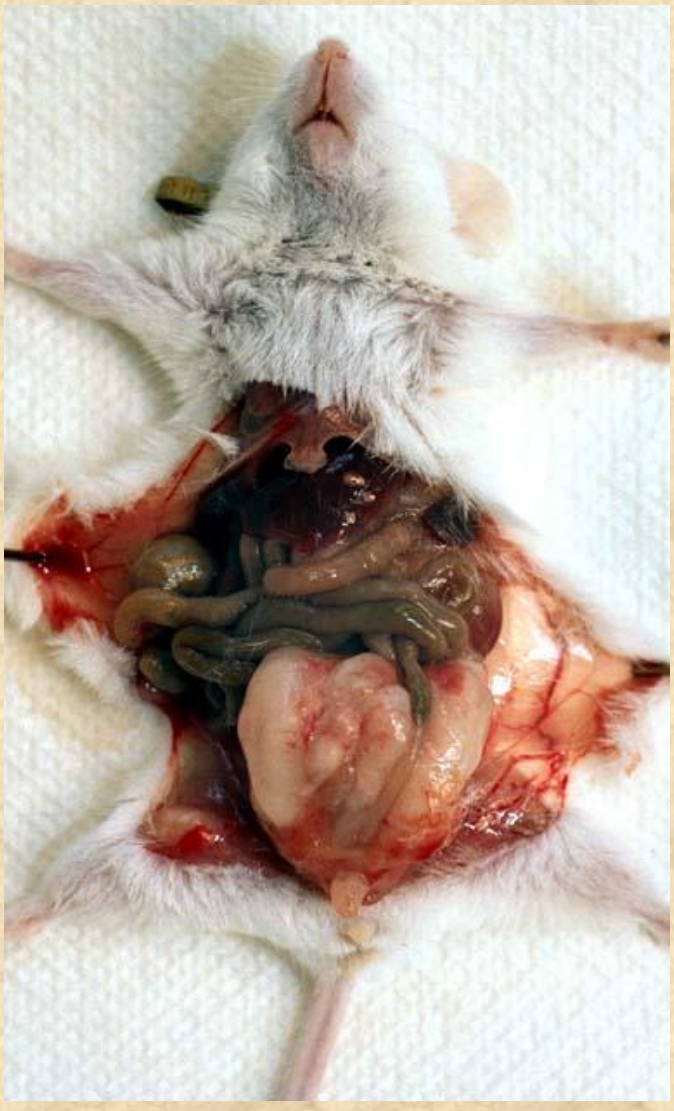
First in vivo experiment to demonstrate the efficiency of alpha targeted therapy using ^{149}Tb produced at ISOLDE, Summer 2001

Survival of SCID mice



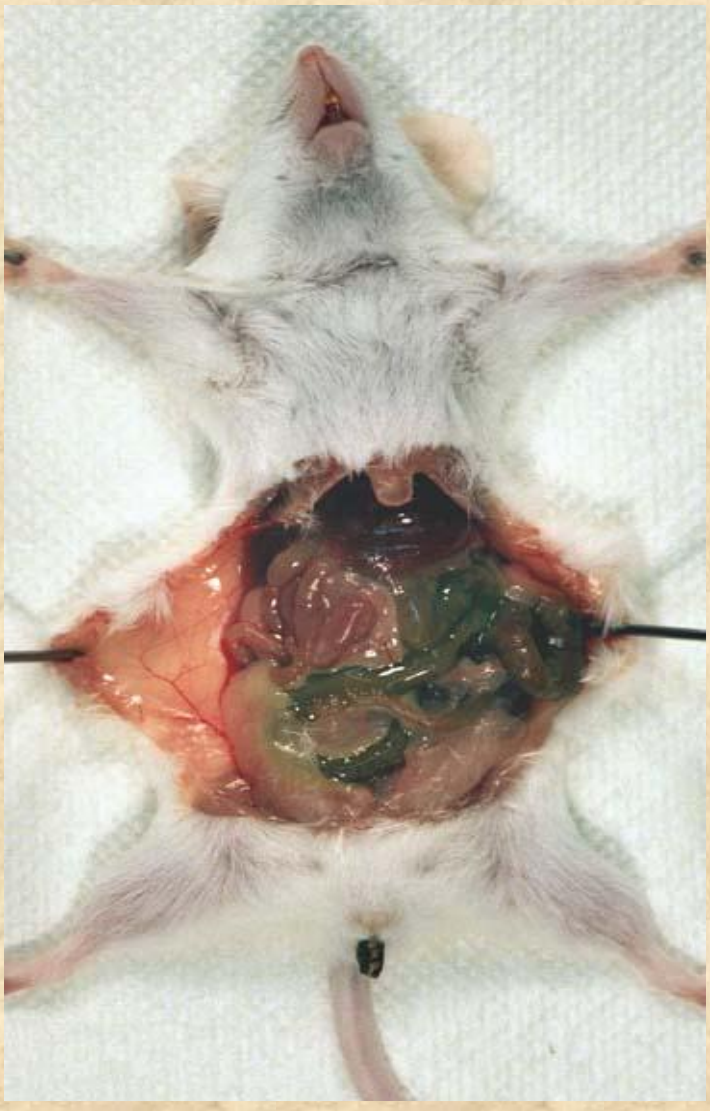
G.J.Beyer, M.Miederer, J.Comor et al. EJNM 2004, 31 (4), 547-554

103 d p.i.



300 µg mab cold

108 d p.i.

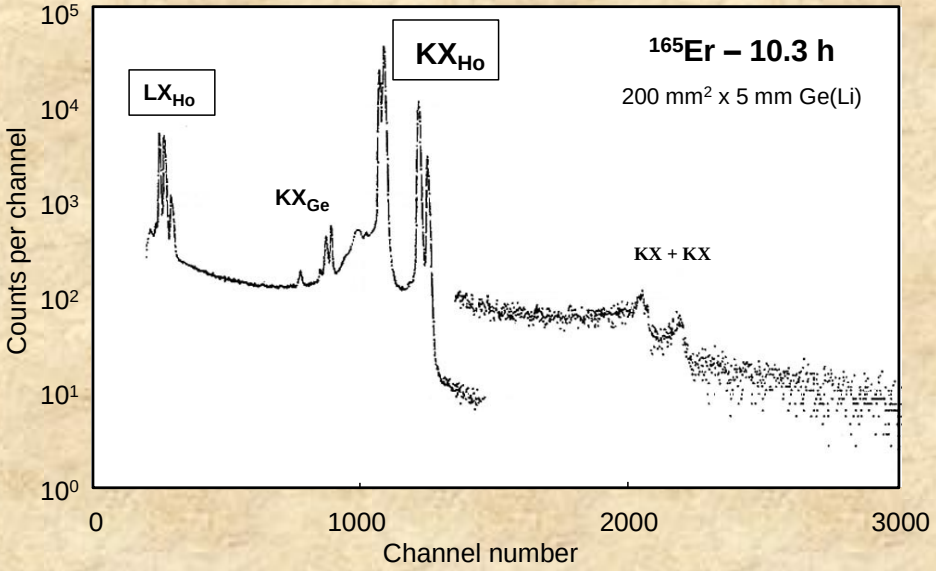


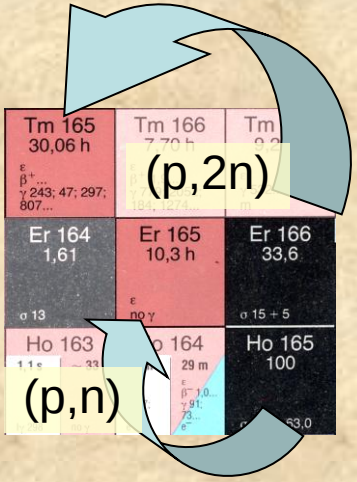
5 MBq ^{149}**Tb**-mab (5 µg)

AUGER electron emitters for therapy

^{165}Er

- Only very few radionuclides exists that decay exclusively by EC-mode without any accompanying radiation
- ^{165}Er is one of them
- All labeling techniques used for the three-valent radionuclides can be adapted without modifications.
- Generated in the EC-decay of the mother isotope ^{165}Tm
- Production routes suitable for theTESLA accelerator:





Yield:

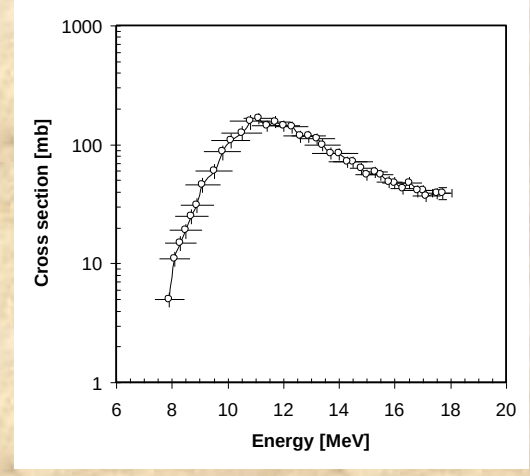
^{165}Ho (p,n) ^{165}Er

15 MeV p

50 µA

5 h

10 GBq



G. J. Beyer, S. K. Zeisler and D. W. Becker
Radiochimica Acta 92 (4-6) , 219, 2004

Isotope Production with Cyclotrons

The classical SPECT isotopes are produced via the (p,2n) process, the related p-energy is ~25 MeV

Because of the continuous high demand of ^{201}Tl, the (p,3n) is usually considered as a main product. The upper p-energy for producing ^{201}Tl is 30 MeV.

The short-lived PET isotopes are based mainly on the (p,n) process, ~15 MeV is the preferable proton energy. Normally dedicated small cyclotrons are used for PET. However, due to the high standard of targetry and production technology a large scale FDG-production can be integrated economically today into the program of a larger cyclotron, because of the low beam time demand.

New trends in radioimmuno therapy require alpha emitting nuclides. The ^{211}At needs to be produced via the (α,2n) Process. The related α-energy is 28 MeV.

A cyclotron, that can accelerate alpha particles to 28-30 MeV can principally accelerate p to energies higher than 30 MeV. Consequently, higher reaction processes such as (p,4n) or generally (p,xn) or even (p,xn,yp) processes are possible.

Such a multipurpose cyclotron with the option of high particle beam intensity and well developed tools for beam diagnosis and a certain variation of particle beam energy is an excellent universal instrument supporting commercial isotope production and R&D in the field of medical isotope application for diagnosis and therapy.

Commercial Isotope Production with cyclotrons
~30 MeV proton beam

- ^{201}Tl: $^{203}Tl\ (p,3n)\ ^{201}Pb \longrightarrow {}^{201}Tl$

  most important SPECT isotope, commercialized by all radiopharmaceutical Co. The worldwide installed production capacity exceeds the demand

- ^{123}I: $^{124}Xe\ (p,2n)\ ^{123}Cs \longrightarrow {}^{123}I$

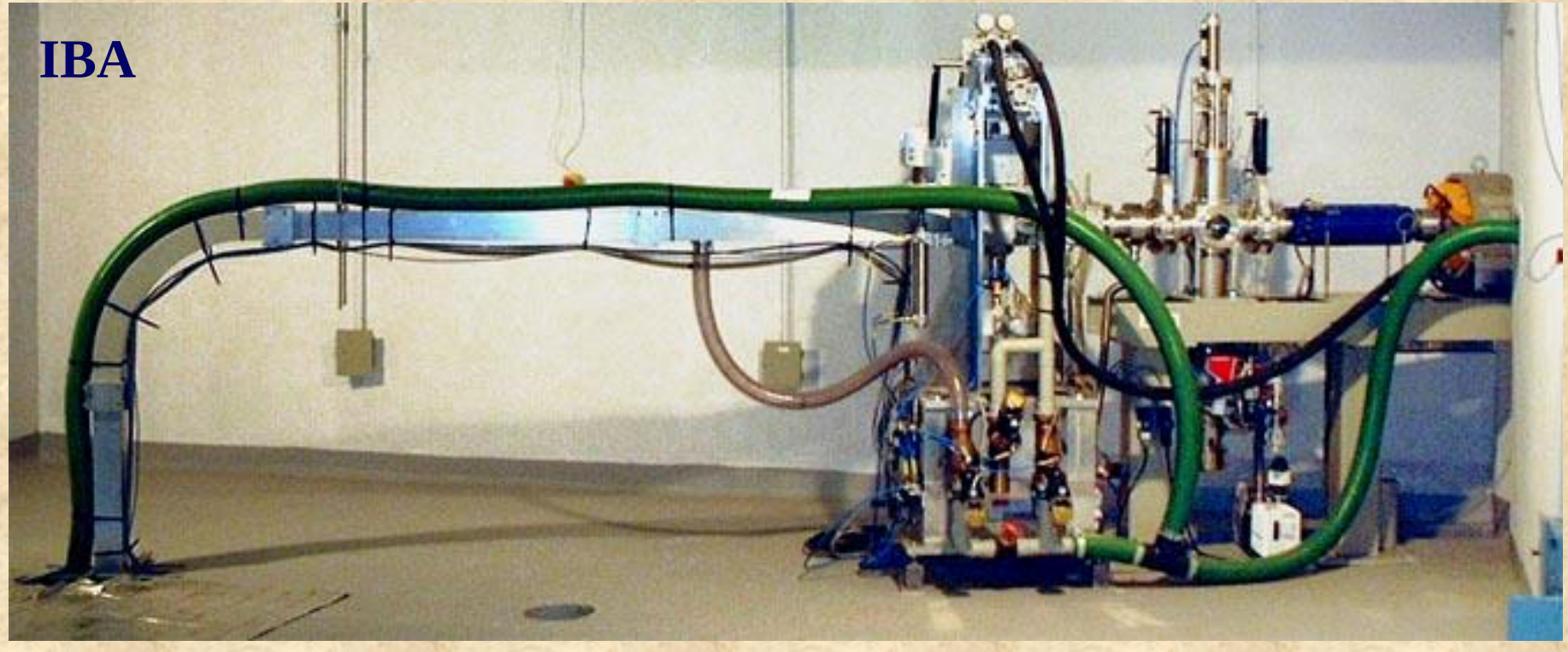
  very important SPECT isotope, corresponding target design from Karlsruhe is installed worldwide. Batch size up to 10 Ci possible.

- ^{111}In: $^{112}Cd\ (p,2n)\ ^{111}In$

  important for certain SPECT techniques, expensive because of low demand

- ^{67}Ga: $^{68}Zn\ (p,2n)\ ^{67}Ga$

  easy to make, low and decreasing demand



Target station for the production of ^{201}Tl

with beam diagnosis elements and
Automatic active target transport chain

Isotope Production with Cyclotrons

(p,n) process with ~15 MeV protons

- **^{18}F:** ^{18}O (p, n) ^{18}F

  most important PET isotope, commercialized by many centers using dedicated small cyclotrons, however also done at 30 MeV or even at 65 MeV cyclotrons as well (Nice)

- **^{124}I:** ^{124}Te (p,n) ^{124}I

  very important PET isotope with commercial interest (in-vivo dosimetry), large scale production technology not yet available, same technology could be used for medium scale ^{123}I production based on ^{123}Te target material

- **^{86}Y:** ^{86}Sr (p,n) ^{86}Y

  very important PET isotope with commercial interest (in-vivo dosimetry)

- **^{64}Cu:** ^{64}Ni (p,n) ^{64}Ga

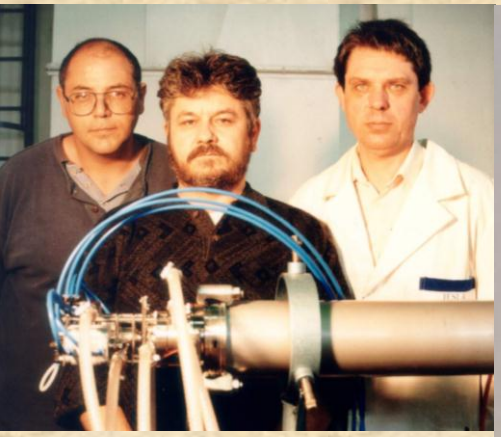
  easy to make, therapeutic isotope for RIT, PET allows the measurement of the biodistribution in sito.

- **^{186}Re:** ^{186}W(p,n) ^{186}Re

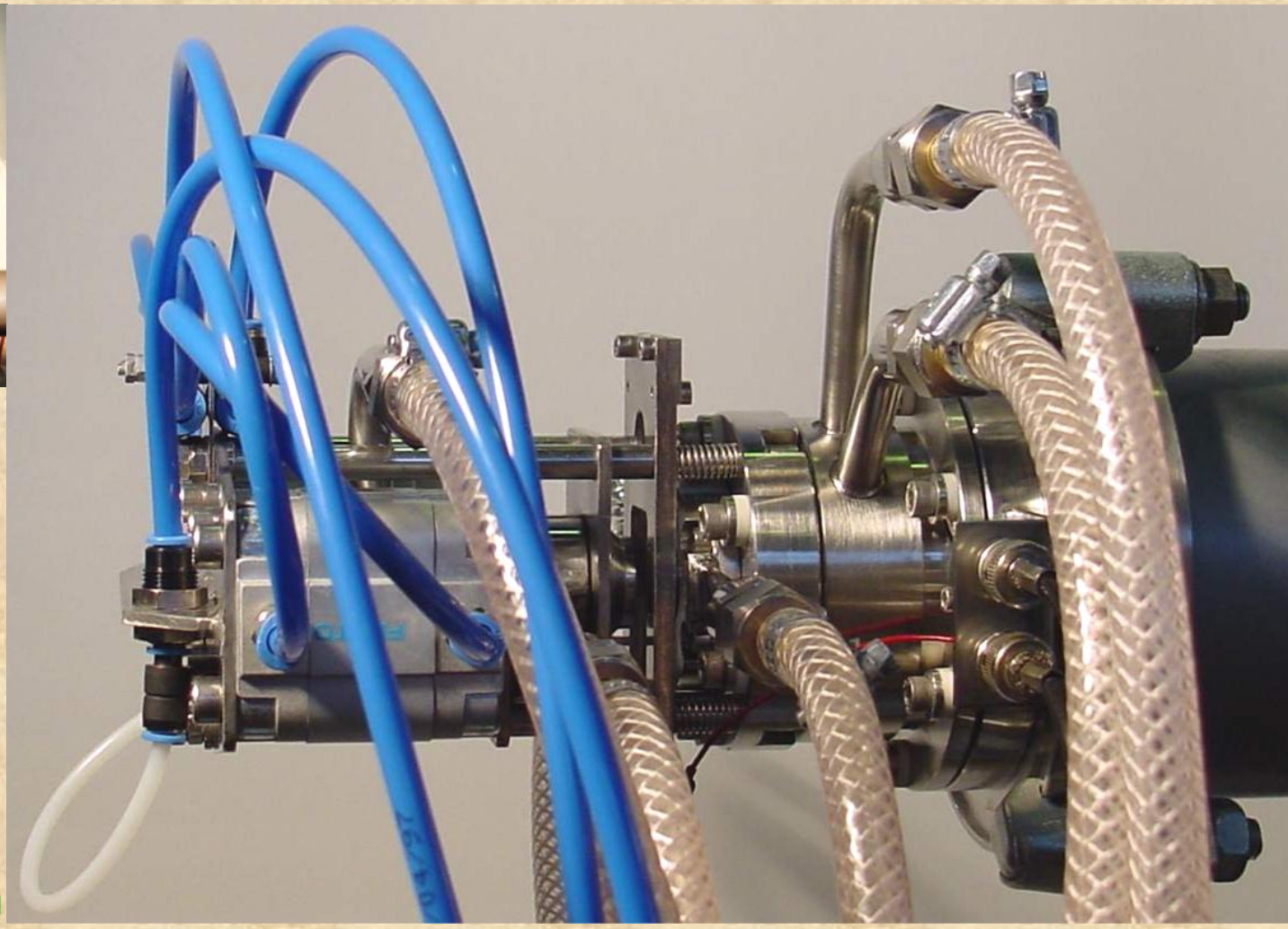
  ^{186}Re (3.7 d) is one of the two important therapeutic isotopes of Re. The advantage over ^{188}Re (16 h) is the longer half-life, the advantage over the reactor based ^{185}Re(n,γ)^{186}Re process is the carrier free quality.

- **Remark:** *The (p,n) process requires ~15 MeV only, and is performed normally at dedicated small PET cyclotrons. However, due to the high productivity of dedicated targets combined with a modern system for beam diagnosis allows to run these reaction under economical conditions at larger cyclotrons as well using only a small fraction of the available beam time.*

COSTIS : Test Installation in Belgrade



COSTIS and its constructors at the low energy beam line of the mVINIS ECR ion source at the TESLA Accelerator Installation in Belgrade, Yugoslavia



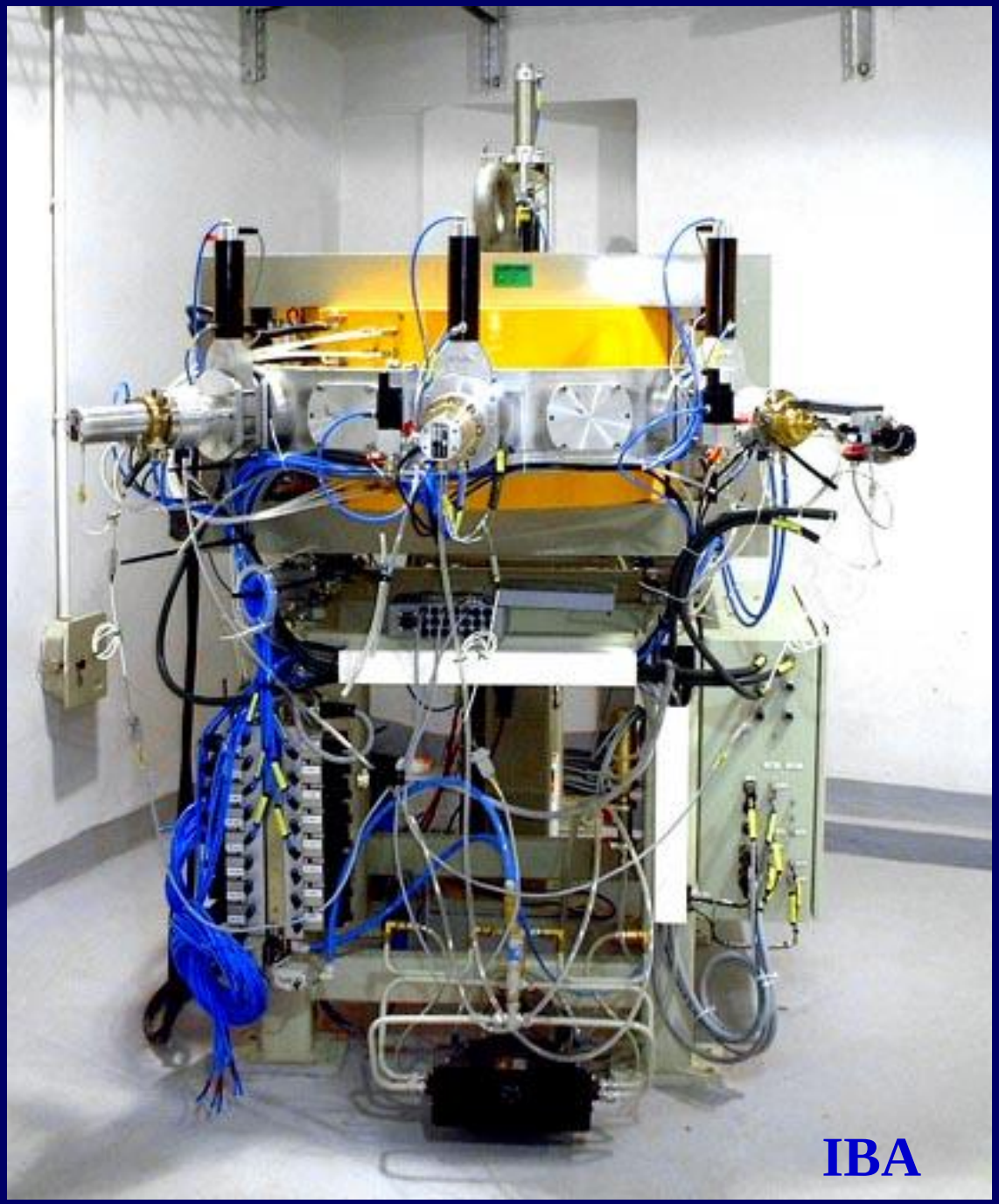
Production of other useful isotopes with < 20 MeV proton induced reactions

Isotope	$T_{1/2}$	Reaction	Batch size	Application
^{45}Ti	3.08 h	$^{nat.}$Sc (p,n) ^{45}Ti	100 GBq	PET: bioconjugates
^{55}Co	17.54 h	^{nat}Fe (p,2n) ^{55}Co	50 GBq	PET, encymes, vitamines
^{64}Cu	**12.7 h**	**^{64}Ni (p,n) ^{64}Cu**	**100 GBq**	**PET & therapy,**
^{67}Cu	61.9 h	^{70}Zn (p,α) ^{67}Cu	50 GBq	therapy, bioconjugates
^{66}Ga	**9.4 h**	**^{66}Zn (p,n) ^{66}Ga**	**50GBq**	**PET**
^{76}Br	16 h	^{76}Se (p,n) ^{76}Br	10 GBq	PET
^{81}Rb/^{81m}Kr	4.58 h	^{82}Kr (p,2n) ^{81}Rb	20 GBq	Generator, SPECT
^{86}Y	**14.7 h**	**^{86}Sr (p,n) ^{86}Y**	**50 GBq**	**PET, bioconjugates**
^{89}Zr	78.4 h	^{89}Y (p,n) ^{89}Zr	20 GBq	PET, bioconjugates
^{90}Nb	14.6 h	^{90}Zr (p,n) ^{90}Nb	20 GBq	PET, bioconjugates
^{94}Tc	4.9 h	^{94}Mo (p,n) ^{94}Tc	20 GBq	PET
^{110}In	69.1 m	^{110}Cd (p,n) ^{110}In	20 GBq	PET
^{120}I	1.35 h	^{120}Te (p,n) ^{120}I	10 GBq	PET
^{123}I	**13.2 h**	**^{123}Te (p,n) ^{123}I**	**20 GBq**	**SPECT**
^{124}I	**4.15 d**	**^{124}Te (p,n) ^{124}I**	**2 GBq**	**PET**
^{165}Er	10.3 h	^{nat}Ho (p,n) ^{165}Er	40 GBq	Auger Therapy
^{186}Re	90.6 h	^{186}W (p,n) ^{186}Re	20 GBq	Therapy

The irradiation of solid materials requires much better beam quality parameters than gas targets. Consequently, beam homogenisation and beam manipulation is needed, usually not possible at the PET cyclotrons.

External beam lines, known from classical isotope production at cyclotrons, will take this function over.

The new generation of multi-purpose cyclotrons will be equipped with high-tech diagnostic tools and provide higher beam current than in the past.



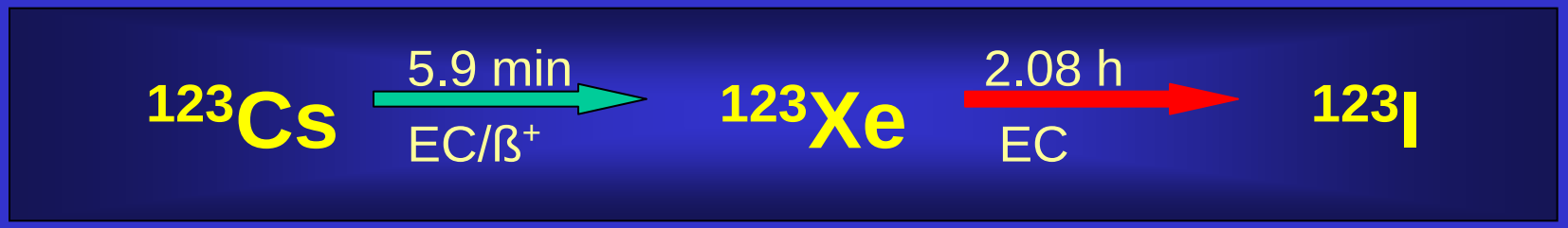
PET-isotope production at the IBA 30 MeV cyclotron:

Target station

at the end of one beam line equipped with 5 target ports

^{18}F: $H_2{}^{18}O$ target
^{11}C: N_2-target
^{15}O: N_2-target
2 positions free

123-IODINE PRODUCTION ROUTES



1985 Karlsruhe, Canada	1980 Würenlingen PSI	1975 many places
^{124}Xe (p,2n)	^{127}I (p,5n)	^{124}Te (p,2n)
20 – 30 MeV p	75 MeV p	22 – 28 MeV
^{125}I < 10-3 %	^{125}I < 1 %	^{124}I = 1 %

ALTERNATIVES:

local ^{123} I production using PET cyclotrons

^{123}Te (p,n) ^{123} I

15 MeV p, 150 MBq/µAh

Fast, easy, reliable, clean product, suitable for direct labeling,

^{124}I: $^{124}TeO_2$ (p,n) ^{124}I

^{124}I

$T_{1/2}$ = 4.17 d

$ß^+$ = 22.8 %

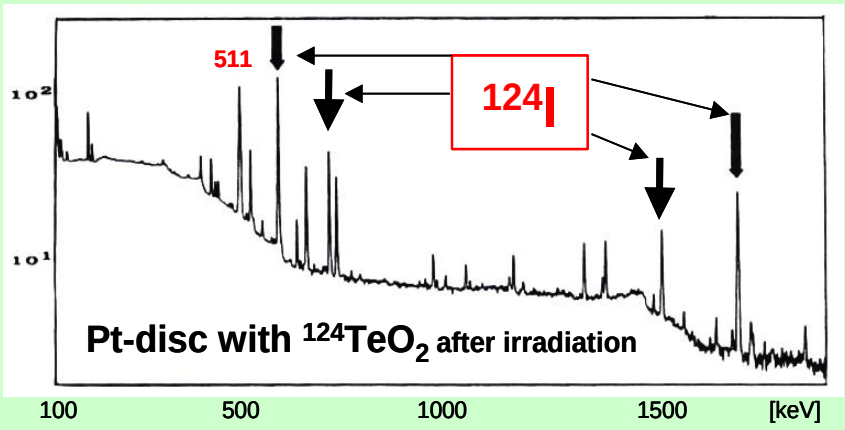
$E_{ß max}$ = 2.1 MeV

~13 MeV, 0.45 mCi/µAh ^{124}I
^{123}I = 0.1 % EOB + 2 d

R.J. Ylimaki, M.Y. Kiselev, J.J. Čomor, G.-J. Beyer

•DEVELOPMENT OF TARGET DELIVERY AND RECOVERY SYSTEM FOR COMMERCIAL PRODUCTION OF HIGH PURITY IODINE-124

WTTC 10, Madison (USA), 2004



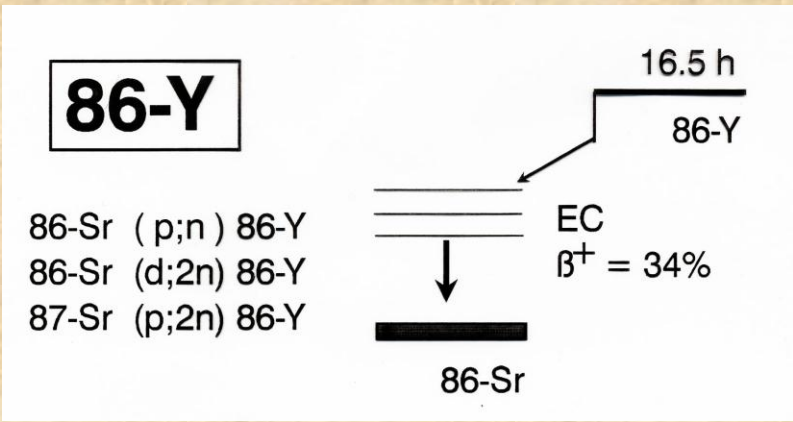
irradiation time: 1 h, 10 µA, protons

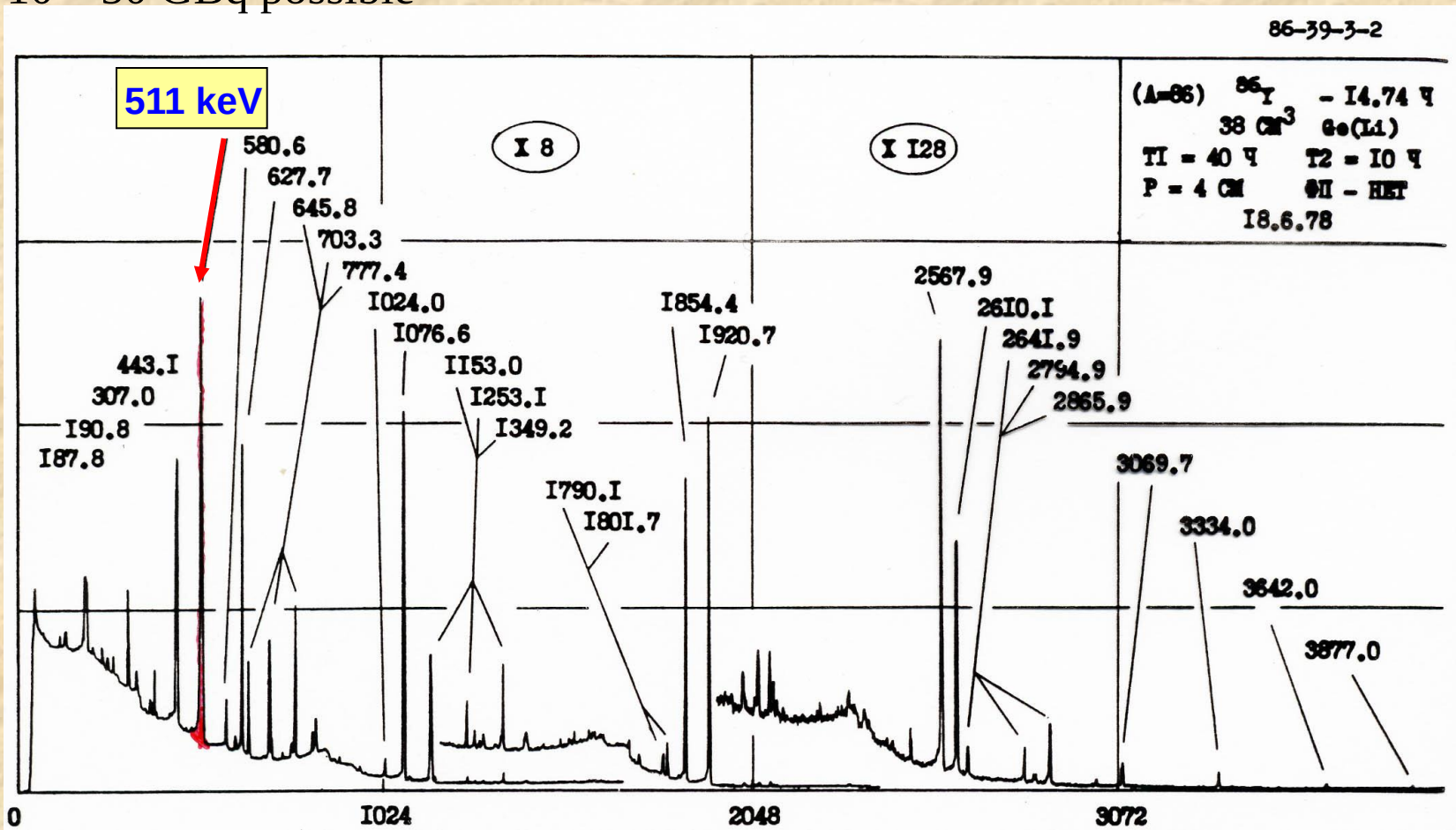
	15	13 MeV
^{124}I : (p,n)	250	150 MBq
^{123}I: (p,2n)	680	75 MBq

After 2 d: 178 / 51 MBq

^{86}Sr (p,n) ^{86}Y

enriched ^{86}SrO target, Pt-backing,
~15 MeV p
electrochemical separation technology
Yield: 3.2 mCi/µAh with 13 MeV,
[Rösch, 1990 ZfK-728]
10 – 50 GBq possible





Isotope Production with Cyclotrons
The (p,4n) process

- **^{82}Sr:** ^{85}Rb (p,4n) ^{82}Sr

  ^{82}Sr generates the short-lived ^{82}Rb (80 sec), which is an positron emitter. This generator nuclide is used for PET in nuclear cardiology. The low availability and the still relatively high price hampered a larger distribution so far. Produced at TRIUMF(Ca), Protvino (Ru), South Africa and LosAlamos. Liquid Rb-metal sealed in silver bodies is used as target. High beam intensity is used.

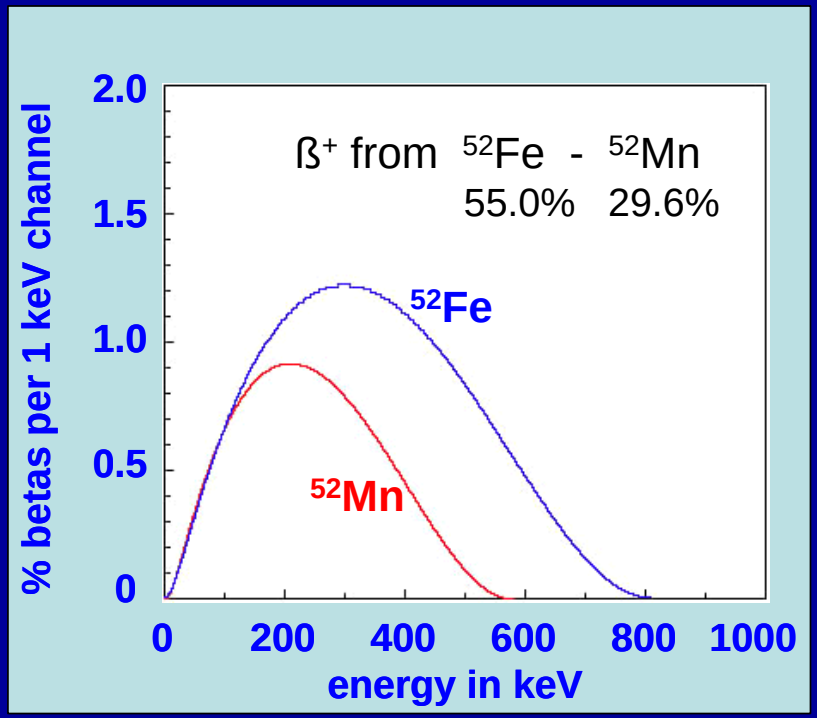
- **^{52}Fe:** ^{55}Mn (p,4n) ^{52}Fe

  ^{52}Fe is an interesting radionuclide for PET, it generates the 20 min ^{52}Mn daughter nuclide that can be used in PET.

- **^{149}Tb:** ^{152}Gd (p,4n) ^{149}Tb

  ^{149}Tb has shown its potential in TAT (targeted alpha therapy) as it is a partial alpha emitting nuclide and any bio-conjugate (monoclonal antibodies or peptides) can be easily labeled with this interesting nuclide

$$^{52}Fe \xrightarrow[8.3\ h]{\beta^+,EC} {}^{52}Mn \xrightarrow[21\ m]{\beta^+,EC} {}^{52}Cr$$



Isotope Production with Cyclotrons
The (α,2n) process

- **^{211}At:** ^{209}Bi(α,2n) ^{211}At

  Among the very few suitable alpha emitting radionuclides for the ^{211}At turns out to be the most suitable candidate for the medical application (targeted alpha therapy) presently a subject of intense international research activity.

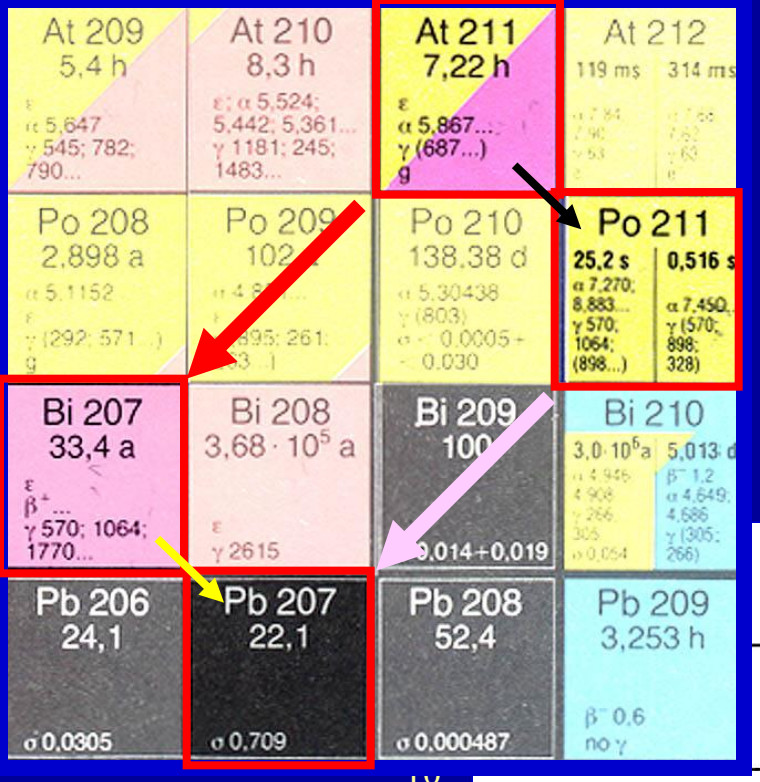
  The ^{211}At can be produced by irradiating of natural Bi targets with 28 MeV alpha particles. Newly developed targets allow a production on large scale:

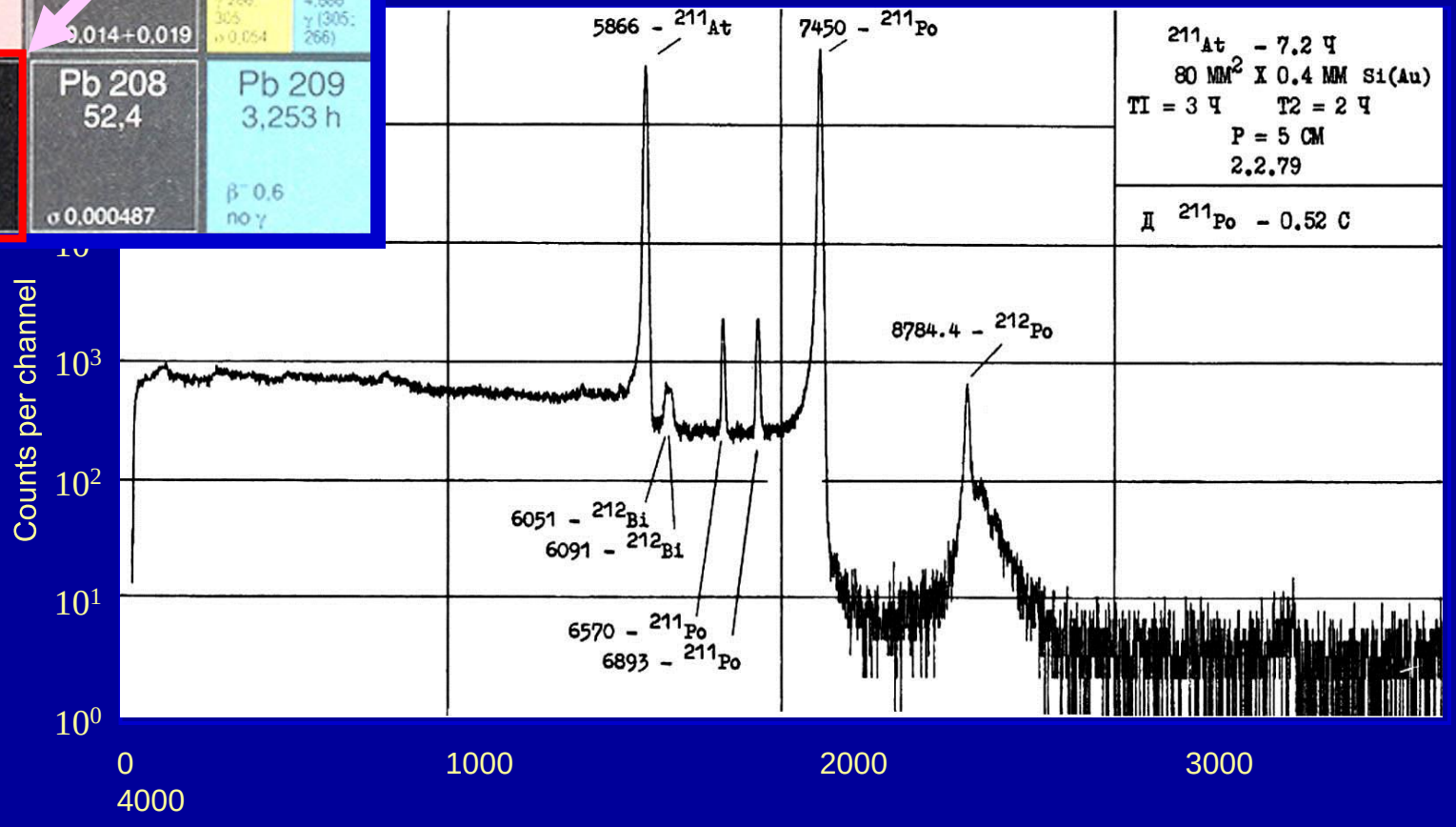
  Production yield is ~ 40 MBq/Ah, production batches of 10 GBq are technically possible. A typical patient dose for therapy will range between 0.4 and 2 GBq.

^{211}At (7.2h)

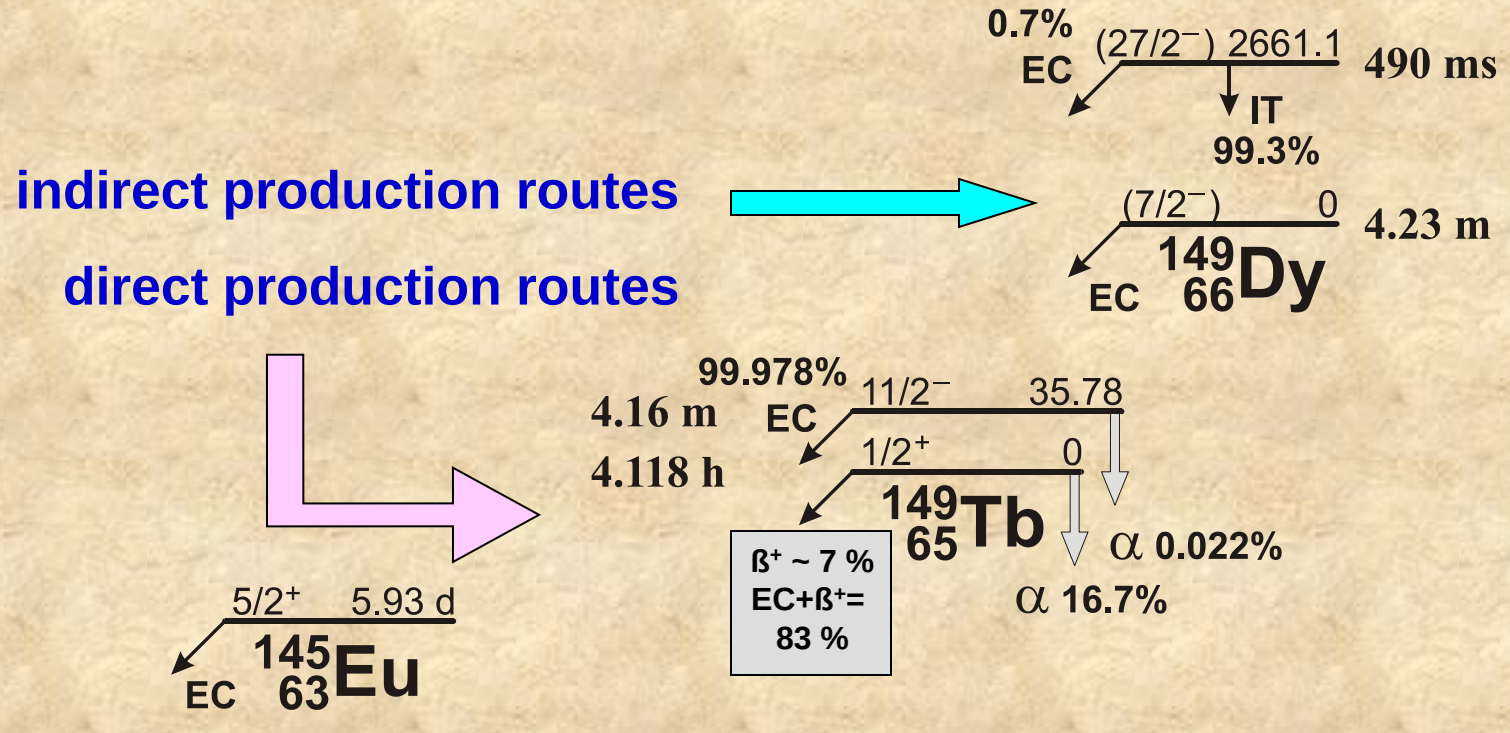
^{207}Bi (α,2n) ^{211}At

28 MeV, ~20 MBq/μAh





Segment of the decay chain A = 149



Indirect production routes

$^{138}Ce(^{16}O,5n)^{149}Dy$

$^{143}Nd(^{12}C,6n)^{149}Dy$

$^{136}Ce(^{16}O,3n)^{149}Dy$

$^{142}Nd(^{12}C,5n)^{149}Dy$

$^{144}Sm(^{9}Be,4n)^{149}Dy$

$^{152}Gd\ (\alpha,7n)\ ^{149}Dy$

$^{152}Gd\ (p,4n)\ ^{149}Tb$

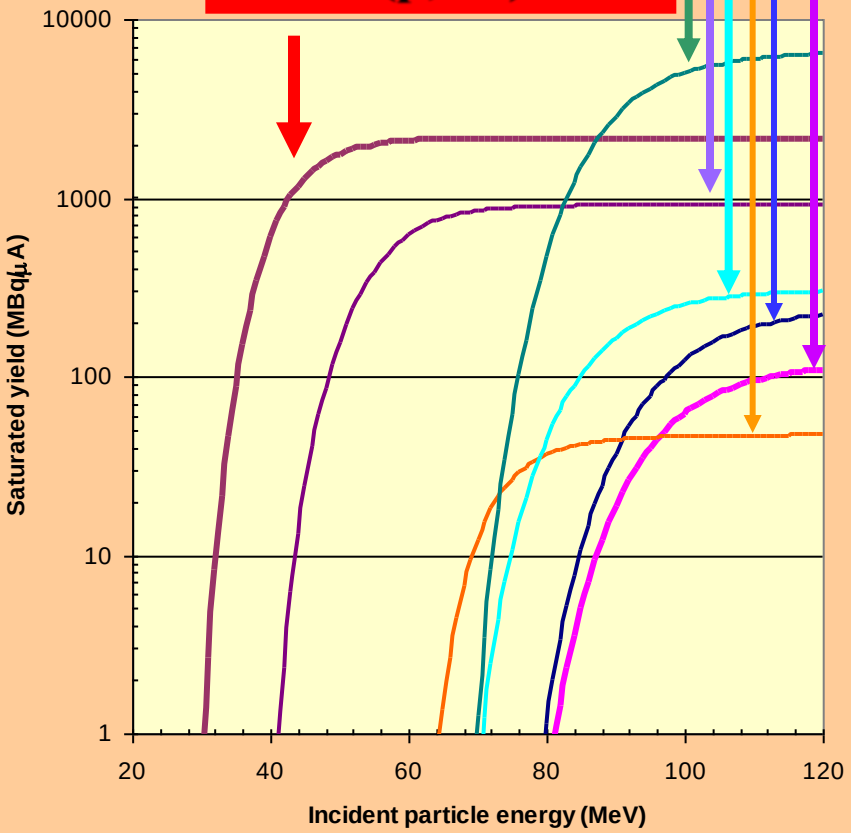
^{4}He

p

^{9}Be

^{12}C

^{16}O



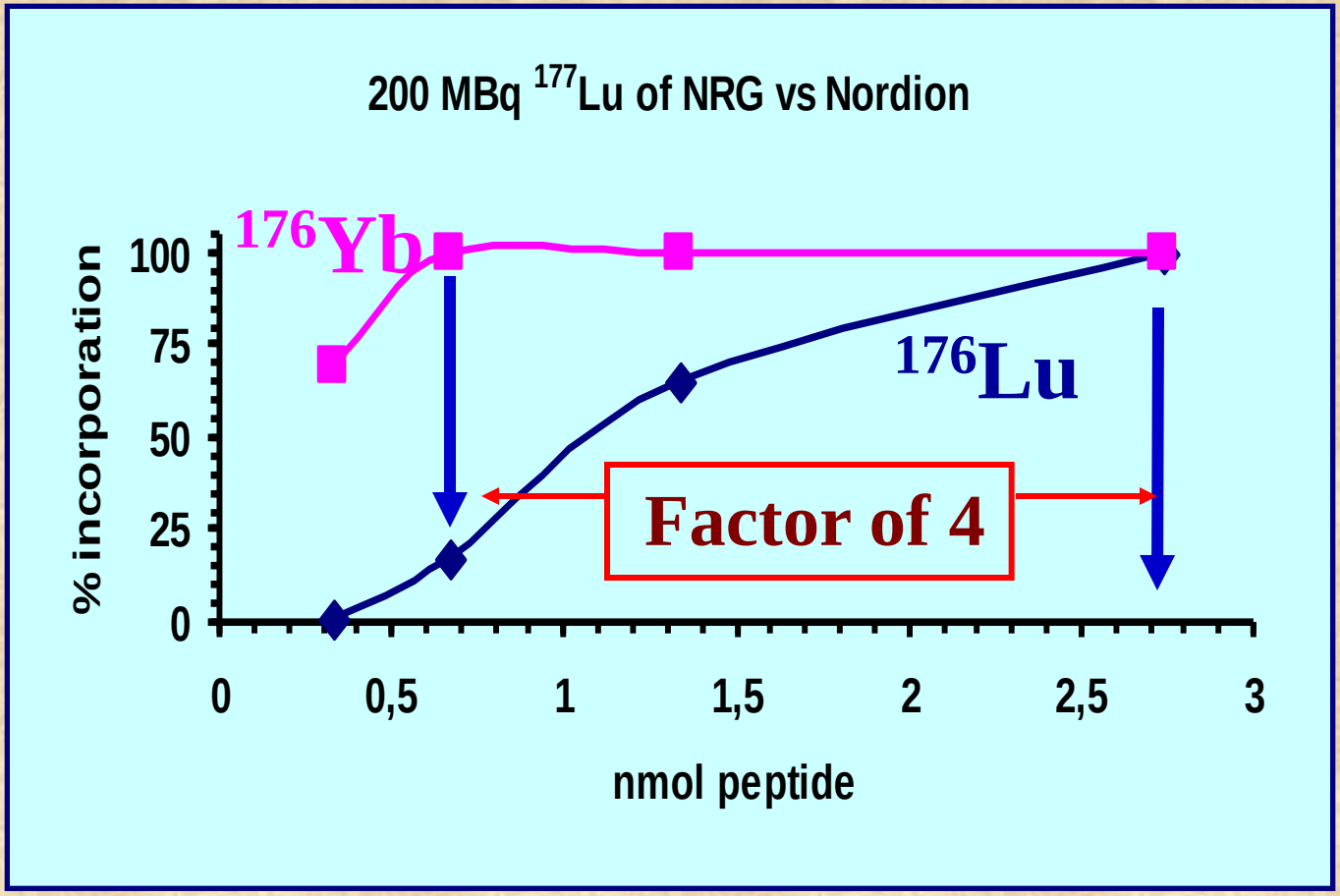
Higher Quality is required

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

- R&D needed for development of alternative technologies producing carrierfree radioisotope preparations for therapy.

- Reactor versus cyclotron production routes:
  $^{185}Re\ (n,\gamma)^{186}Re$ // $^{186}W\ (p,n)\ ^{186}Re$
  67Cu
  others
- Other alternatives:
  spallation reaction (CERN)
  isotope separation (of radioactive preparations)

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

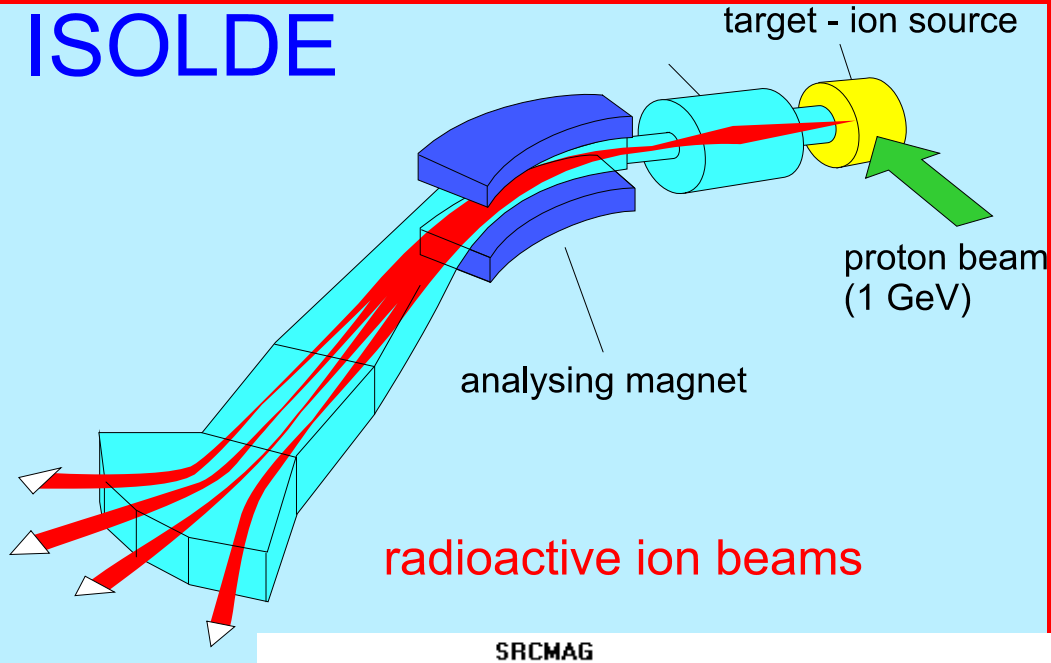
122 g/cm^2 Ta (rolls of 25 μm foils)

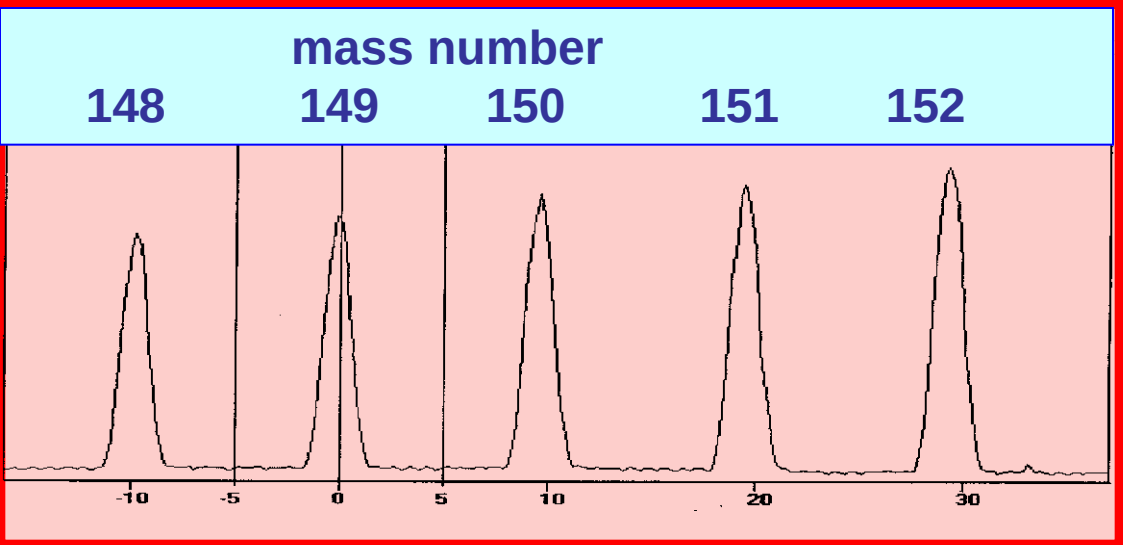
at 2400 ^{o}C

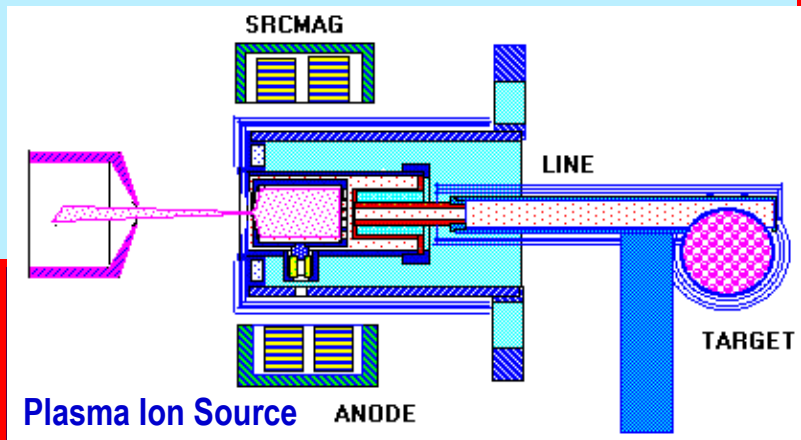
W-tube as ionizer at 2800^{o}C

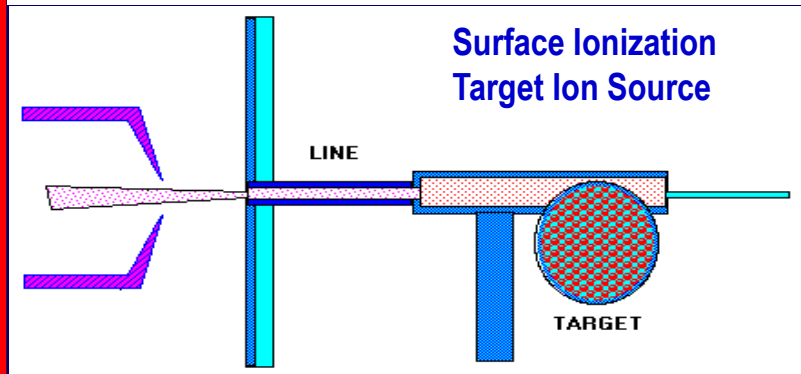
Radioactive Ion Beams of

40 elements possible today







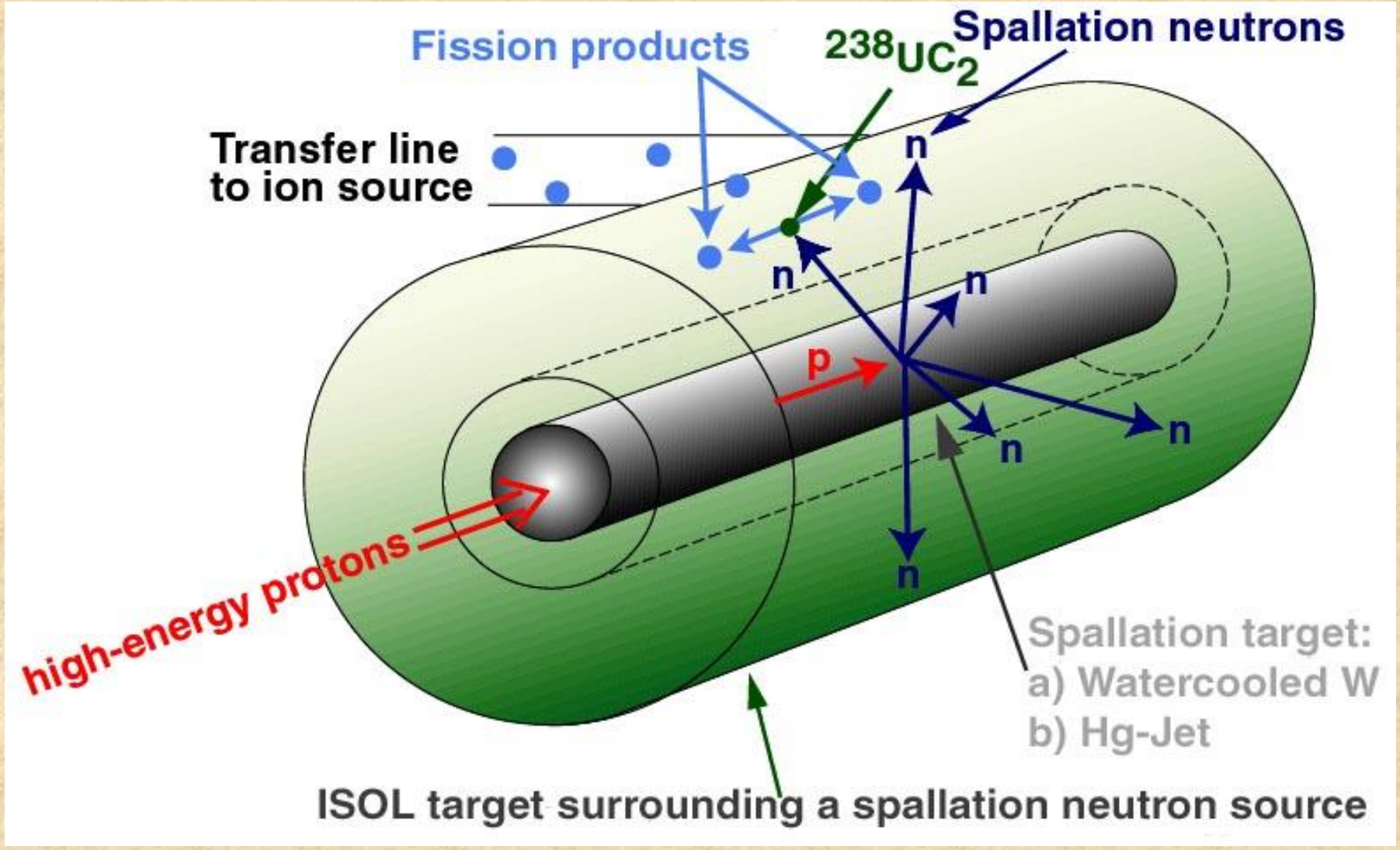


Alterantive Production Route:

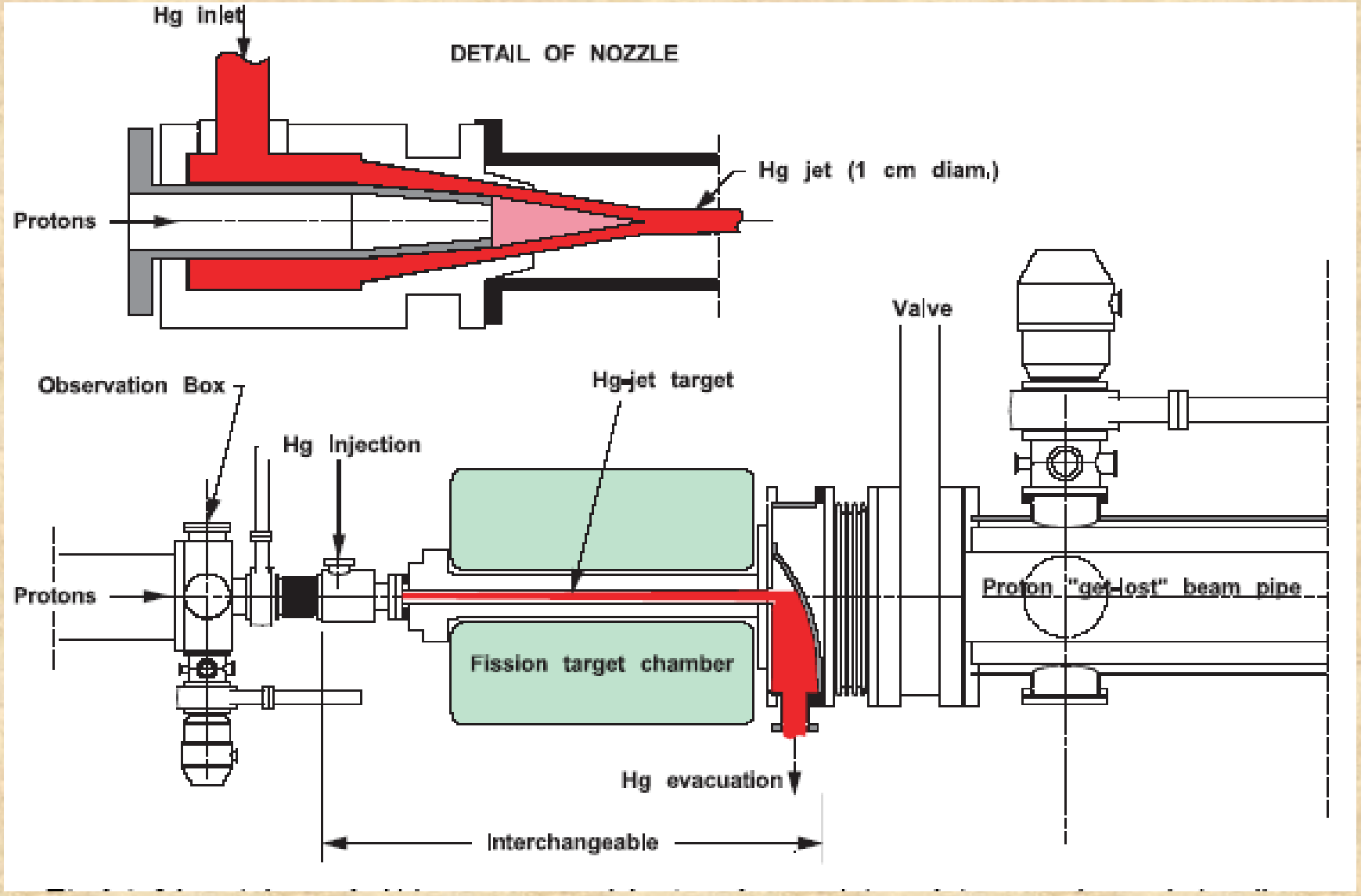
high energy proton induced

Spallation Reaction

1 MW target for 10^{15} fissions per s

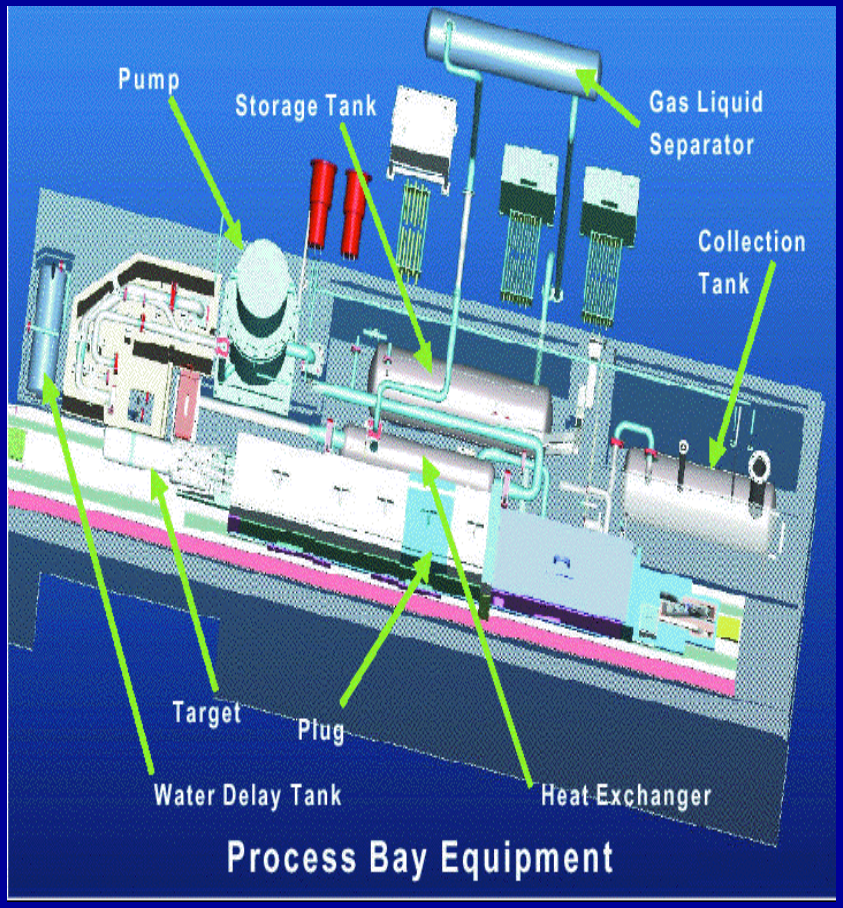


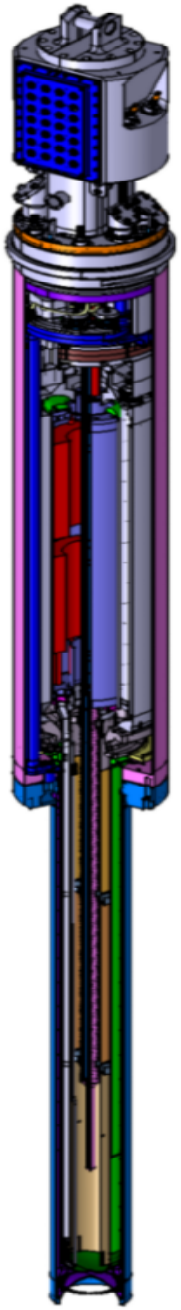
Hg-jet p-converter target



The SNS neutron source target station under construction

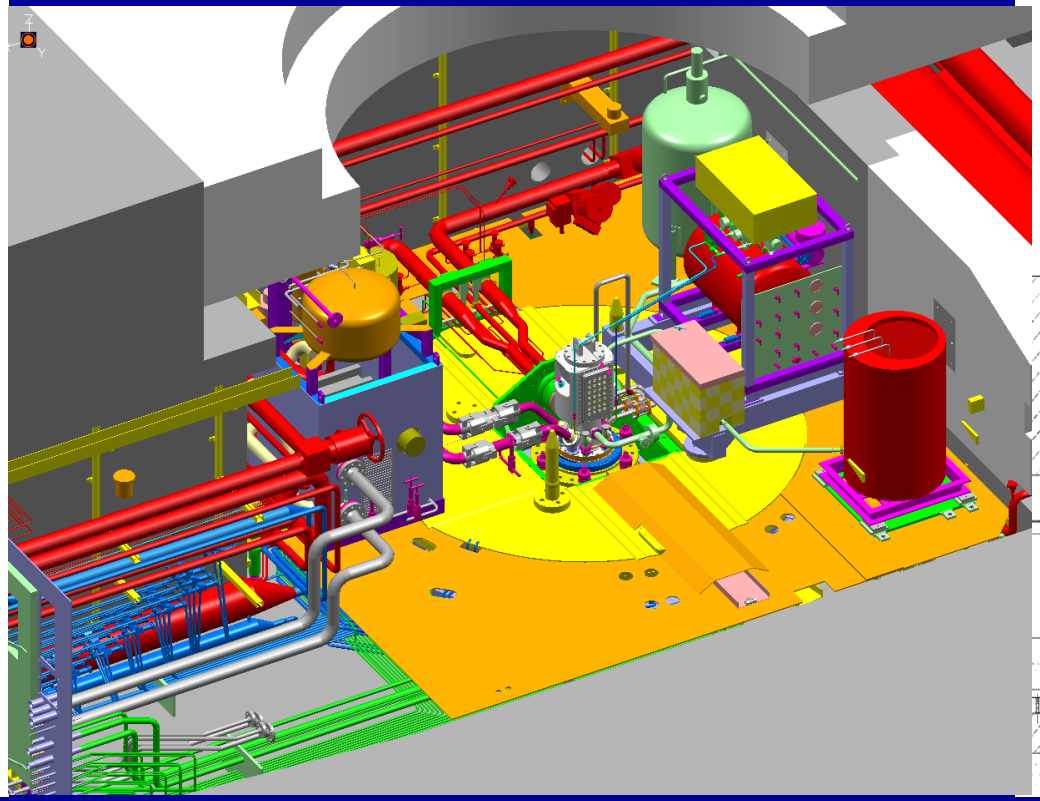
- Operating pressure 100 Bar
- Flow rate 2 t/m
- Jet speed 30 m/s
- Jet diameter 10 mm
- Temperature
  - Inlet to target 30° C
  - Exit from target 100° C
- Power absorbed in Hg-jet 1 MW
- Total Hg inventory 10 t
- Pump power 50 kW

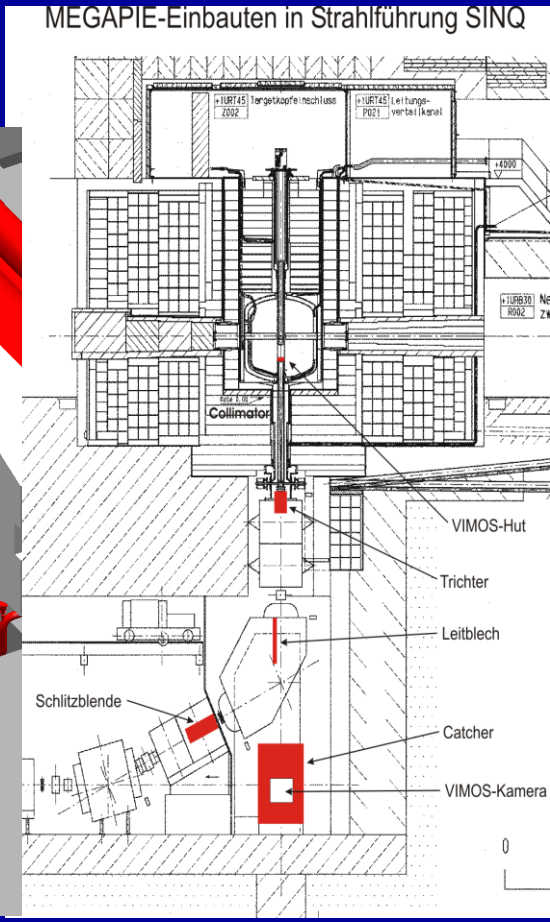




The MEGAPIE 1MW molten PbBi target under construction at PSI

Operation scheduled for 2006





What can nuclear centers do?

- Own specific medical isotope programs
- Keep existing classical facilities running (^{211}At)
- 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