Non-conventional radionuclides

in

personalised medicine

Thierry STORA – CERN

Academic Training Lecture Regular Programme

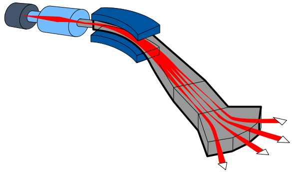
https://indico.cern.ch/event/1145660/

CERN

Did you say ?

non conventional radionuclides (production/purification)

in personalised medicine

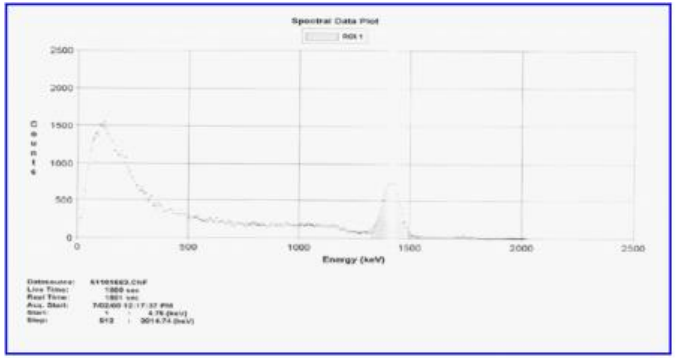


Radioisotopes in biological organisms

Daily, we “internalize” radiomarkers with rather well defined protocols

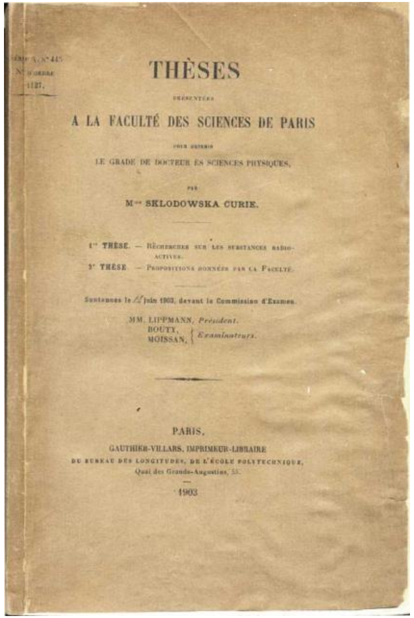
Country	France
Source	Évian-les-Bains
Type	still
pH	7.2
Calcium (Ca)	80
Chloride (Cl^-)	6.8
Bicarbonate (HCO_3)	360
Magnesium (Mg)	26
Nitrate (NO_3)	3.7
Potassium (K)	1
Silica (SiO_2)	15
Sodium (Na)	6.5
Sulfates (SO)	12.6
Website	http://www.evian.com

All values in milligrams per liter (mg/l)



M Goma et al

The early days


THÈSES

A LA FACULTÉ DES SCIENCES DE PARIS

LE GRADE DE DOCTEUR ÈS SCIENCES PHYSIQUES,

M^me SKLODOWSKA CURIE.

1^re THÈSE. — Recherches sur les substances radio-actives.

2^e THÈSE. — Propositions données par la Faculté.

Soutenues le 25 juin 1903, devant la Commission d'Examen.

MM. LIPPMANN, Président.
BOUTY, MOISSAN, Examinateurs.

PARIS,
GAUTHIER-VILLARS, IMPRIMEUR-LIBRAIRE
DU BUREAU DES LONGITUDES, DE L'ÉCOLE POLYTECHNIQUE,
Quai des Grands-Augustins, 55.
1903

Marie Sklodowska-Curie
1867-1934

Published:
May 12th 1921
© The New York Times

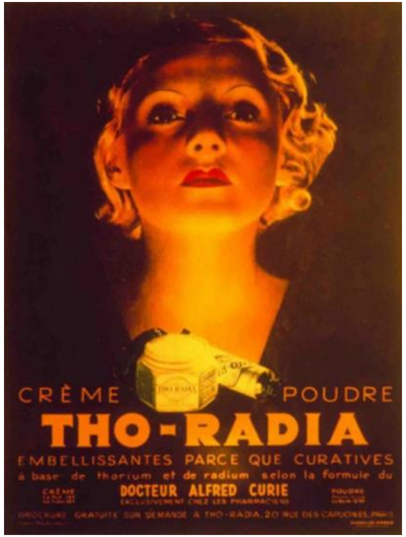

The New York Times.

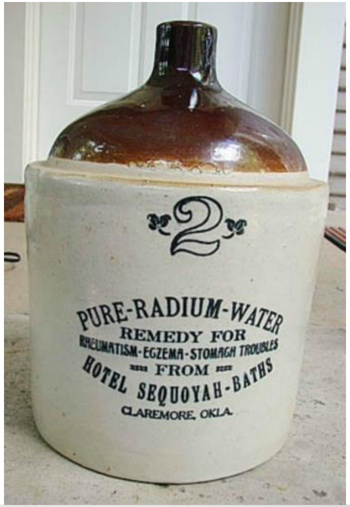
MME. CURIE PLANS TO END ALL CANCERS

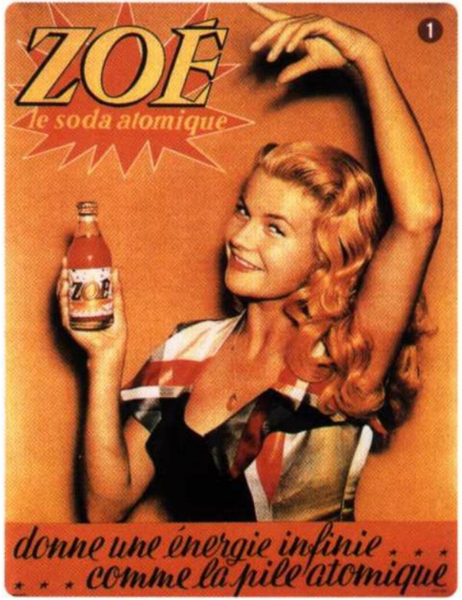
Says Radium Is Sure Cure, Even in Deep-Rooted Cases, if Properly Treated.

Courtesy prof O. Ratib

And soon after…







While flying to a workshop in Manchester

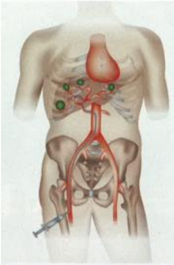
While flying
to a workshop in Manchester


100 Advertorial

Mikrokugeln gegen Leberkrebs
Tiny beads used to treat liver cancer

Die Hirslanden Klinik St. Anna in Luzern führt eine neuartige Behandlung für Lebertumore durch, bei der hohe Strahlungsdosen mittels kleinster Kügelchen direkt in die Tumore injiziert werden.

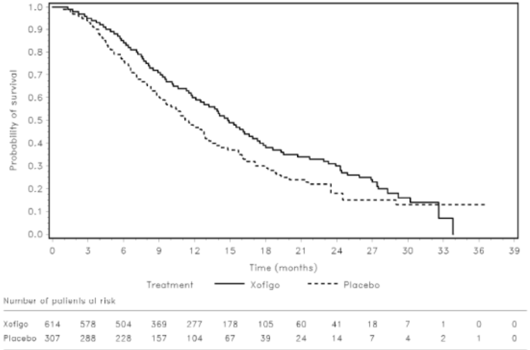
Hirslanden Klinik St. Anna in Lucerne, Switzerland, provides a new high-dose radiotherapy treatment for liver tumours which works by injecting tiny beads straight into the tumours.



Leaver treatment with microspheres loaded with ^{90}Y

2015

Figure 1 – Courbes de survie globale de Kaplan-Meier (analyse actualisée)

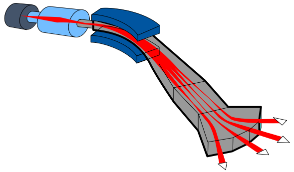


ALSYMPCA Phase III clinical trial
https://www.vidal.fr/medicaments/xofigo-1100-kbq-ml-sol-inj-164403.html

Courtesy Prof. Ratib

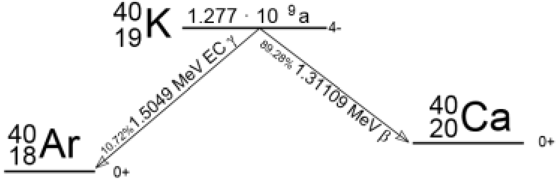
Did you say ?

(production/purification)



^{40}K, a radioisotope “bio” for imaging and treatment ?

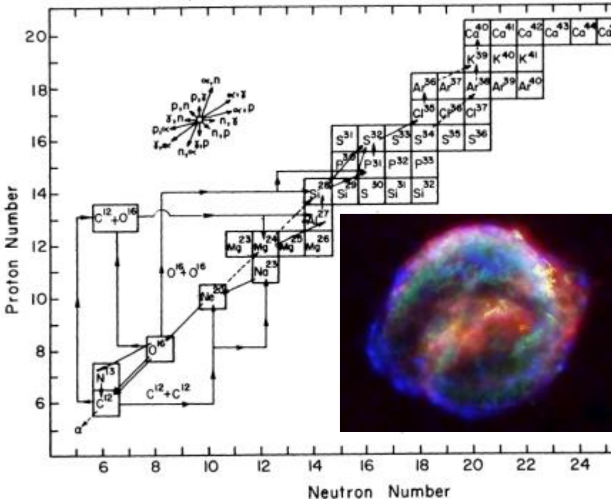
There is ~0.01% natural ^{40}K on Earth
Our whole body natural activity
is of ca 4 kBq (0.2 mSv/year)



Neutron capture s-process
in stars $^{39}K(n,\gamma)^{40}K$

Method of production :

Nucleosynthesis in supernovae explosion
12C+16O→X, etc



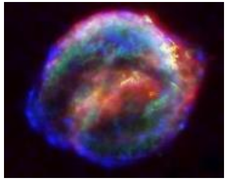
S. Woosley, Astrophys j

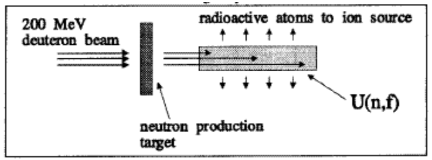
But none of these production sites are yet found in our lab

Which facility (accelerator, particle, other) for which isotope ??

Aka how to translate isotope production to machine parameters ?

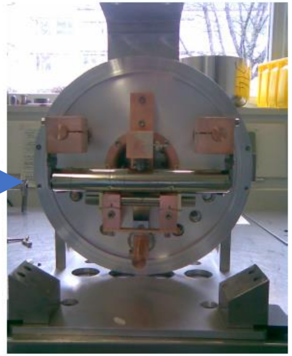
Particle conversion in
Accelerator (d→n)
Ion Linac, cyclotron,
PSBooster@2GeV ?

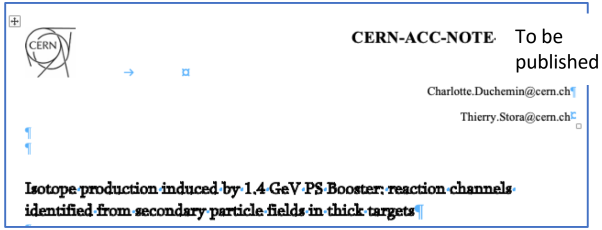




J. Nolen, Report to Users of ATLAS,
ANL, USA, 1995

P-> d,α, t
P-> n





CERN-ACC-NOTE

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Thierry.Stora@cern.ch

Isotope production induced by 1.4 GeV PS Booster: reaction channels identified from secondary particle fields in thick targets

To be published

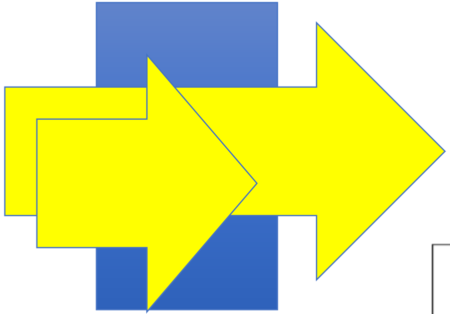
From excitation function to production rate

$\mathbf{I}_{[pps]} \sim \Phi_{[pps]}\ \sigma_{[barn]}\ \mathbf{N}_{[g/cm2]}$ **production rate**

10^{10}pps 100µA (6.10^{14}) 1mbarn 1g/cm^2 for A_{target}=30g/mol

R [Bq] = Iλ/(1-λ) = **I** for 5 $T_{1/2}$ (λ=0.606/$T_{1/2}$ **)** **saturation activity**

Incident particle
Beam intensity



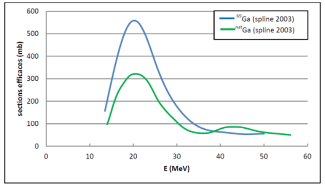
Bragg peak possibly
in a dump

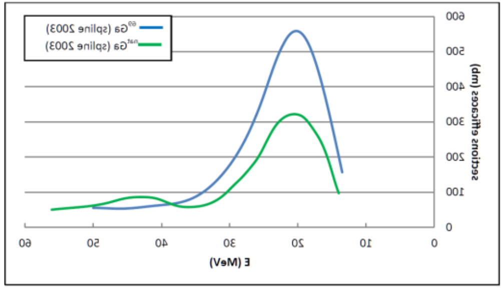
$$Y(E_{\mathrm{in}}) = \frac{N_A}{A_T}\int_0^{E_{\mathrm{in}}} \sigma(E)\,\frac{1}{S(E)}\,dE,$$

An individual dose

For imaging is ~100`s MBq
For treatment ~ 1 GBq
For alpha-therapy ~ 2 MBq

Target thickness





Production of ^{47}Sc radionuclide using accelerators

- Direct reaction on Ti targets for proton and deuteron bombardment:
  - **$^{50}Ti(p,\alpha)^{47}Sc$;**
  - **$^{49}Ti(p,3He)\ ^{47}Sc$;**
  - **$^{48}Ti(p,2p)\ ^{47}Sc$;**
  - $^{50}Ti(d,\alpha n)\ ^{47}Sc$;
  - $^{49}Ti(d,\alpha)\ ^{47}Sc$;
  - $^{48}Ti(d,3He)\ ^{47}Sc$;
  - $^{47}Ti(d,2p)\ ^{47}Sc$;
- Direct reaction on Ca targets for proton, deuteron and α particle bombardment:
  - $^{48}Ca(p,2n)\ ^{47}Sc$;
  - $^{48}Ca(d,3n)\ ^{47}Sc$;
  - $^{46}Ca(d,n)\ ^{47}Sc$;
  - $^{44}Ca(\alpha,p)\ ^{47}Sc$;
- Direct reaction on V target for proton:
  - $^{51}V(p,\alpha p)\ ^{47}Sc$;

- Indirect reaction on Ti targets for proton and deuteron bombardment:
  - **$^{50}Ti(p,p3He)^{47}Ca \rightarrow ^{47}Sc$ ($t_{1/2}$=4,536 d);**
  - **$^{49}Ti(p,3p)^{47}Ca \rightarrow ^{47}Sc$;**
  - $^{50}Ti(d,\alpha p)^{47}Ca \rightarrow ^{47}Sc$.
- Indirect reaction on Ca targets for proton and deuteron bombardment:
  - $^{48}Ca(p,d)^{47}Ca \rightarrow ^{47}Sc$;
  - $^{46}Ca(d,p)^{47}Ca \rightarrow ^{47}Sc$;
  - $^{48}Ca(d,t)^{47}Ca \rightarrow ^{47}Sc$.

$^{48}Ti(\gamma,p)$ @ ANL

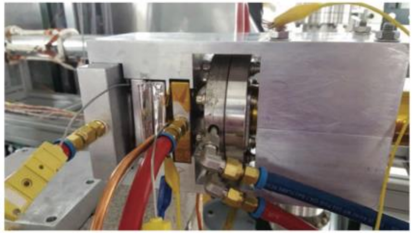


Figure 4: Clam shell target station with targets in place.

The three targets were irradiated with an electron-beam energy of 35 MeV at 2 kW. The beam was on target for three hours.

ISBN 978-3-95450-180-9

ANL: Low Energy Accelerator Facility (LEAF) is a newly upgraded 55 MeV/25-kW

Courtesy E. Mamis

Direct production

	E_{in} (MeV)	E_{out} (MeV)	Target (98%)	Target thickness (µm)	^{47}Sc activity at EOB (MBq)	^{47}Sc activity after cooling (MBq)	Activity of other Sc after cooling (MBq)	Radioisotopic Purity (%)
$^{50}Ti(p,\alpha)^{47}Sc$	20	8	^{50}Ti	1132	93	76	0.5	99
$^{49}Ti(p,^{3}He)^{47}Sc$	40	28	^{49}Ti	2262	580	472	353	57
$^{48}Ti(p,2p)^{47}Sc$	25	18	^{48}Ti	922	69	56	26	68
$^{50}Ti(d,\alpha n)^{47}Sc$	27	20	^{50}Ti	581	341	278	24	92
$^{49}Ti(d,\alpha)^{47}Sc$	12	3	^{49}Ti	321	41	34	0.67	98
$^{48}Ti(d,^{3}He)^{47}Sc$	44	34	^{48}Ti	1214	800	651	315	67
$^{47}Ti(d,2p)^{47}Sc$	25	10	^{47}Ti	993	292	237	246	49
$^{48}Ca(p,2n)^{47}Sc$	23	18	^{48}Ca	1659	3518	2936	297	91
$^{48}Ca(d,3n)^{47}Sc$	29	24	^{48}Ca	1184	2807	2348	630	79
$^{46}Ca(d,n)^{47}Sc$	5	2	^{46}Ca	164	168	137	0.70	99
$^{44}Ca(\alpha,p)^{47}Sc$	17.8	7	^{44}Ca	220	50	41	0.19	≈100
$^{51}V(p,\alpha p)^{47}Sc$	30	20	^{51}V (99.75%)	1127	25	20	0.004	≈100

Table 1. Comparison of direct production routes of ^{47}Sc on Ca, Ti and V targets (24 h irradiation, 24 h cooling time, 1 eµA beam current)
Therapeutic Radiopharmaceuticals Labelled with Copper-67, Rhenium-186 and Scandium-47, International Atomic Energy Agency, 2021, IAEA TECDOC series, ISSN 1011–4289; no. 1945, ISBN 978-92-0-134921-7

Target	Abundance (%)
^{51}V	99.750%
^{50}Ti	5.18%
^{49}Ti	5.41%
^{48}Ti	73.72%
^{48}Ca	0.187%
^{46}Ca	0.004%
^{44}Ca	2.09%

Table 2. Natural abundance of target materials for ^{47}Sc production
Therapeutic Radiopharmaceuticals Labelled with Copper-67, Rhenium-186 and Scandium-47, International Atomic Energy Agency, 2021, IAEA TECDOC series, ISSN 1011–4289; no. 1945, ISBN 978-92-0-134921-7

IAEA TECDOC series

^{xx}Sc production cross sections from ^{nat}Ti – experimental data

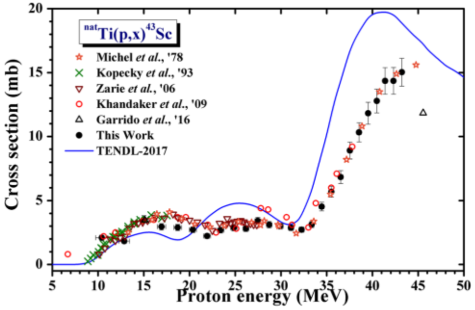


Fig. 2 Excitation function of $^{nat}Ti(p,x)^{43}Sc$ reaction compared with the literature data as well as the data from TENDL-2017 library based on the TALYS 1.9

M. Shahid, et. All. Measurement of excitation functions of residual radionuclides from natTi(p,x) reactions up to 44 MeV," *Journal of Radioanalytical and Nuclear Chemistry,* vol. 318, p. 2049–2057, 2018

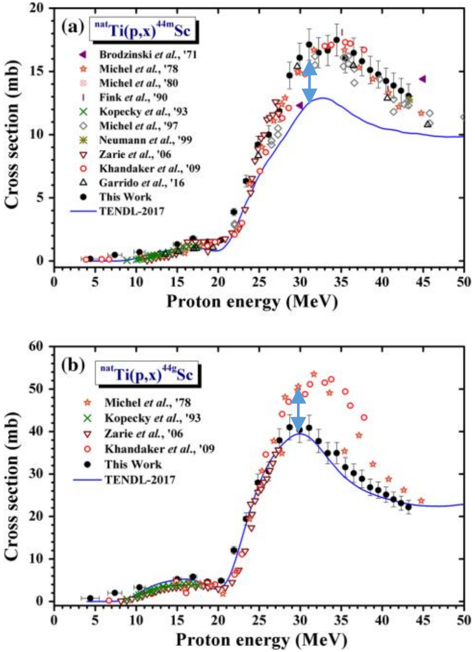


Fig. 3 Excitation function of **a** $^{nat}Ti(p,x)^{44m}Sc$ reaction and **b** $^{nat}Ti(p,x)^{44g}Sc$ reaction compared with the literature data as well as the data from TENDL-2017 library based on the TALYS 1.9

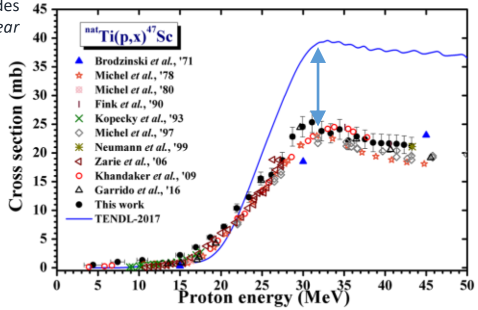


Fig. 5 Excitation function of $^{nat}Ti(p,x)^{47}Sc$ reaction compared with the literature data as well as the data from TENDL-2017 library based on the TALYS 1.9

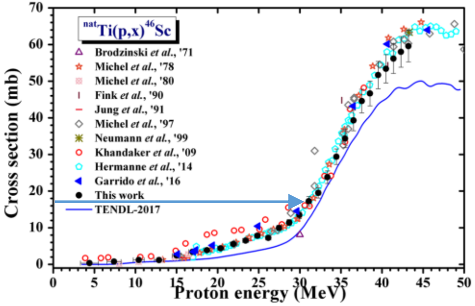


Fig. 4 Excitation function of $^{nat}Ti(p,x)^{46g}Sc$ reaction compared with the literature data as well as the data from TENDL-2017 library based on the TALYS 1.9

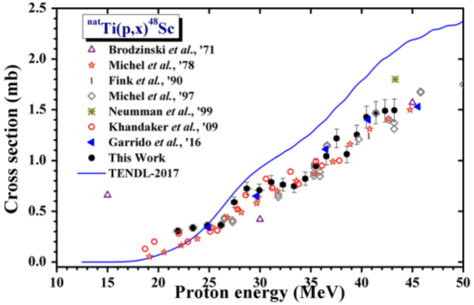


Fig. 6 Excitation function of $^{nat}Ti(p,x)^{48}Sc$ reaction compared with the literature data as well as the data from TENDL-2017 library based on the TALYS 1.9

« Radionuclidic » impurities do matter

- Purification methods:
  - Physical – **isotope mass-separation**
  - Chemical – precipitate method or ion exchange columns.
    + Effective for ^{48}V and Ti removal
    - Use of strong and corrosive acids

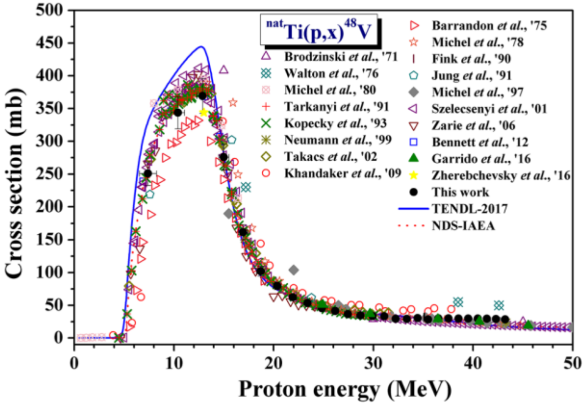


Fig. 7. Excitation function of $^{nat}Ti(p,x)^{48}V$ reaction compared with the literature data as well as the data from TENDL-2017 library based on the TALYS 1.9

M. Shahid, et. All. Measurement of excitation functions of residual radionuclides from natTi(p,x) reactions up to 44 MeV," *Journal of Radioanalytical and Nuclear Chemistry,* vol. 318, p. 2049–2057, 2018

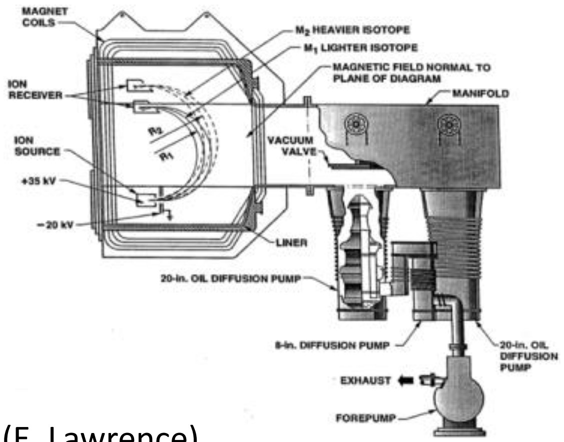
Nuclei	Half-life	Decay mode (%)	E_γ (keV)	I_γ (%)	Production route	*Q*-value (MeV)	Threshold value (MeV)
^{48}V	15.97 days	EC (50.09)	944.13	7.87	$^{47}Ti(p,\gamma)$	6.83	0.0
		β^+ (49.91)	983.52	99.98	$^{48}Ti(p,n)$	− 4.79	4.89
			1312.1	98.2	$^{49}Ti(p,2n)$	− 12.93	13.20
					$^{50}Ti(p,3n)$	− 23.88	24.36
^{43}Sc	3.89 h	EC (11.9)	372.8	22.5	$^{46}Ti(p,\alpha)$	− 3.07	3.14
		β^+ (88.1)			$^{47}Ti(p,n\alpha)$	− 11.95	12.21
					$^{48}Ti(p,2n\alpha)$	− 23.58	24.07
					$^{49}Ti(p,3n\alpha)$	− 31.72	32.37
^{44m}Sc	2.44 days	IT (98.8)	271.2	86.7	$^{47}Ti(p,\alpha)$	− 2.25	2.30
		EC (1.2)	1002	1.2	$^{48}Ti(p,n\alpha)$	− 13.88	14.17
^{44g}Sc	3.93 h	EC (5.73)	1157.0	99.9	$^{49}Ti(p,2n\alpha)$	− 22.02	22.47
		β^+ (94.27)			$^{50}Ti(p,3n\alpha)$	− 32.96	33.63
^{46g}Sc	83.79 days	β^- (100)	889.28	99.98	$^{47}Ti(p,2p)$	− 10.46	10.69
			1120.54	99.99	$^{48}Ti(p,^3He)$	− 14.37	14.67
					$^{49}Ti(p,\alpha)$	− 1.94	1.98
					$^{50}Ti(p,n\alpha)$	− 12.87	13.13
^{47}Sc	3.35 days	β^- (100)	159.38	68.3	$^{48}Ti(p,2p)$	− 11.44	11.68
					$^{49}Ti(p,^3He)$	− 11.87	12.11
					$^{50}Ti(p,\alpha)$	− 2.23	2.28
^{48}Sc	43.67 h	β^- (100)	175.36	7.48	$^{49}Ti(p,2p)$	− 11.35	11.59
			1037.52	97.6	$^{50}Ti(p,^3He)$	− 14.58	14.87

Table 3. The decay data of ^{48}V and $^{43,44m,44g,46,47,48}Sc$ radionuclides produced from the $^{nat}Ti(p,x)$ reactions

M. Shahid, et. All. Measurement of excitation functions of residual radionuclides from natTi(p,x) reactions up to 44 MeV," *Journal of Radioanalytical and Nuclear Chemistry,* vol. 318, p. 2049–2057, 2018

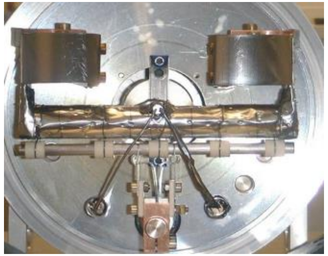
(Stable) Isotope mass separation added value

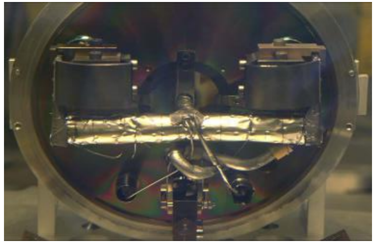
Non carrier added radioisotope fraction (high specific activity)
Efficiencies to be developed
Can this process be applied in large scale ?
A first terrifying use: 235 uranium enrichment of “Little Boy”
And later a much more positive application :
isotope enrichment for medical isotope production

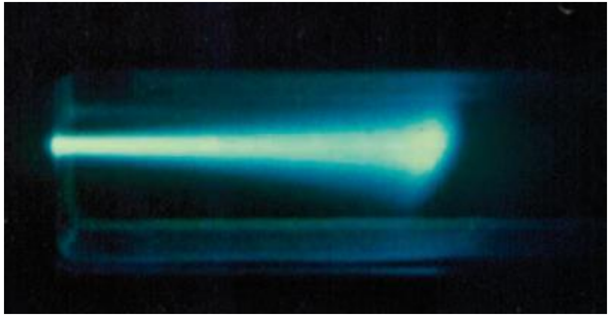


The Calutron (E. Lawrence)

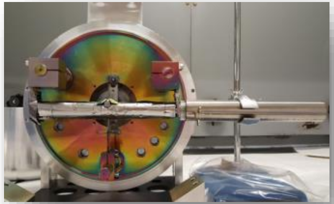
Beam – target interaction and chemical aspects



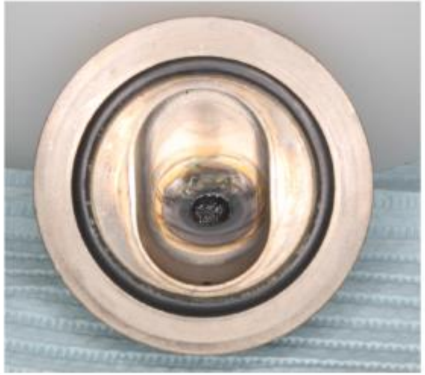




Gas target
(ie N_2 + trace of O_2 for $^{14}N(p,\alpha)^{11}CO_2$)



Cyclotron target transfer
into Isotope mass separation unit

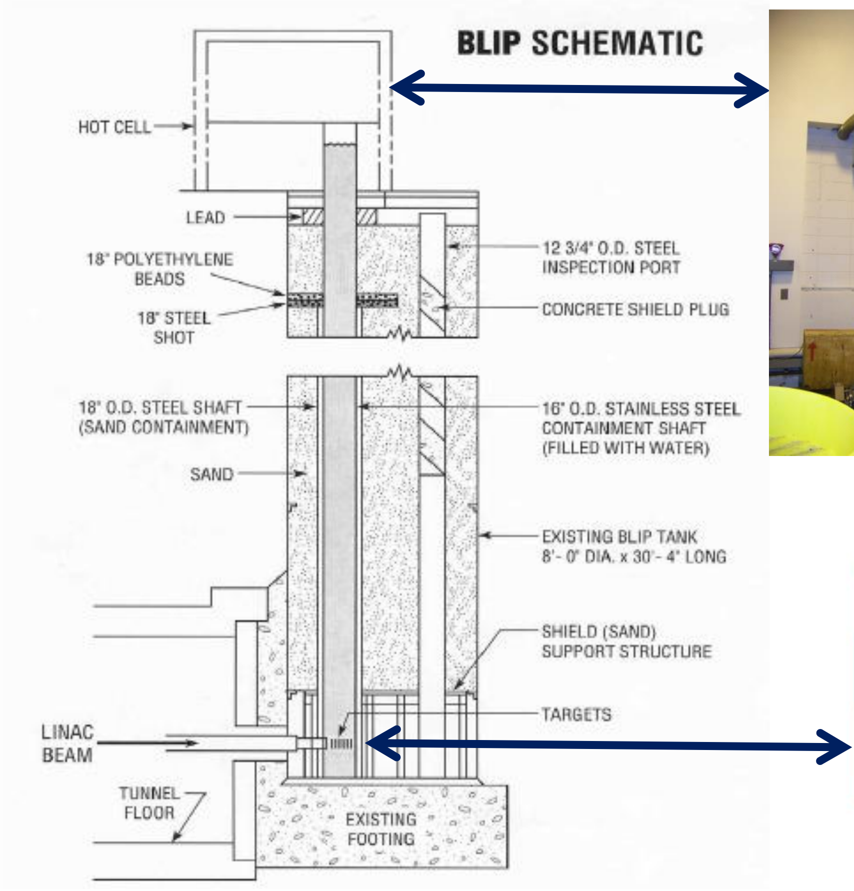


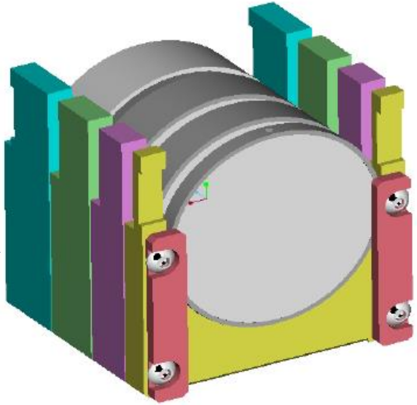
M. Stokely, BTI Targetry

https://youtu.be/p3sjf7ZMPZQ

http://isotopes.lanl.gov/

Brookhaven Linear Isotope Producer (BLIP)

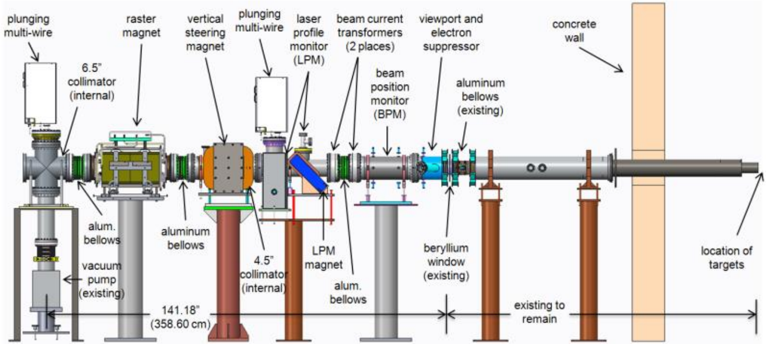


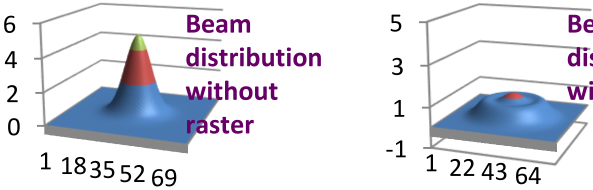


Courtesy C. Cutler

Increase Isotope Production Capabilities at a Linac

- Brookhaven Linac Isotope Producer (BLIP) Beam Raster System
  - Added equipment to
    - Raster the proton beam
    - Provide enhanced beam diagnostics
  - Enabled increase in beam current on target (greater isotope yields)
    - Max. design current increased from 125 to 140 µA due to project to modify proton pulses
    - Actually achieved >160 µA
    - Current had been limited to <100 µA to prevent target failure
  - Lowered possibility of target failures





Integral of beam distribution is the same for both plots

Courtesy C. Cutler

U.S. DEPARTMENT OF ENERGY Office of Science

Equation to express radionuclide production and mass separation yields

RIB intensity [s^{-1} μA^{-1}]

Proton beam Intensity [s^{-1} μ A^{-1}]

Avogadro Numb.

Diffusion+ Effusion Efficiency

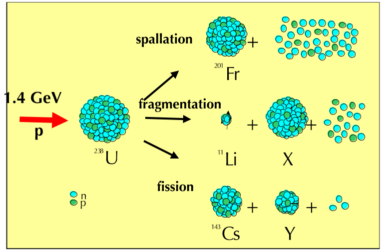
$$I = \int \sigma(E)\, \Phi(E, x)\, \rho(x)\, N/A\, dx\, \varepsilon_{diff+eff}\, \varepsilon_{ion}$$

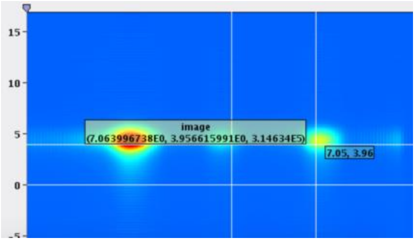
Cross section [cm^2]

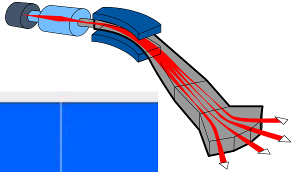
Target density [$g\ cm^{-3}$]

Target Atomic Mass [g]

Ionization Efficiency







Low specific activity
Impurities

High (specific) Molar activity
And purity

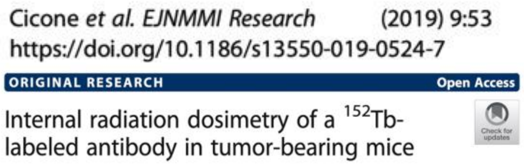
Did you say ?

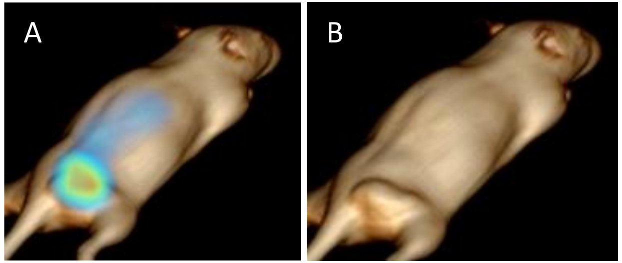
non conventional radionuclides

Example of theranostics concept in pre-clinical research

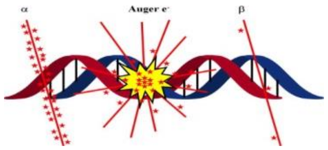
- PET 152-Terbium radionuclide in antibody-based targeted moleculer therapy

Diagnostics

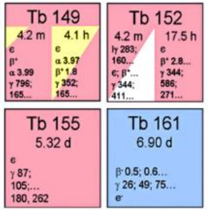

Cicone *et al. EJNMMI Research* (2019) 9:53
https://doi.org/10.1186/s13550-019-0524-7
ORIGINAL RESEARCH Open Access
Internal radiation dosimetry of a ^{152}Tb-labeled antibody in tumor-bearing mice



THERAPY

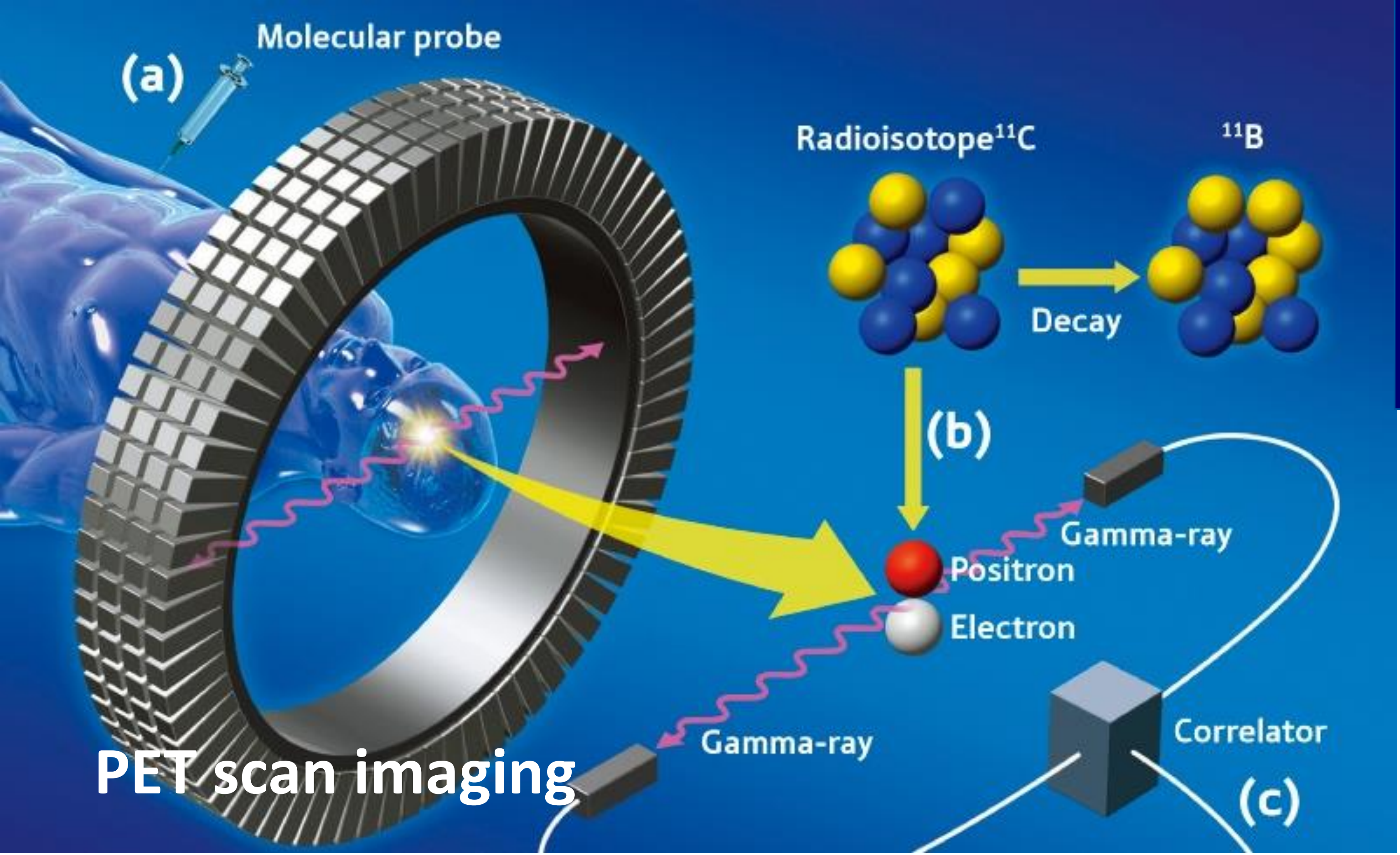


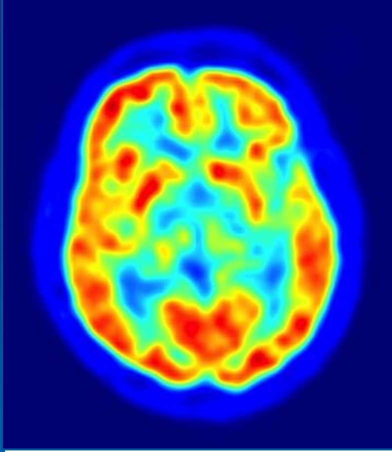
Matched therapeutic Tb

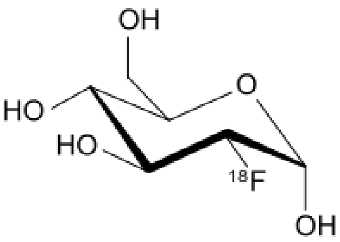


C. Müller et al.,
Journal of nuclear medicine 53.12 (2012): 1951.

PET scan imaging

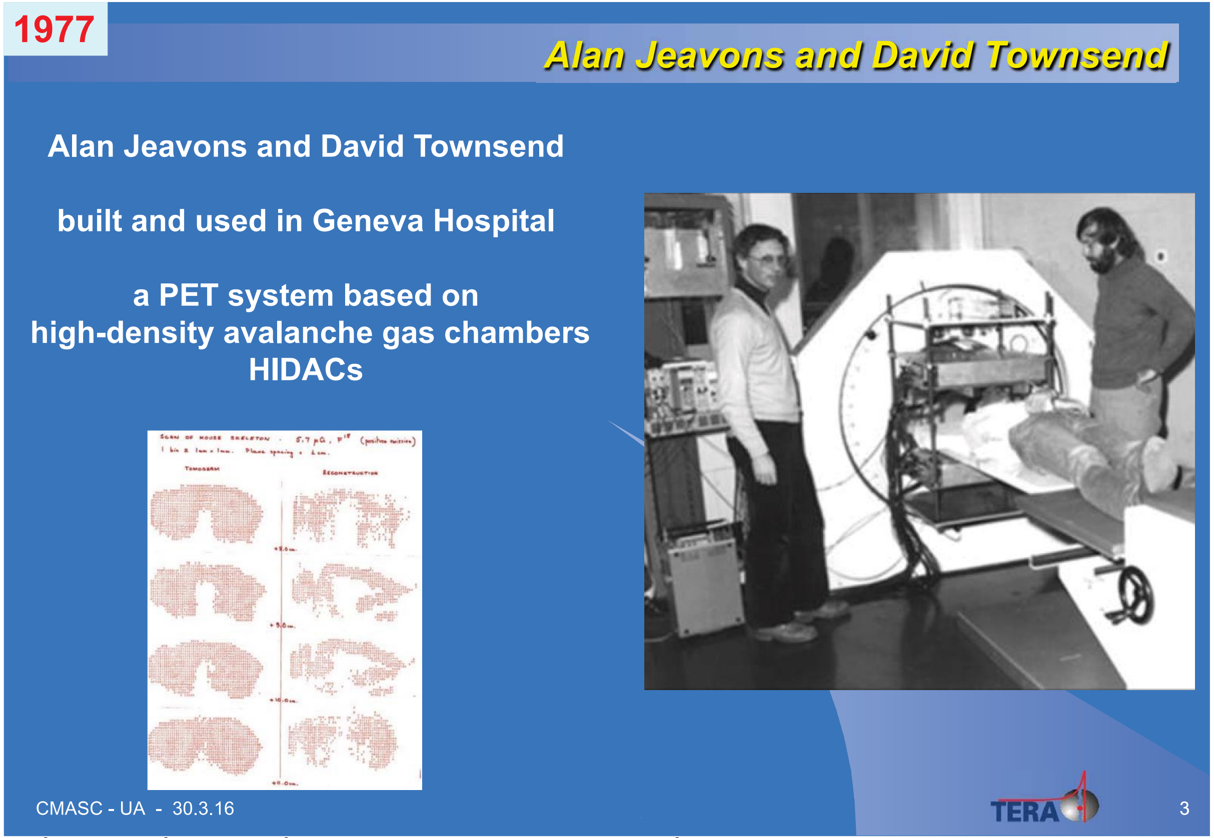






Fluorodésoxyglucose (^{18}F)

PET-CT scan imaging



Courtesy Ugo Amaldi

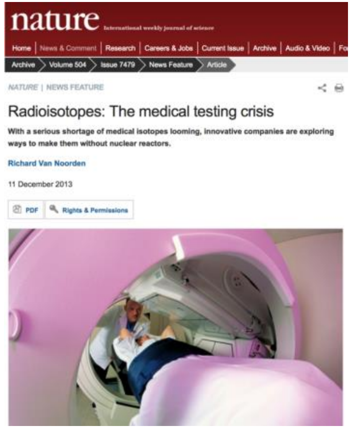
https://home.cern/news/news/knowledge-sharing/forty-years-first-pet-image-cern

Biomedical projects and radionuclide match

- Biomedicine at large
- Protocols, technology (imaging, pharma targets, whole body PET)
- Radionuclide grade (non carrier added, isotope decay chain)
- Innovative isotopes for imaging and treatment in theranostics
- Studies on cells, animals « preclinical », *possibly pilot clinical phases*

Field of Application	Radiation	Chemical elements	Half lives
PET (Positron Emission Tomography)	β^+	Alkaline earth Halogen Lanthanide Transition metals …	Hours Days Months
SPECT (Single Photon Emission Computed Tomography)	γ		
TAT (targeted alpha therapy)	α		
Beta therapy	β^-		
Auger therapy	e^-		

Which Radioisotopes used in Nuclear Medicine


nature International weekly journal of science

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Archive > Volume 504 > Issue 7479 > News Feature > Article

NATURE | NEWS FEATURE

Radioisotopes: The medical testing crisis

With a serious shortage of medical isotopes looming, innovative companies are exploring ways to make them without nuclear reactors.

Richard Van Noorden

11 December 2013

PDF | Rights & Permissions

Classification of isotopes for Medicine:

1. Established isotopes → Industrial suppliers
^{99m}Tc, ^{18}F, ^{123,125,131}I, ^{111}In, ^{90}Y

2. Emerging isotopes → Small innovative suppliers
^{68}Ga, ^{82}Rb, ^{89}Zr, ^{177}Lu, ^{188}Re

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,…

Courtesy U. Koester

Règles pour utilisation des radioisotopes dans un médicament : cas en Suisse

swissmedic

Fabrication du radionucléide :

Les **réactions nucléaires employées**…la **demi-vie**, le type et l'énergie du **rayonnement** ainsi que les **effets perturbateurs engendrés par les impuretés**.

Nucléides obtenus par bombardement de cibles : matériau cible et enveloppe de la cible :
- composition, forme chimique, pureté chimique, état physique et additifs chimiques éventuels, susceptibles d'influer sur le produit
- méthode d'irradiation, environnement physique et chimique (support de la cible)
- rendement

Nucléides produits par fission :
Il convient d'indiquer l'ensemble de la chaîne de nucléides, de la matière première initiale (impuretés comprises) jusqu'aux nucléides filles stables correspondants, y compris la demi-vie, le type et l'énergie du rayonnement. Les effets perturbateurs provoqués par les impuretés ou la matière première doivent être discutés.

Traitement du radionucléide :
- description détaillée de l'isolation (séparation de la cible) et de l'enrichissement du radionucléide souhaité ; rendement.

Propriétés physiques du radionucléide :
Il faut indiquer en détail la demi-vie, le type et l'énergie du rayonnement ainsi que l'évolution dans le temps à compter de la fabrication du radionucléide et jusqu'à la date d'expiration du médicament ainsi que les aspects importants pour l'élimination.

Contrôle du produit fini :
- identité des nucléides
- pureté des nucléides
- pureté radiochimique
- pureté chimique
- activité spécifique

Ident. QM : ZL000_00_003f_WL / V01 / bg, stb, cas / zro / 01.04.2015

Translation : Regulation of radiopharmaceuticals : Swiss example

swissmedic

Fabrication :
Used nuclear reaction - isotope half life
Radiation type and energy
Pertubation induced by impurities

Nuclides produced by target irradiation
Target material, target envelop
Composition, chemical form, purity, physical state,
Chemical additives, capable to impact the end product
Irradiation method, physical and chemical environment
Target support
Yield

Nuclide treatment
- Description of isolation (separation from the target), nuclide concentration, yield.

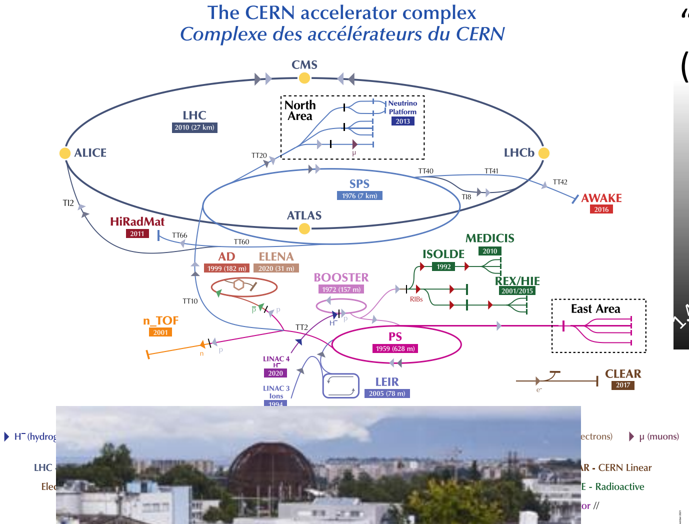
Physical properties of nuclides
In detail : half life, type and energy of radiation, evolution over time from the fabrication to the date of peremption of the drug, important aspects for disposal

Nuclides from fission
Full nuclide reaction chain, initial material (including impurities), daughter nuclides, half lifes, radiation type and energy
Pertubation from impurities

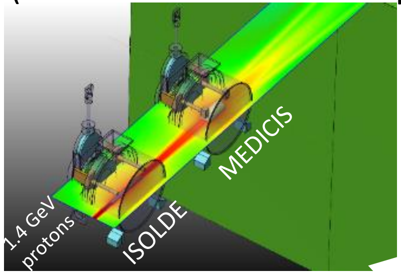
End product control
- identité des nucléides
- Nuclide identity
- Purity of nuclides
- Radiochemical purity
- Chemical purity
- Specific activity

Ident. QM : ZL000_00_003f_WL / V01 / bg, stb, cas / zro / 01.04.2015

Mass separation as applied in MEDICIS in a snapshot

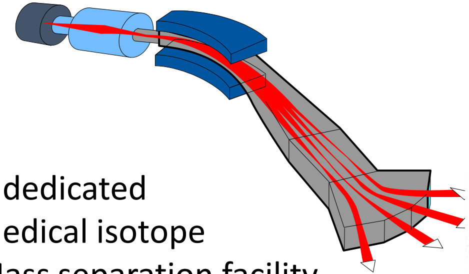


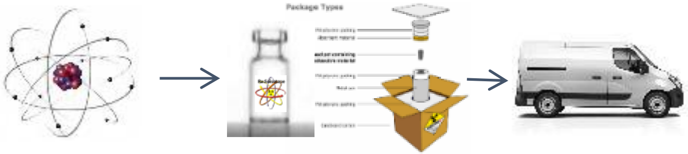
“Free” proton beam
(otherwise lost in the dump)



Some **MEDICIS isotopes** :

High activity Sm-153, Ba/Cs-128, Tm/Er-165

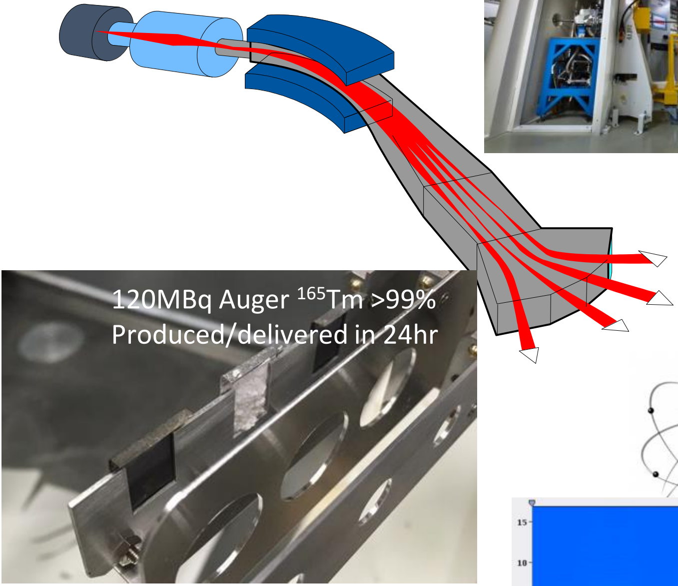


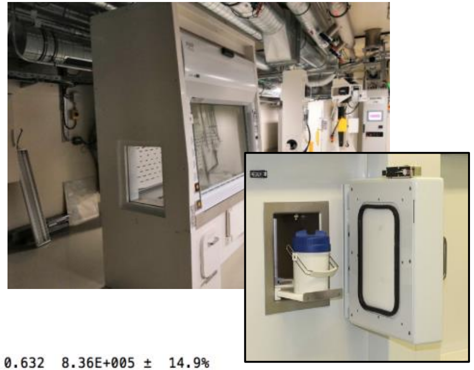


A dedicated
medical isotope
Mass separation facility
in Europe.

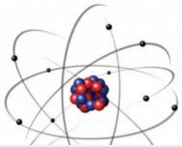
From CERN- MEDICIS to the lab/Hospital

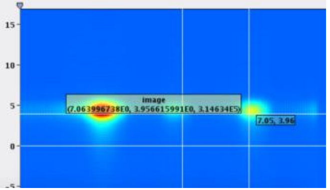
From CERN- MEDICIS to the lab/Hospital

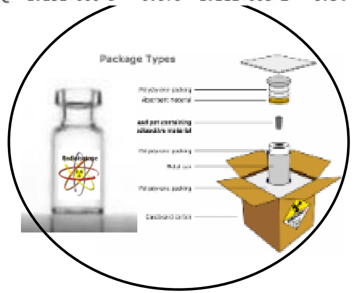




Gd-149	@	9.28E+000 D	0.632	8.36E+005	±	14.9%
Tb-149	@	4.12E+000 H	0.964	1.71E+006	±	9.4%
Er-165		1.04E+001 H	0.894			
Tm-165	@	1.25E+000 D	0.979	1.21E+008	±	6.3%



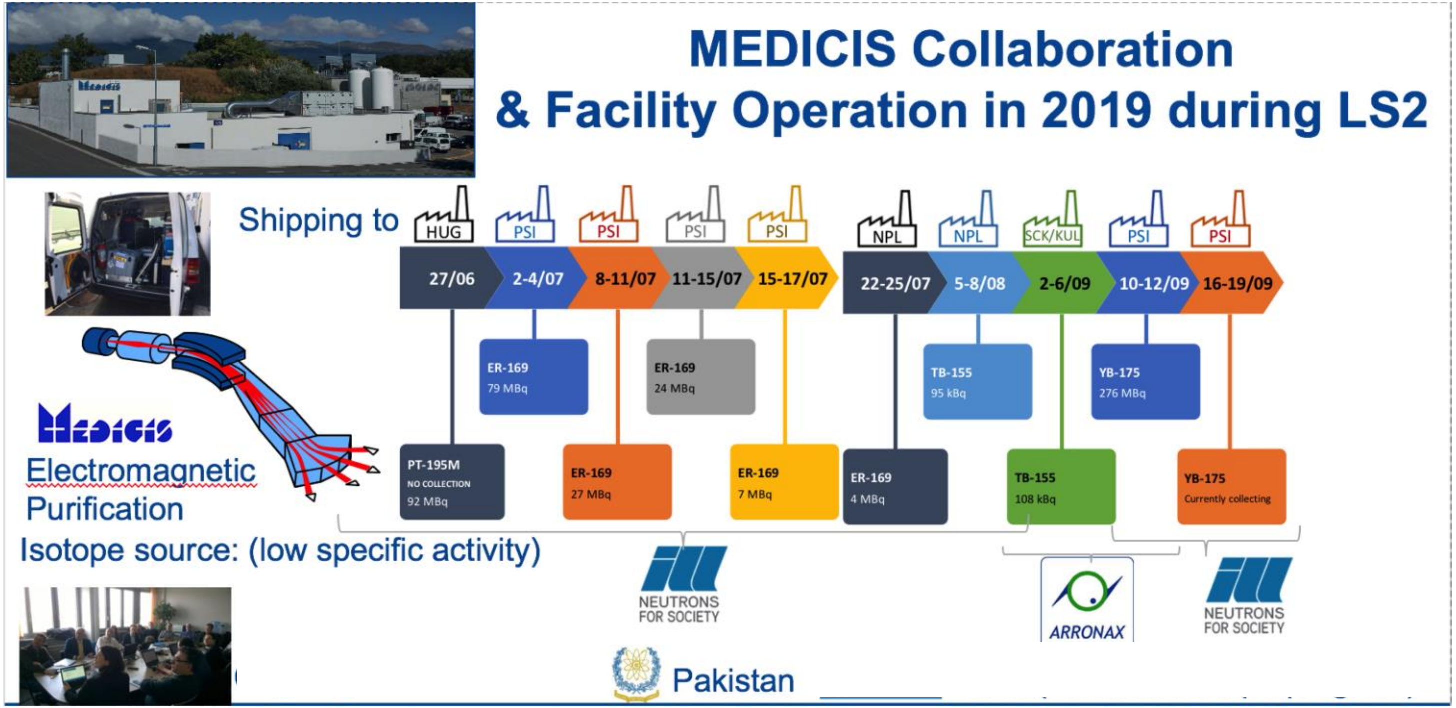




Isotope separation for experiment MED011
from external 168/169Er source

From CERN- MEDICIS to the lab/Hospital
(Countries: BE, CH, FR, PK, PT, LV, UK)

Example of schedule when CERN Accelerator complex is in Long Shutdown



How to supply "novel" radionuclides with mass separation

- **PRISMAP** proposes to federate a consortium of high energy cyclotrons, research reactors, and isotope mass separation facilities in Europe.

Accelerator

Isotope mass separation

Research reactor

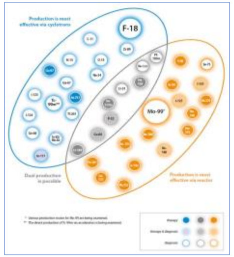
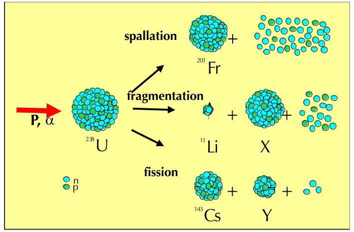


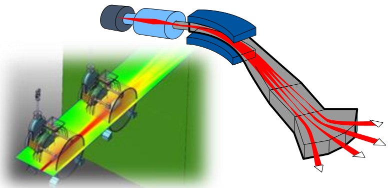
Figure 31 : Main medical radioisotopes production process

European Commission ENER/17/NUCL/SI2.755660

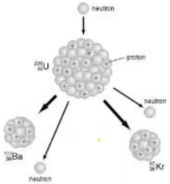


$I_{[pps]} \sim F_{[pps]}\ S_{[barn]}\ N_{[g/cm2]}$ **production rate**

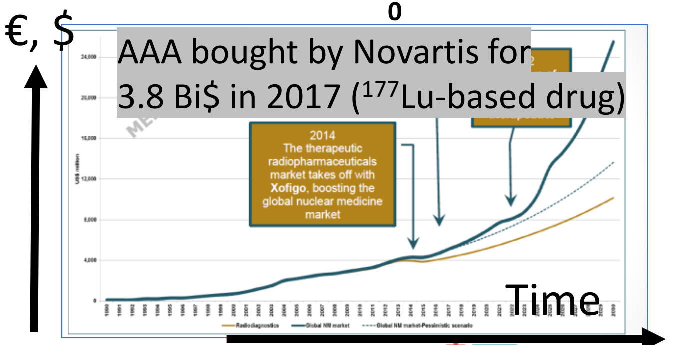
10^{10}pps 100µA (6.10^{14}) 1mbarn 1g/cm² for A_{target}=30g/mol



$I_{[pps]} \sim F_{[pps]}\ S_{[barn]}\ N_{[g/cm2]}\ e_{[\%]}$



$$\frac{dN'}{dt} = n v \sigma_{act} N_T$$



AAA bought by Novartis for 3.8 Bi$ in 2017 (^{177}Lu-based drug)

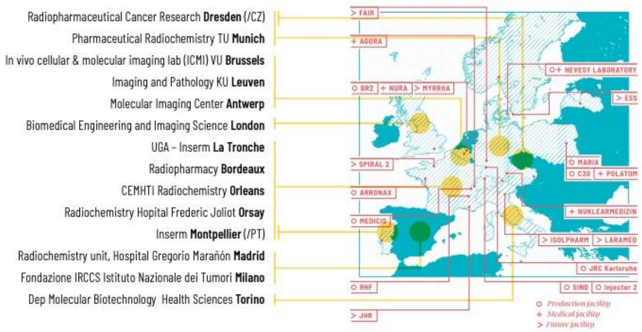
Figure 8: Possible market evolution for radiotherapeutics – source MedRaysIntell (2016)

Economics, Innovators

PRISMAP – The European medical radionuclides programme (2021-2025)

https://medical-radionuclides.eu

- Achievements in 2022:
  - 15 projects for biomedical research with novel radionuclides were selected for services across Europe
    www.prismap.eu/access/user-projects (BE, CZ, DE, ES, FR, IT, PT, UK)

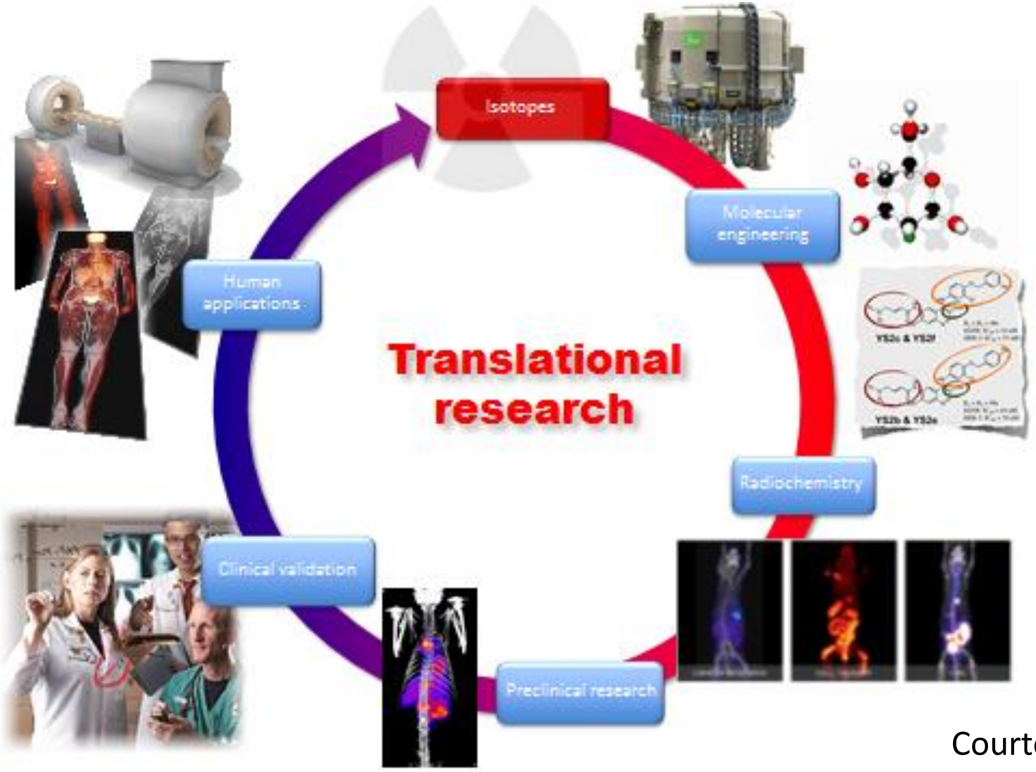


- PRISMAP is invited to present research needs in the field of novel biomedical radionuclides to the EU Commissioner for research and education Mariya Gabriel

Did you say ?

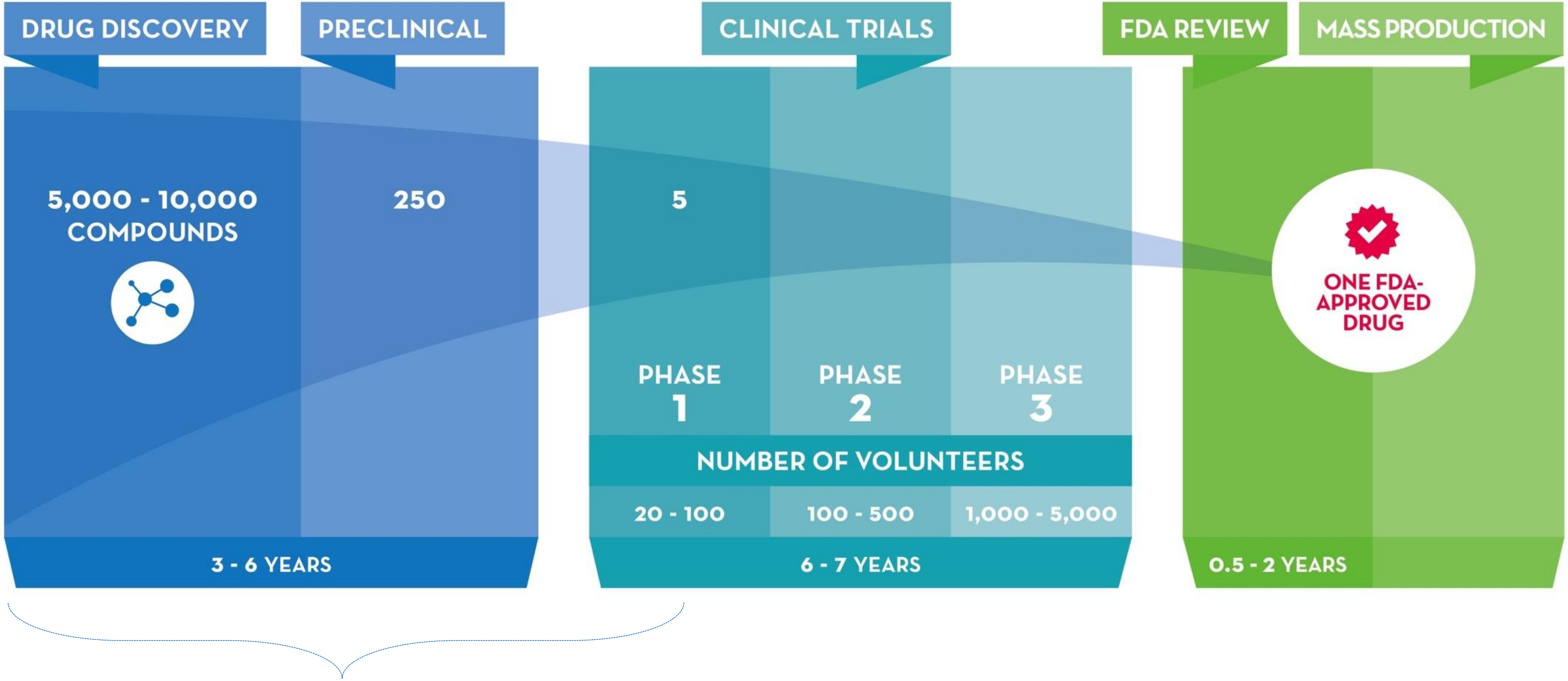
in personalised medicine

How to progress in the field ?

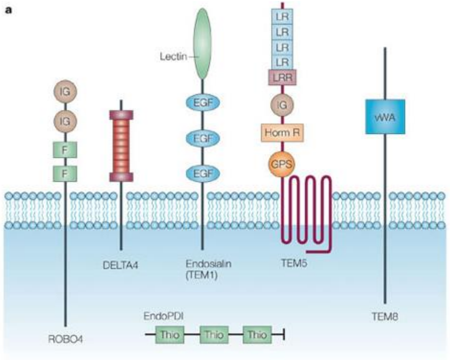


Courtesy Prof. MD Osman Ratib
in the context of CERN-MEDICIS

Drug development cycle



The (biological !!) Target : Tumor Endotelial Marker-1 (TEM1)



Overexpressed by:

Tumor vessels

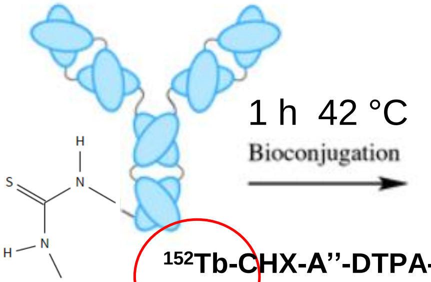
Tumor cells

Host microenvironment (fibroblasts, pericytes)

One «cold» antibody fragment

Morab 0004 is in clinical phase 2

«targetted therapy»

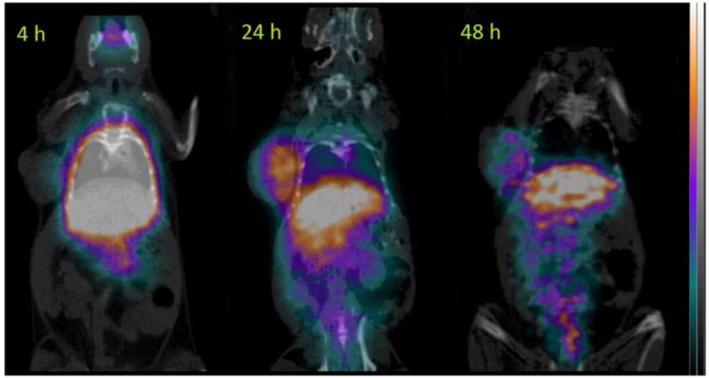


^{152}Tb-CHX-A''-DTPA-FcTEM1

MD,PhD Cicone F et al.

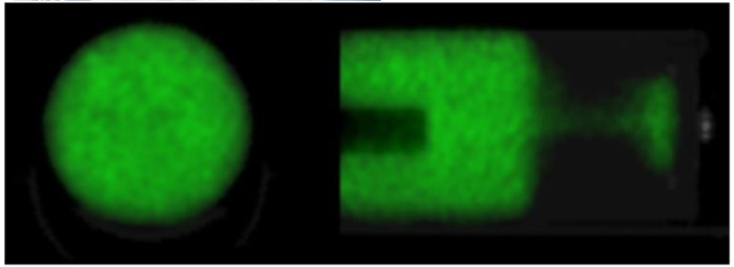
First PET imaging of ^{152}Tb-CHX-A''-DTPA-ScFv78Fc

Ewing Sarcoma cell line A673



UNIL | Université de Lausanne
Faculté de biologie et de médecine
CHUV

Phantom, calibration and dosimetry



This is a phantom !

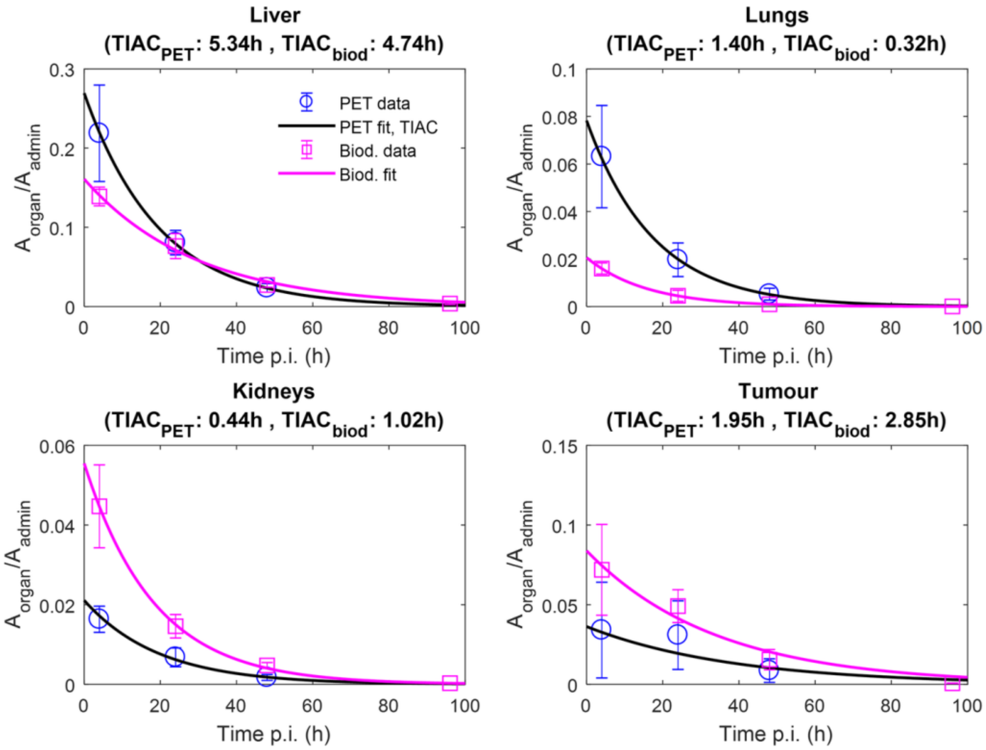
Cicone et al. EJNMMI Research (2019) 9:53
https://doi.org/10.1186/s13550-019-0524-7

EJNMMI Research

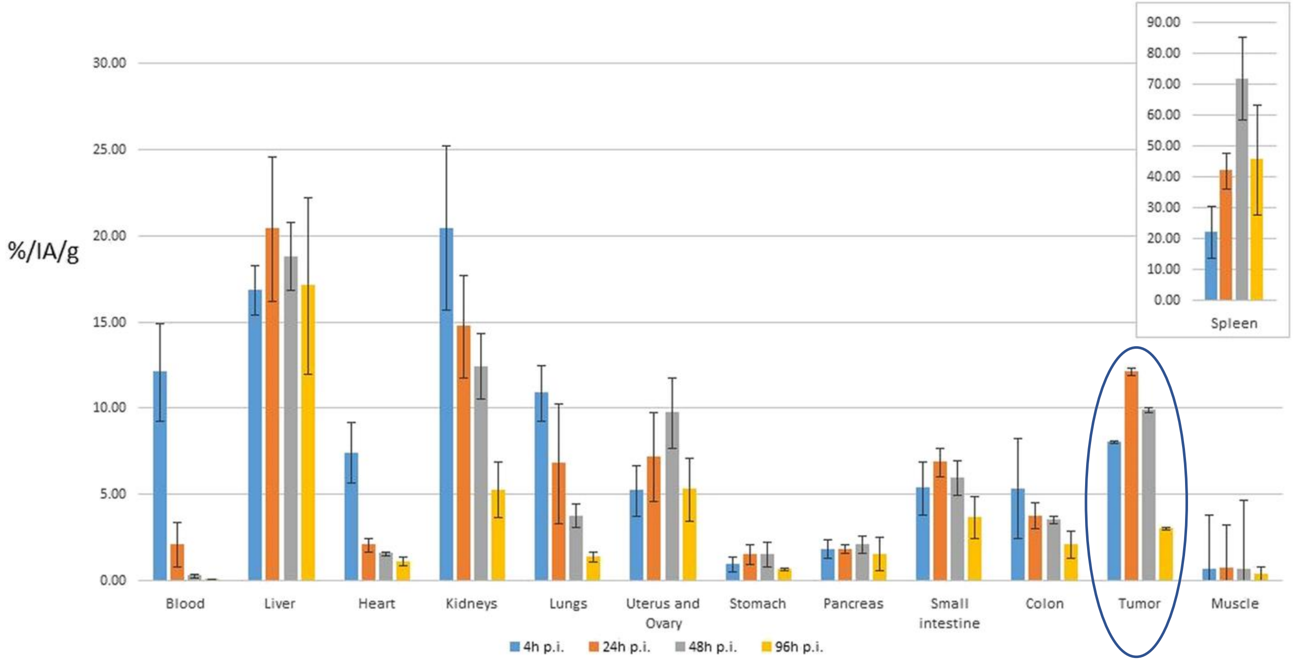
ORIGINAL RESEARCH | Open Access

Internal radiation dosimetry of a ^{152}Tb-labeled antibody in tumor-bearing mice

Francesco Cicone[1*], Silvano Gnesin[2], Thibaut Denoël[1], Thierry Stora[3], Nicholas P. van der Meulen[4,5], Cristina Müller[4], Christiaan Vermeulen[4], Martina Benešová[4], Ulli Köster[6], Karl Johnston[3], Ernesto Amato[7], Lucrezia Auditore[7], George Coukos[8], Michael Stabin[9], Niklaus Schaefer[1], David Viertl[1] and John O. Prior[1]



Forecast of activity vs time



Biological organ kinetic of the radiolabeled antibody corrected for radioisotope physical decay. For each time point, color bars represent the average percent of injected activity per gram of tissue (%IA/g) ± 1SD

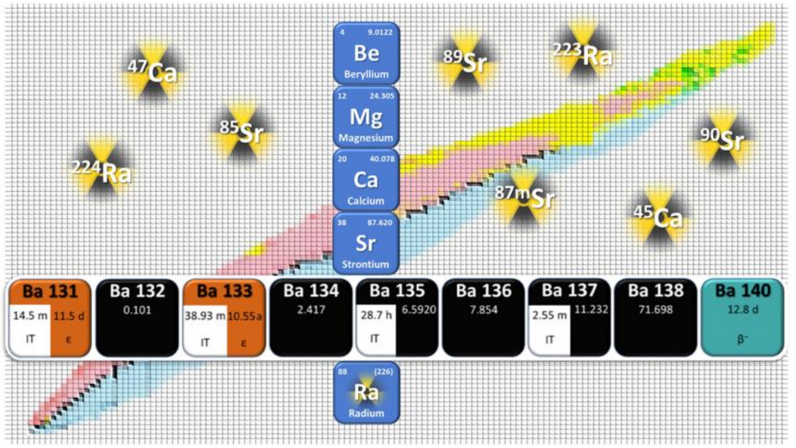
The idea in the back of PRISMAP : The European Medical Radionuclide Programme

Element	Z	Isotope	Property / Application	Imaging/Treatment/ Generator	Production ~~reaction~~
Sc	21	44g/m	PET	I	^{44}Ca(p,n) or ^{44}Ca(d,2n)
Sc	21	47	b^- therapy, SPECT	I/T	^{46}Ca(n,g)^{47}Ca(b^-)
Cu	29	64	PET	I	^{64}Ni(p,n) or ^{64}Ni(d,2n)
Cu	29	67	b^- therapy, SPECT	I/T	^{68}Zn(p,2p) or ^{70}Zn(p,a)
Ag	47	111	b^- therapy, SPECT, TDPAC	I/T	^{110}Pd(n,g)^{111}Pd(b^-) or ^{110}Pd(d,n)
La	57	135	Auger emitter	T	^{135}Ba(p,n)- or ^{nat}Ta(p,spall)+mass separation
Tb	65	149	a therapy, PET	I/T	^{nat}Ta(p,spall) +mass separation
Tb	65	152	PET	I	^{nat}Ta(p,spall)+mass separation
Tb	65	155	Auger emitter, SPECT	I	^{nat}Ta(p,spall)+mass separation
Tb	65	161	b^- therapy, SPECT	I/T	^{160}Gd(n,g)b^-
Dy	66	166	Generator for ^{166}Ho (b^-, SPECT)	G	^{164}Dy(n,g)(n,g)
Er	68	165	Auger emitter	T	^{165}Ho(p,n)
Tm	69	165	Generator for ^{165}Er (Auger em.)	G	^{nat}Ta(p,spall)+mass separation
Er	68	169	b^- therapy	T	HSA ^{168}Er(n,g) +mass separation
Yb	70	175	b^- therapy, (SPECT)	T	HSA ^{174}Yb(n,g) +mass separation
Pt	78	195m	Auger emitter, SPECT	I/T	^{194}Pt(n,g)
Bi	83	213	a therapy	T	^{225}Ac generator
At	85	211	a therapy	T	^{209}Bi(a,2n)
Ac	89	225	a therapy	T	^{229}Th generator
Ac	89	225	a therapy	T	^{232}Th(p,spall)+mass separation

^{128}Ba/^{128}Cs an in-vivo generator to treat osteosarcoma

F. Reissig, K. Kopka and C. Mamat Nuclear Medicine and Biology 98

- Theranostics approach by Auger therapy & PET imaging in preclinical osteosarcoma model
- ^{128}Ba/^{128}Cs enters the bone matrix as a surrogate of Ca^{2+} like ^{223}Ra and ^{89}Sr. It is metabolized, concentrated secreted through the matrix vesicles by the osteoblast

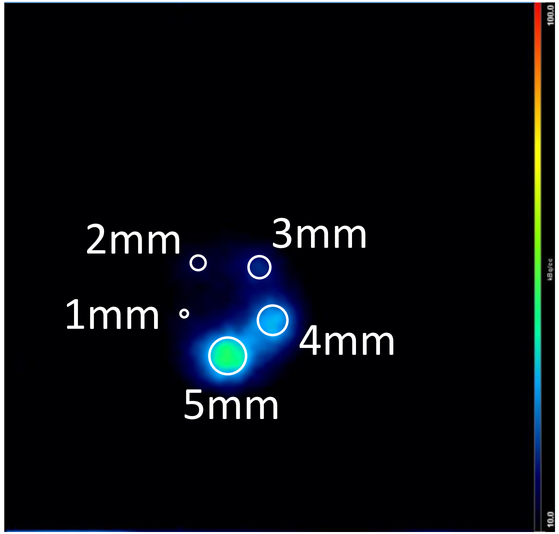


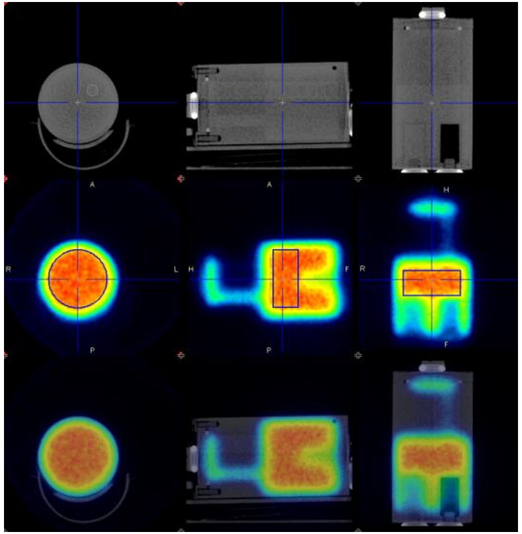
Ba 128	Cs 128
2.43 d	**3.64 m**
ε no β^+ γ 273...	β^+ 2.9... ε γ 443, 527...

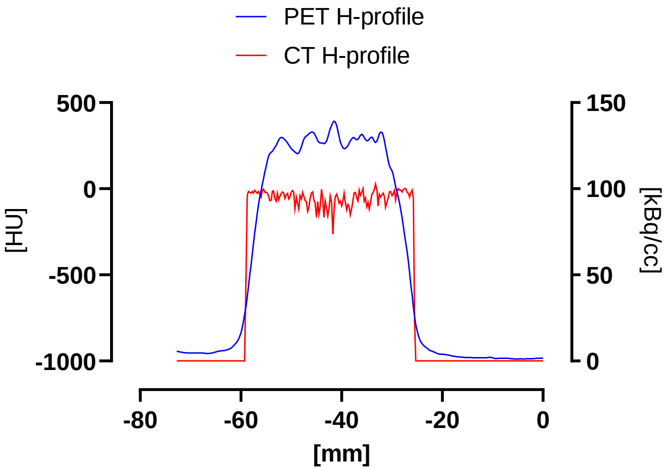
Generator system	Half-life	Decay Mode	Emission	Application	Daughter	Half life	Decay mode	Emission	Application
^{128}Ba/^{128}Cs	2.4 d	EC	γ, **Auger e$^-$** (2.5-5.7 keV 79.3%)	Auger therapy	^{128}Cs	3.66 m	EC, β+	γ, Auger e$^-$, **β+** (1315.9 keV 53.2%)	PET

D. Viertl et al., MED-028
https://medicis.cern/approved-projects

First phantom study of $^{128}Ba/^{128}Cs$ PET imaging



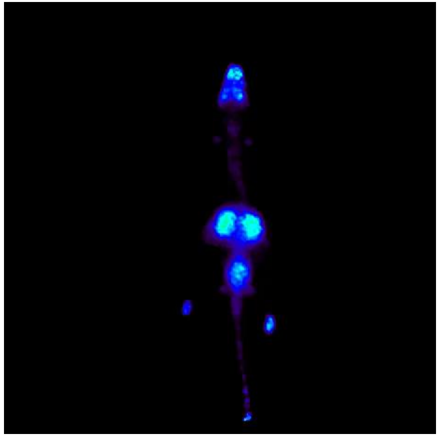




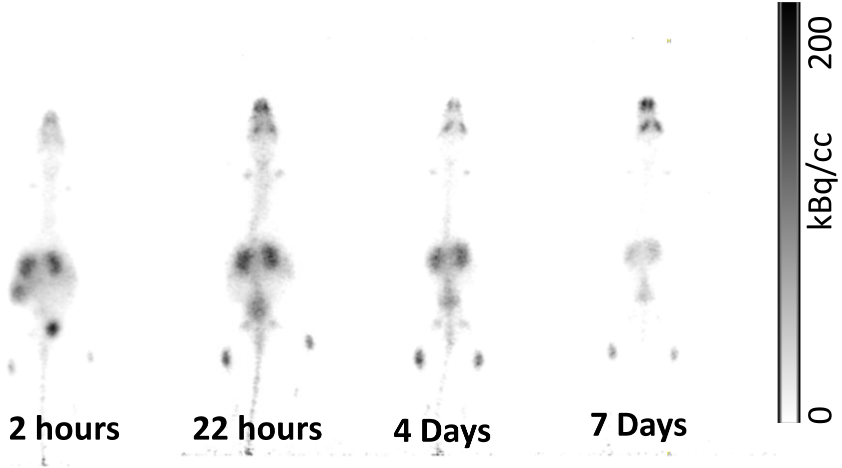
Micro-PET IQ Phantom
(according to NEMA NU 4-2008)

4 MBq in 21 ml → 190 kBq/ml
In VOI → 134 kBq/ml
MLEM 12 iteration

Whole body PET imaging of $^{128}Ba/^{128}Cs$ in a naïve mouse



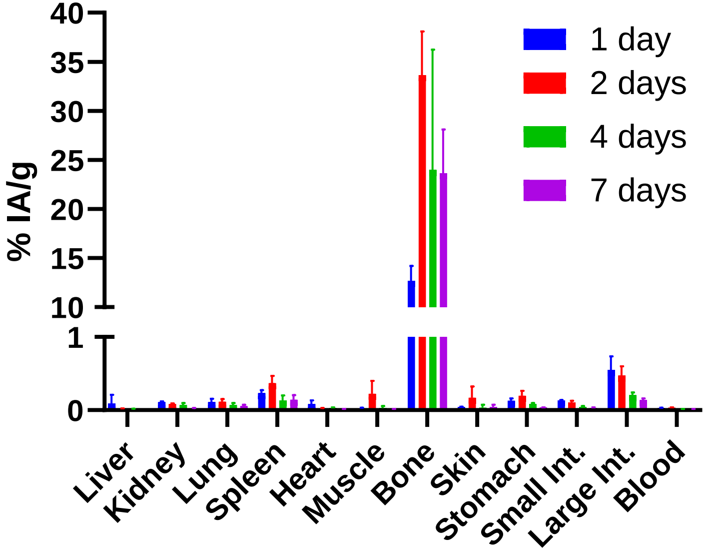
22 hours



2 hours 22 hours 4 Days 7 Days

Movies and MIP projections of PET images of a mouse injected with 5 MBq of Ba/Cs-128 in a longitudinal study over seven days

Biodistribution of $^{128}Ba/^{128}Cs$ in naïve mice & Dosimetry



Source organ	TIAC (h)
Tumour	2.46E-03
Liver	4.42E-02
Kidney	5.20E-02
Lung	2.70E-02
Spleen	3.46E-02
Heart content	1.14E-01
Muscle	1.69E-02
Bone	2.00E+01
Skin	3.21E-02
Stomach	4.24E-02
Small Int.	1.90E-01
Large Int.	5.01E-01
Tail	9.04E+00
Head	1.69E+01
Blood	1.82E-02
ROB	5.00E+00

Ba-128 Target Organ	Alpha	Beta	Gamma	Total [mGy/MBq]]
Brain	0.00E+00	1.44E+00	3.63E+00	5.06E+00
Large Int	0.00E+00	5.34E+00	2.64E+00	7.98E+00
Small Intestine	0.00E+00	1.59E+00	1.98E+00	3.57E+00
Stomach Wall	0.00E+00	4.97E+00	2.62E+00	7.59E+00
Heart	0.00E+00	3.72E+00	4.49E+00	8.21E+00
Kidneys	0.00E+00	1.88E+00	2.53E+00	4.41E+00
Liver	0.00E+00	1.32E+00	2.97E+00	4.29E+00
Lungs	0.00E+00	4.56E+00	5.59E+00	1.02E+01
Pancreas	0.00E+00	1.07E+00	2.26E+00	3.33E+00
Skeleton	0.00E+00	6.56E+01	5.80E+00	**7.14E+01**
Spleen	0.00E+00	2.54E+00	2.14E+00	4.68E+00
Testes	0.00E+00	1.03E+00	2.30E+00	3.33E+00
Thyroid	0.00E+00	1.55E+00	5.38E+00	6.93E+00
Urin Blad	0.00E+00	1.04E+00	2.36E+00	3.40E+00
Total Body	0.00E+00	2.78E+00	2.92E+00	5.69E+00

Cs-128 Target Organ	Alpha	Beta	Gamma	Total [mGy/MBq]
Brain	0.00E+00	5.83E+02	2.24E+01	6.05E+02
Large Int	0.00E+00	1.75E+02	1.47E+01	1.89E+02
Small Intestine	0.00E+00	1.18E+02	1.33E+01	1.31E+02
Stomach Wall	0.00E+00	2.49E+02	1.59E+01	2.65E+02
Heart	0.00E+00	8.94E+02	2.74E+01	9.21E+02
Kidneys	0.00E+00	2.20E+02	1.62E+01	2.36E+02
Liver	0.00E+00	3.71E+02	1.92E+01	3.90E+02
Lungs	0.00E+00	1.09E+03	3.02E+01	1.12E+03
Pancreas	0.00E+00	1.23E+02	1.40E+01	1.37E+02
Skeleton	0.00E+00	2.74E+03	3.40E+01	**2.78E+03**
Spleen	0.00E+00	1.84E+02	1.24E+01	1.96E+02
Testes	0.00E+00	1.52E+02	1.40E+01	1.66E+02
Thyroid	0.00E+00	9.33E+02	3.54E+01	9.69E+02
Urin Blad	0.00E+00	1.14E+02	1.54E+01	1.29E+02
Total Body	0.00E+00	5.27E+02	1.83E+01	5.46E+02

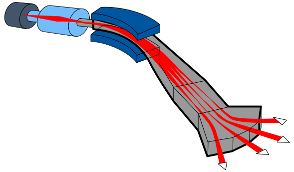
Biodistributions of naive mice injected with Ba/Cs-128
Time activity curves derived from biodistributions
Dose to organs calculated with OLINDA

Did you say (take-home message) ?

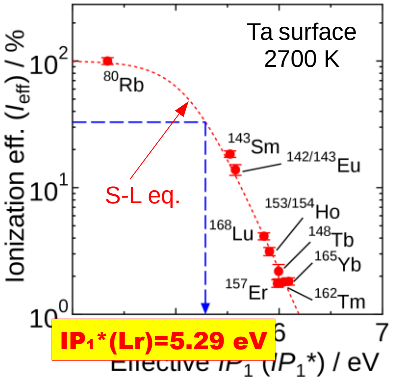
non conventional radionuclides

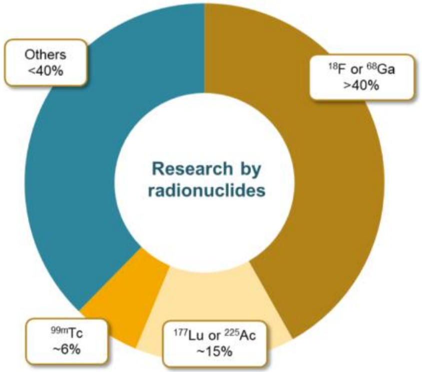
(production/purification)

in personalised medicine

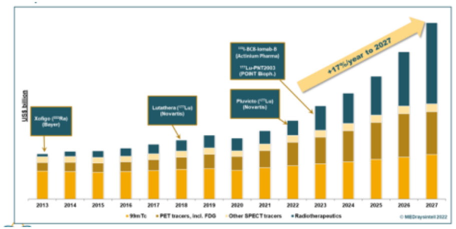


Fom one-atom-at-a-time experiments to large production needs



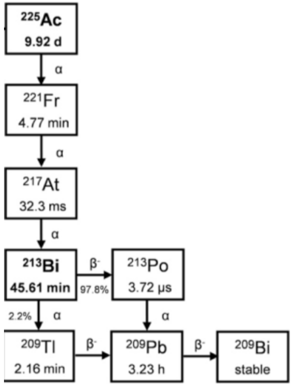


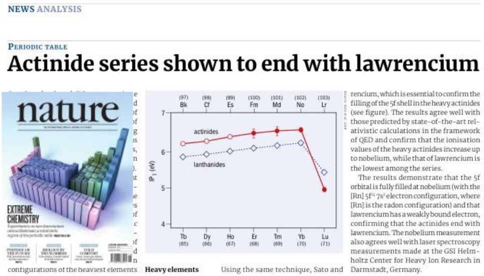
MEDraysintell



Ionisation efficiencies

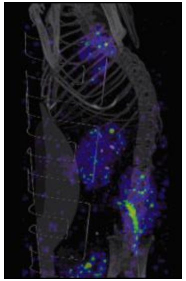
^{153}Sm	12.7
^{167}Tm	55 %
^{155}Tb	1-6
^{225}Ac	15.1 %





SCIENTIFIC REPORTS

From low to high specific activity radiopharmaceuticals for theranostics



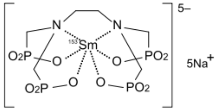
[Production of Sm-153 with high specific activity for targeted radionuclide therapy]

M. van Voorde et al.

$^{223}RaCl_2$

^{177}Lu-DOTATATE

^{153}Sm-EDTMP
(low specific activity)

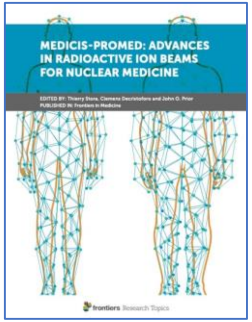


→

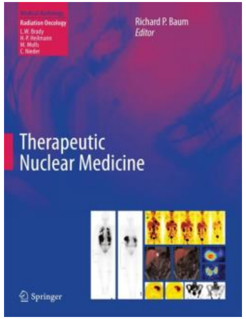
^{153}Sm-DOTATATE or other ?

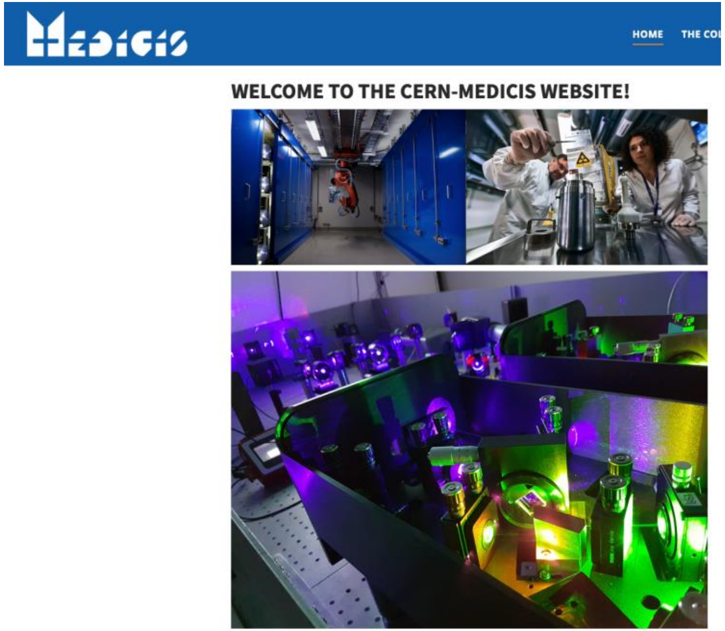
Thank you ! Questions ?

- Some references:
- Therapeutic nuclear medicine, Richard Baum ed. ISBN: 978-3-540-36719-2
- https://medical-radionuclides.eu
- Frontiers in Medicine : Advances in Radioactive Ion Beams for Nuclear Medicine (J. Prior, C. Decristoforo, T. Stora eds) ISBN 978-2-83250-522-9
- IAEA TecDoc https://www.iaea.org/topics/nuclear-science/isotopes



- Acknowlegement:
- Edgars Mamis, Charlotte Duchemin, Laura Lambert, David Viertl, Marteen Ooms, Jake Johnson,
- The MEDICIS Collaboration,





https://medicis.cern
https://medical-radionuclides.eu

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-018-4015-2

ORIGINAL ARTICLE

Prolonged survival in secondary glioblastoma following local injection of targeted alpha therapy with ^{213}Bi-substance P analogue

Leszek Krolicki[1] & Frank Bruchertseifer[2] & Jolanta Kunikowska[1] & Henryk Koziara[3] & Bartosz Królicki[3] & Maciej Jakuciński[4] & Dariusz Pawlak[5] & Christos Apostolidis[2] & Saed Mirzadeh[6] & Rafał Rola[7] & Adrian Merlo[8] & Alfred Morgenstern[2]

Received: 5 December 2017 / Accepted: 9 April 2018

Fig. 3 Whole body PET/CT scan shows biodistribution 30 min after intralesional injection of 10 MBq ^{68}Ga-DOTA-SP analogue: the signal detected in the body outside the brain is very faint or negligible in liver, kidney, spleen and bone marrow. The cleaved linear peptidic vector is excreted into the bladder and can show a weak signal corresponding to <5% of injected activity

New treatments in nuclear medicine : a large and “recent” interest in Europe

Physics & Chemistry Nobel Prizes

The New York Times.

MME. CURIE PLANS TO END ALL CANCERS

Says Radium Is Sure Cure, Even in Deep-Rooted Cases, if Properly Treated.

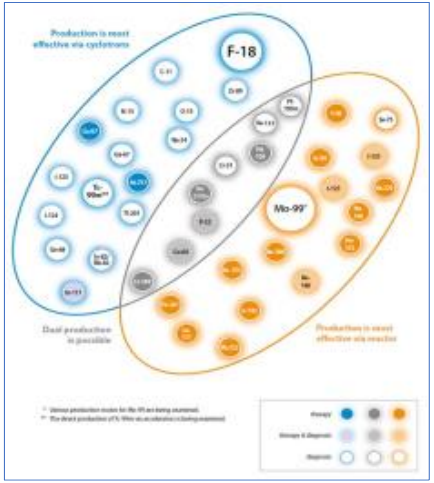


Figure 31 : Main medical radioisotopes production process

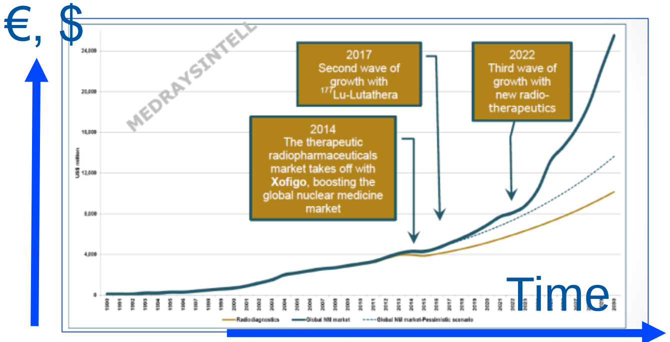
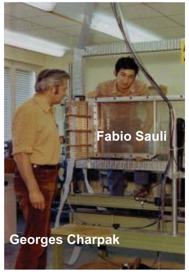


Figure 8: Possible market evolution for radiotherapeutics – source MedRaysIntell (2016)

Economics, Innovators



Helene Langevin-Joliot at MEDICIS, professor in nuclear physics, grand-daughter of Marie Curie

European Commission ENER/17/NUCL/SI2.755660

Accelerator Labs Worldwide
(eg PSI, TRIUMF),
You Today !


le dauphiné libéré

GENEVOIS

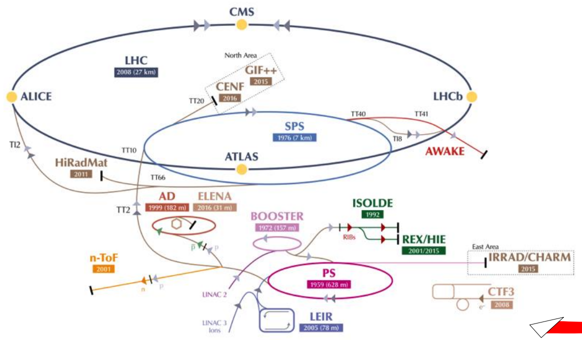
La lutte anti-cancer se prépare au Cern

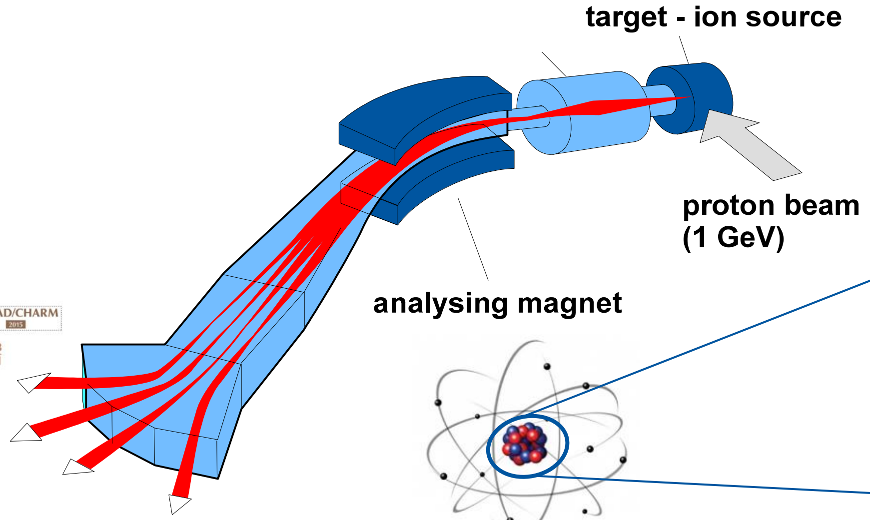
Finally Monsieur et Madame tout le monde

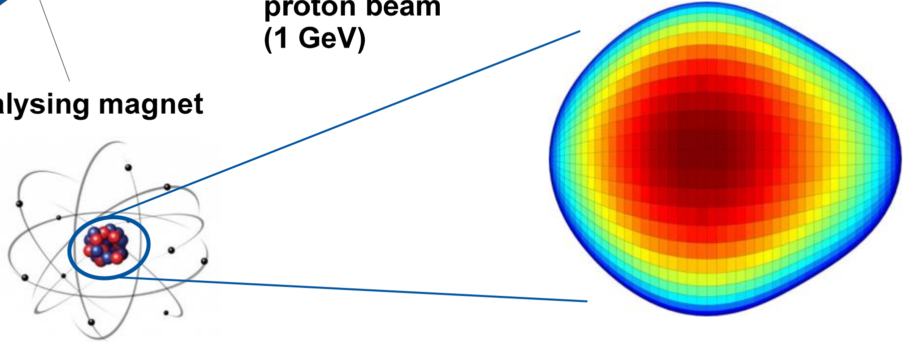
ISOLDE….

^{224}Radium is pear shaped.

Highlighted by Physics World as one of the 10 breakthroughs in 2013







CERN-MEDICIS : A new facility

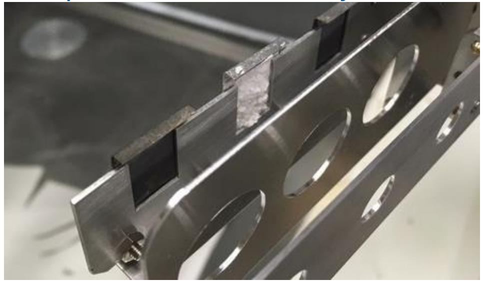
September 2013

October 2014

Equipment, services

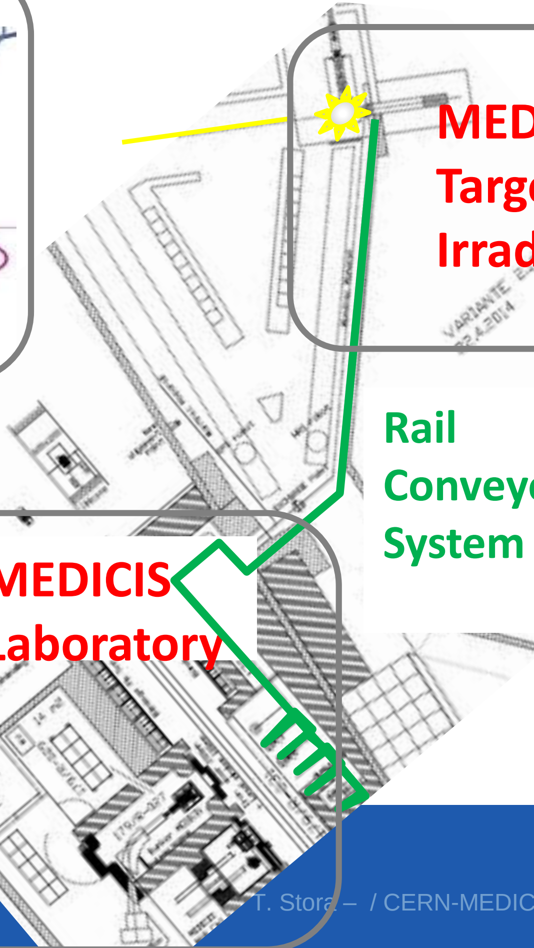
1st collected isotope : December 2017

Isotopes collected in salt layer in 2018

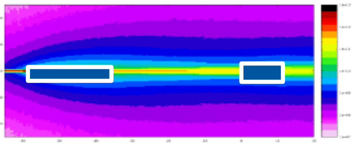


Principle of isotope production

CERN protons



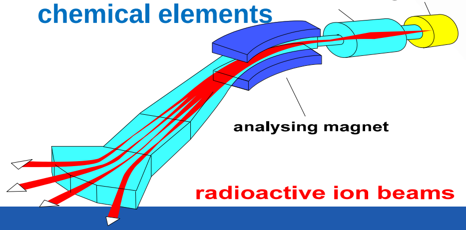
MEDICIS Target Irradiation



Rail Conveyor System

MEDICIS Laboratory

1000+ isotopes of 70+ chemical elements



CERN