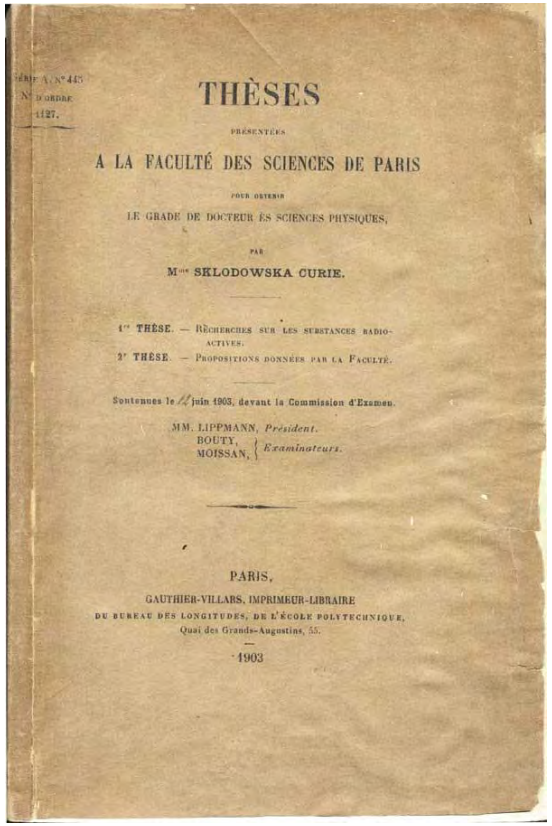
Radioactive Ion Beams : from large scale facilities to nuclear medicine applications

Thierry STORA - CERN

IAEA International Conference on Accelerators for Research and Sustainable Development: From Good Practices Towards

The early days



THÈSES

PRÉSENTÉES

A LA FACULTÉ DES SCIENCES DE PARIS

POUR OBTENIR

LE GRADE DE DOCTEUR ÈS SCIENCES PHYSIQUES,

PAR

Mme SKLODOWSKA CURIE.

1re THÈSE. — RECHERCHES SUR LES SUBSTANCES RADIO-ACTIVES.

2e THÈSE. — PROPOSITIONS DONNÉES PAR LA FACULTÉ.

Soutenues le 11 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

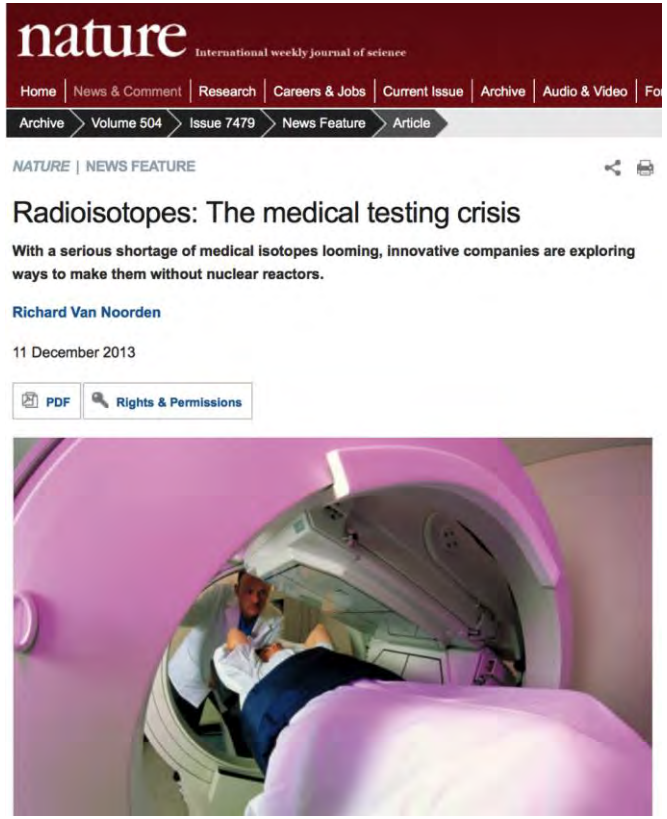
The New York Times.

MME. CURIE PLANS TO END ALL CANCERS

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

Courtesy prof O. Ratib

Radioisotopes & Nuclear Medicine



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

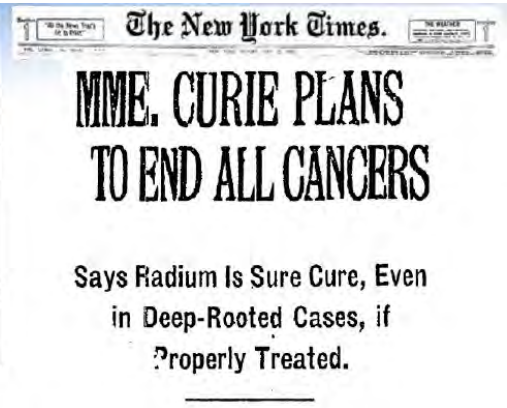
3. R&D isotopes → Research labs
^{44,47}Sc, ^{64,67}Cu, ^{134}Ce, ^{140}Nd, $^{149, 152, 155, 161}$Tb, ^{166}Ho, ^{195m}Pt, ^{211}At, ^{212,213}Bi, ^{223}Ra, ^{225}Ac,…

Courtesy U. Koester

New treatments in nuclear medicine : a large interest in Europe

Physics & Chemistry Nobel Prizes

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.

Helene Langevin-Joliot at MEDICIS, professor in nuclear physics, grand-daughter of Marie Curie (2017)

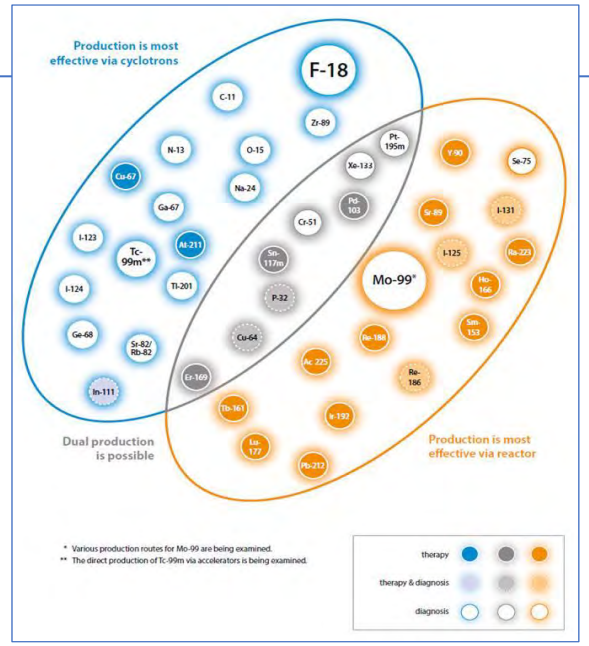


Figure 31 : Main medical radioisotopes production process

European Commission ENER/17/NUCL/SI2.755660 (2018)

Accelerator Labs Worldwide (eg PSI, TRIUMF)

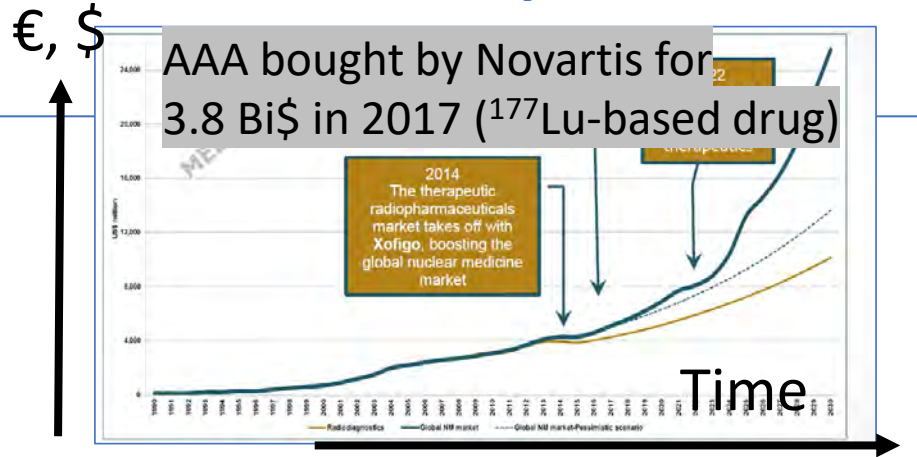


Figure 8: Possible market evolution for radiotherapeutics – source MedRaysIntell (2016)

Economics, Innovators

le dauphiné libéré

BELLEGARDE & PAYS DE GEX

GENEVOIS LE SAVOIR DES PHYSICIENS AU SERVICE DE LA MÉDECINE DE DEMAIN

La lutte anti-cancer se prépare au Cern

Finally Monsieur et Madame tout le monde

Example of theranostics concept in pre-clinical research

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

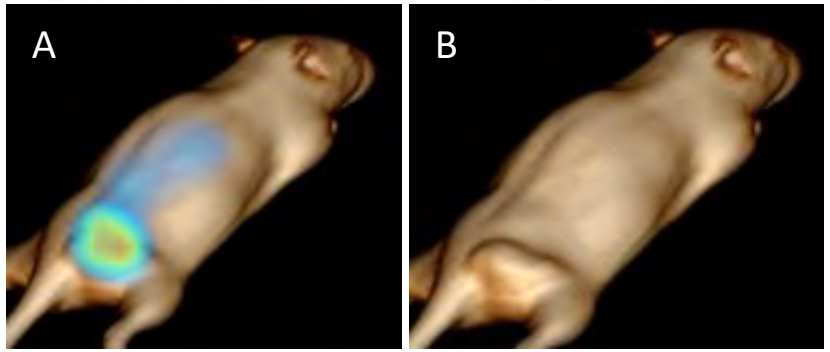
Diagnostics

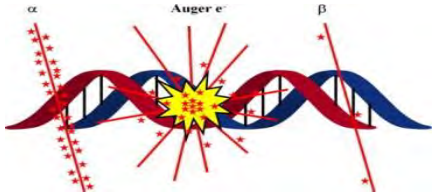
THERAPY

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

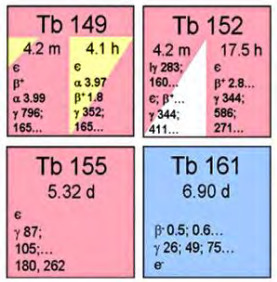
ORIGINAL RESEARCH Open Access

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





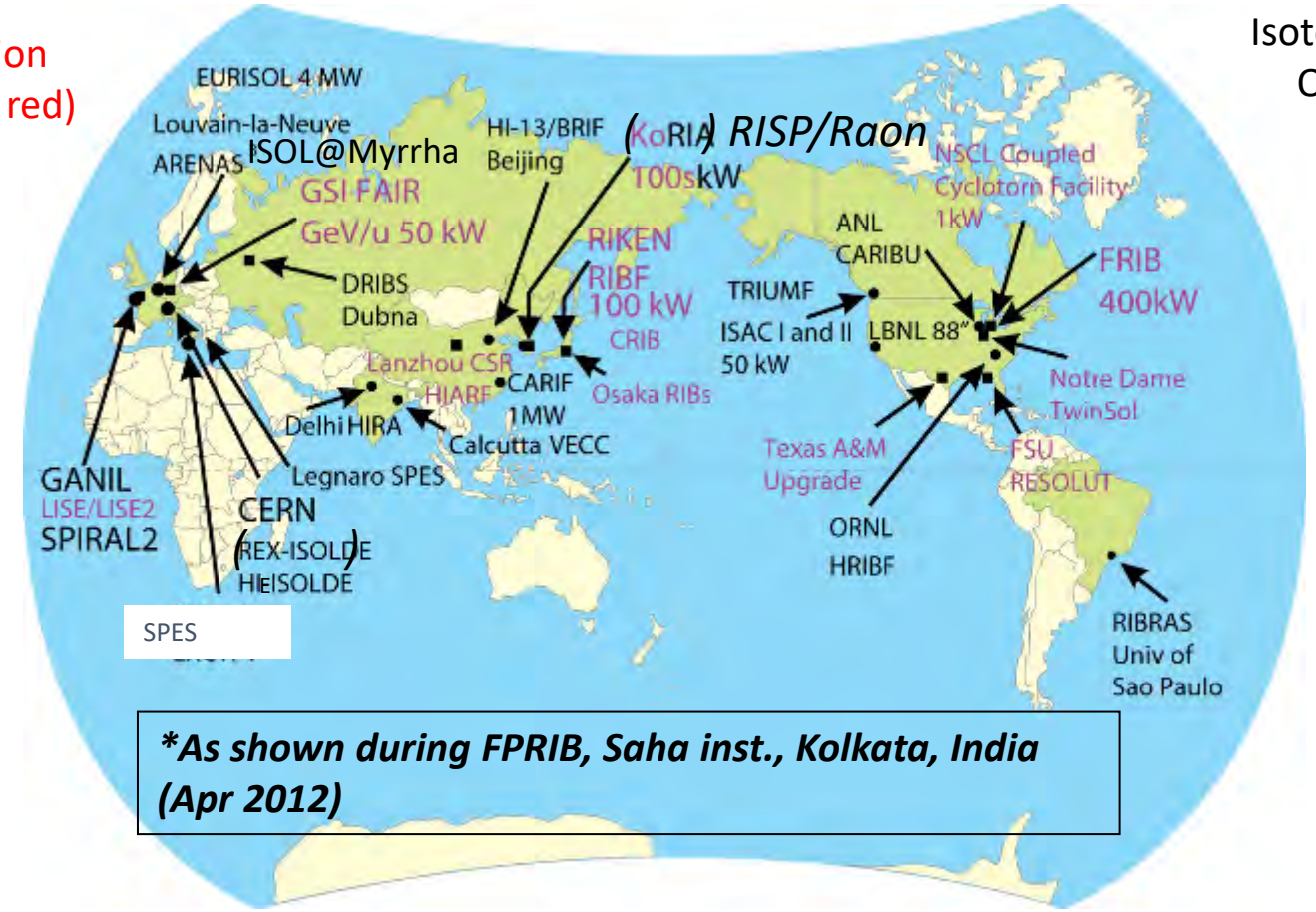
Matched therapeutic Tb



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

World map of radioisotope ion beam facilities*

In-flight Fragmentation Facilities (in red)

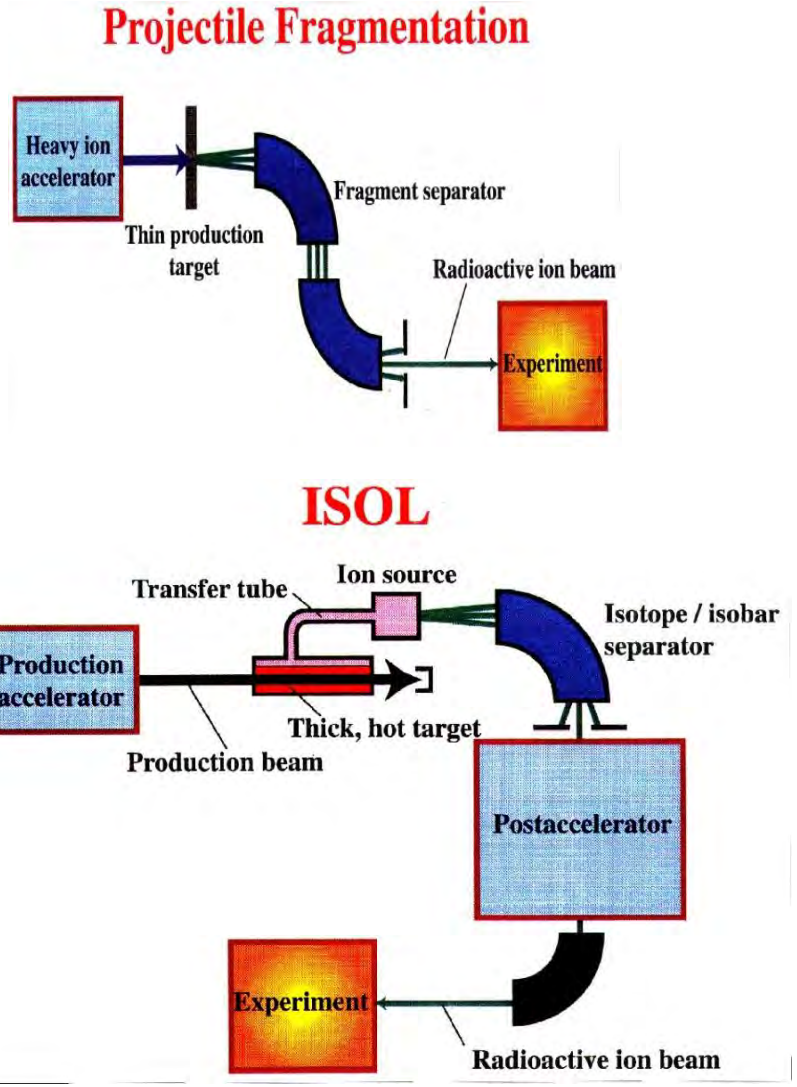


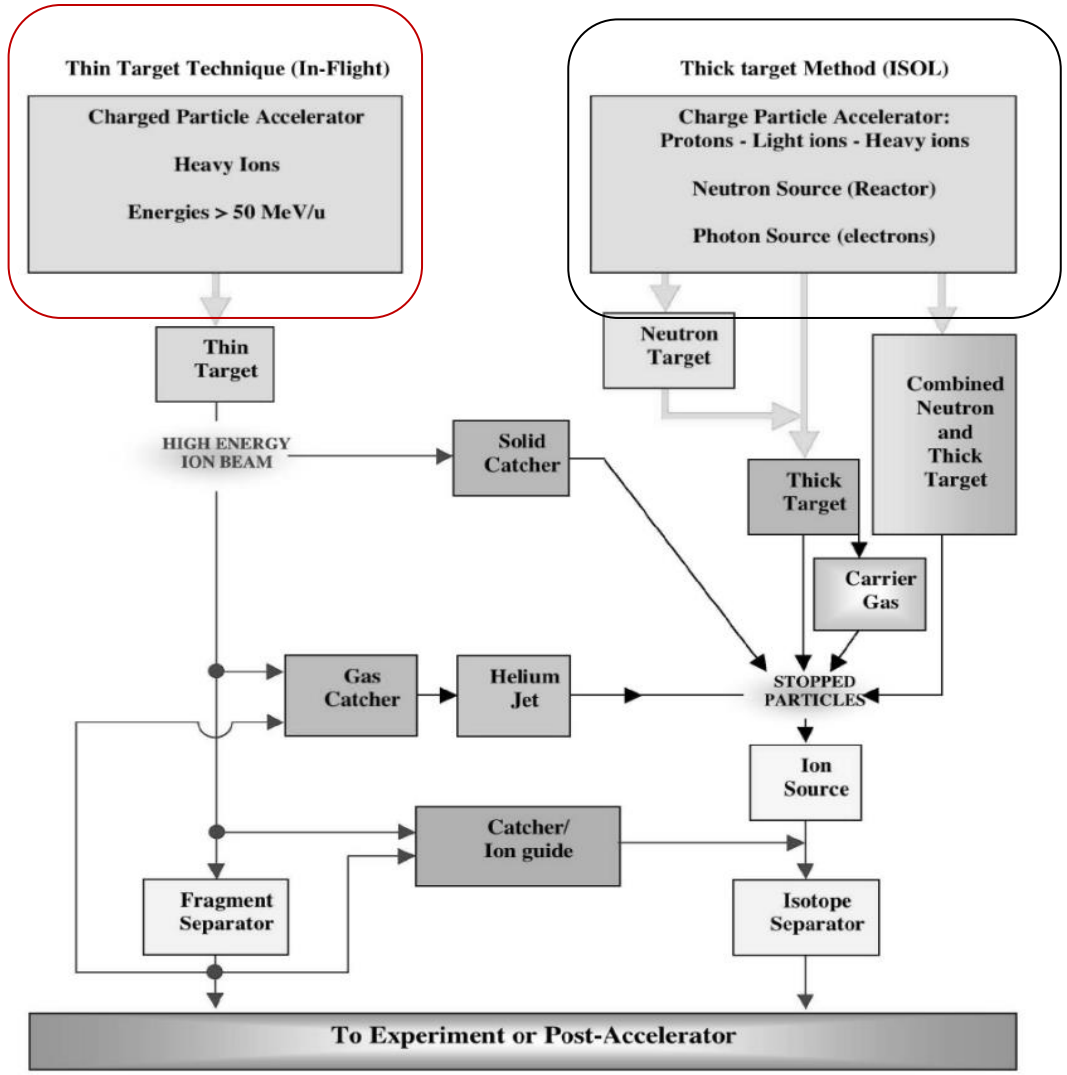
As shown during FPRIB, Saha inst., Kolkata, India (Apr 2012)

Isotope Separation OnLine Facilities ISOL (in black)

RAON is expected to start this year
SPES is expected to start
ISOL@Myrrha project has started constructiom

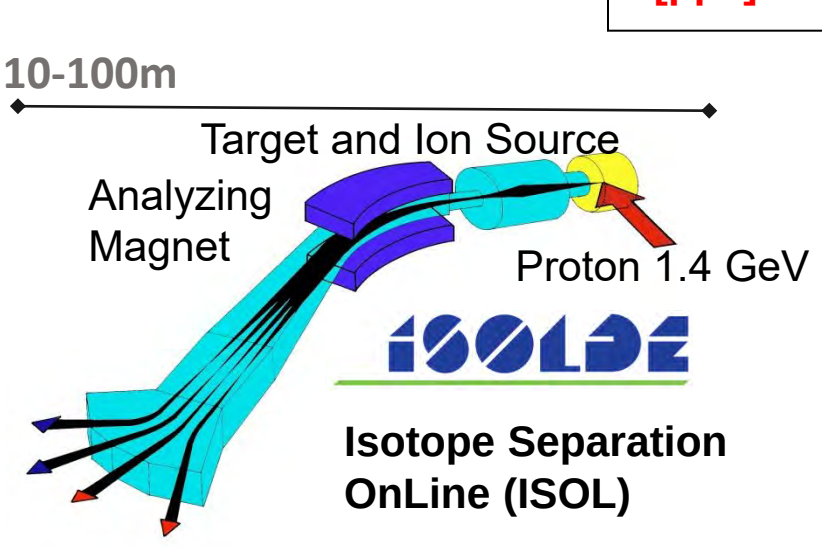
The main ingredients :An accelerator for isotope production + mass purification



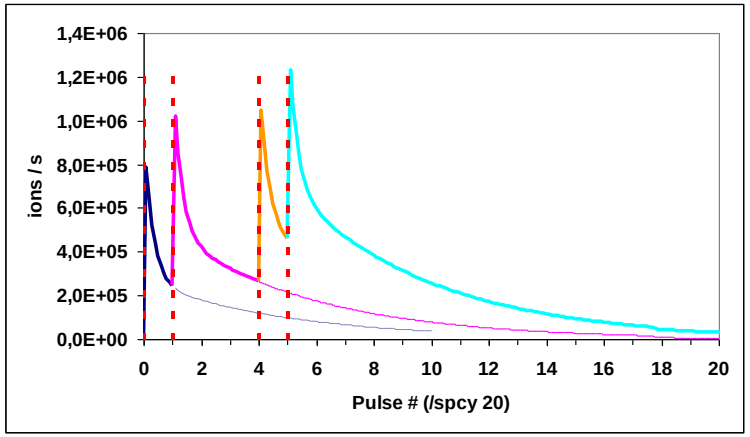


Radioisotope Beam Production at ISOLDE

$$I_{[pps]} \sim \Phi_{[pps]}\ \sigma_{[barn]}\ N_{[g/cm2]}\ \varepsilon\ [\%]$$



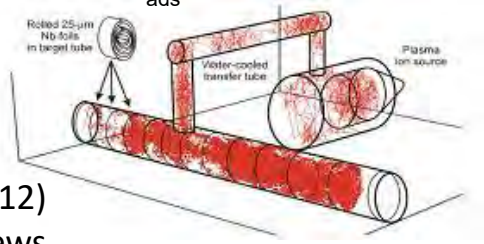
Intensity
Purity (quality)
Reliability



Diffusion
Physical Chemistry

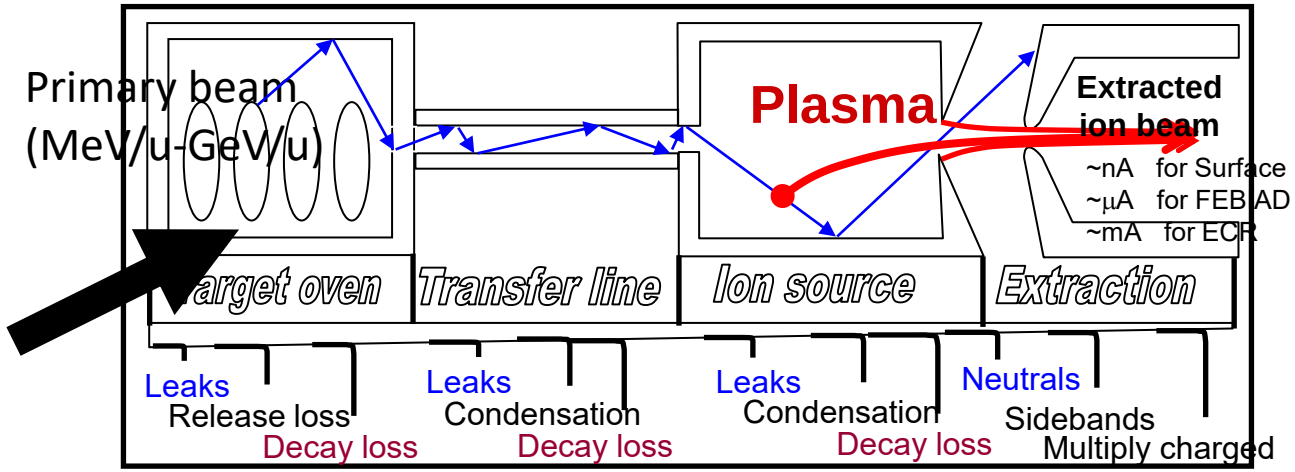
$$p(t) \propto p_{eff}(t) \star p_{diff}(t$$

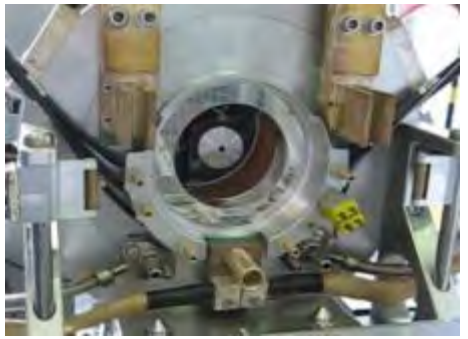
ΔH_{ads} = 145 ± 15 kJ/mol



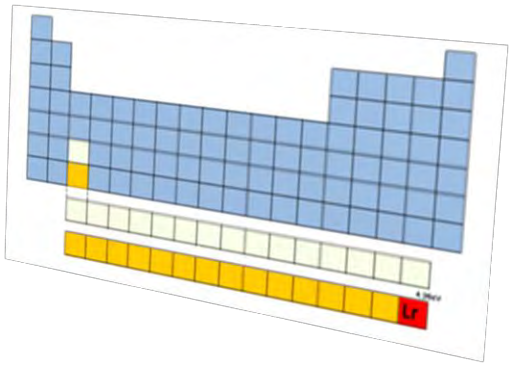
Eur. Phys. Lett. 98, 32001 (2012)
Highlighted in Europhysics news

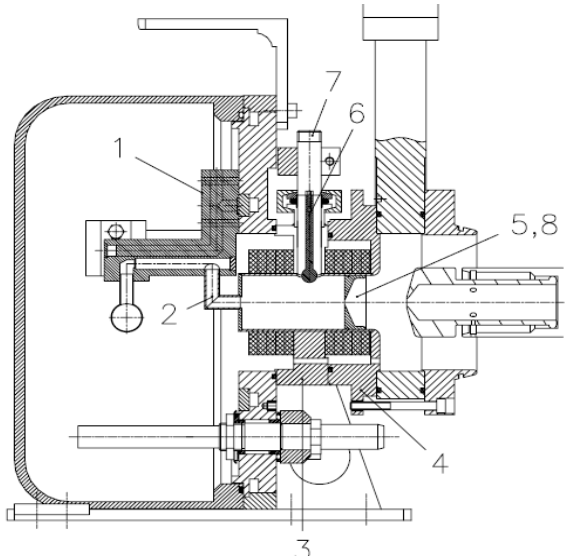
Principles of radioactive beam production



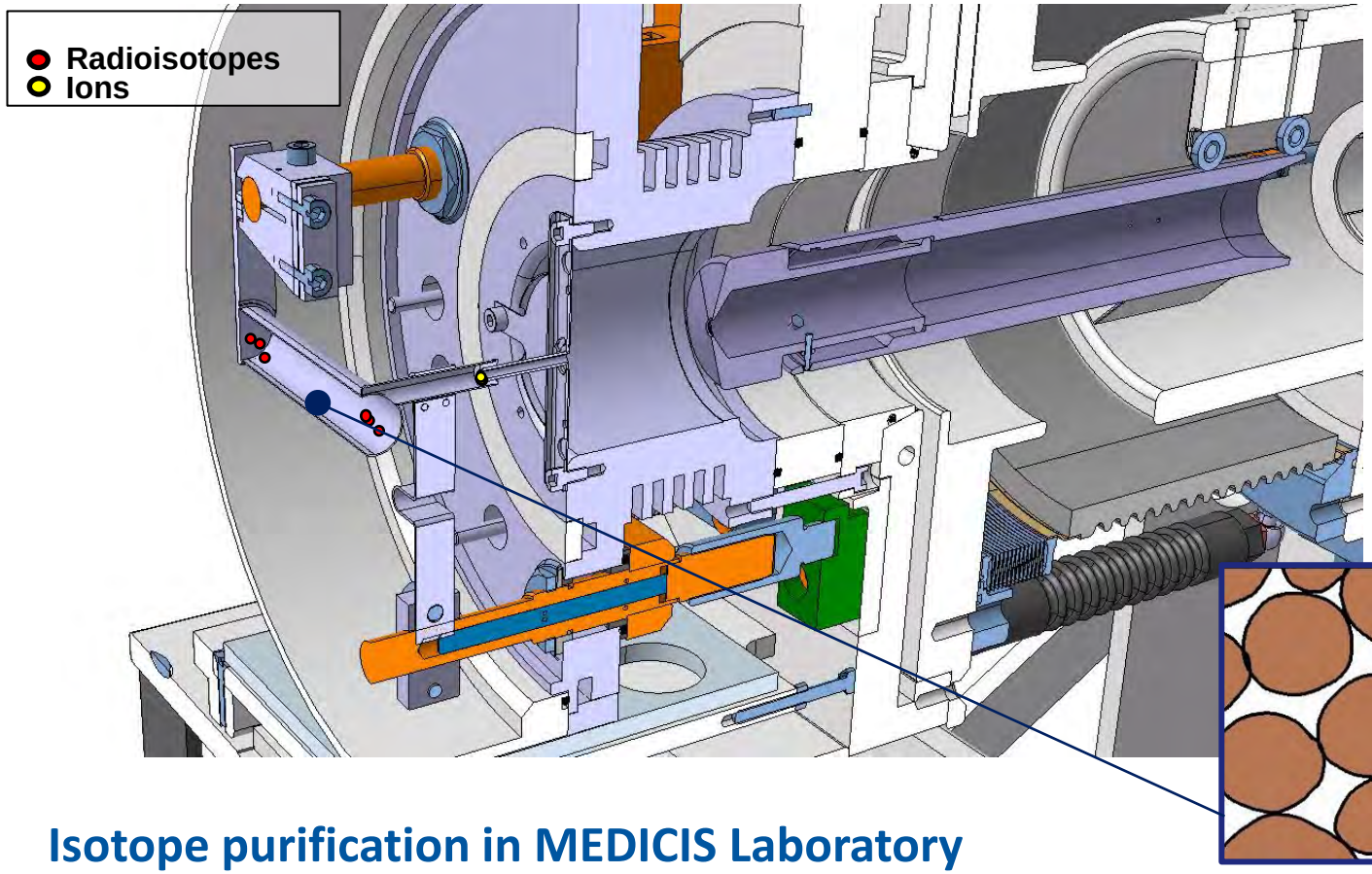


Ion sources: compact, simple and withstand 1 MGy
Ionize trace radioelements in larger impurities loads
Used to measure Ion. Pot. Lr (Z=103)
at “1 atom at a time” rate



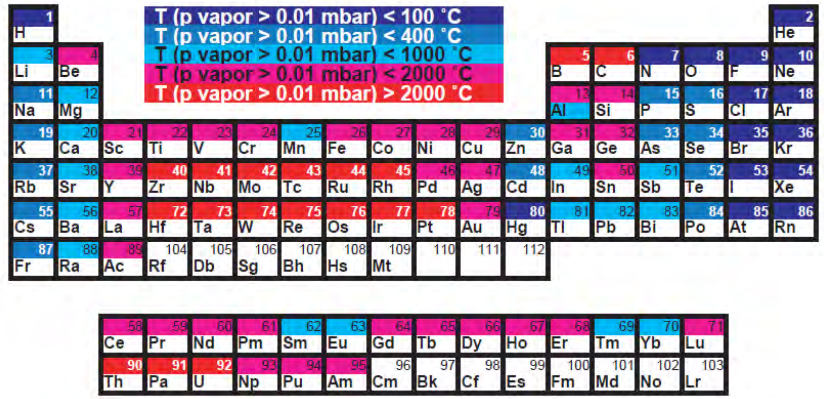


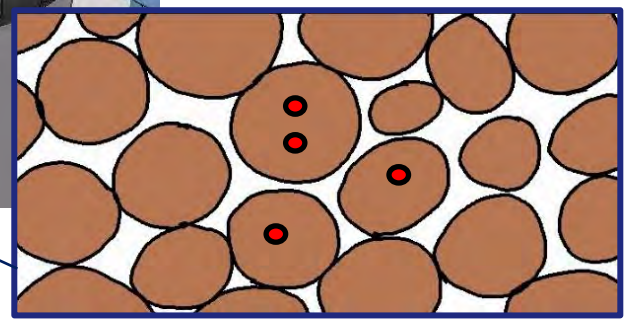
Principle of isotope production, release and acceleration



Isotope purification in MEDICIS Laboratory

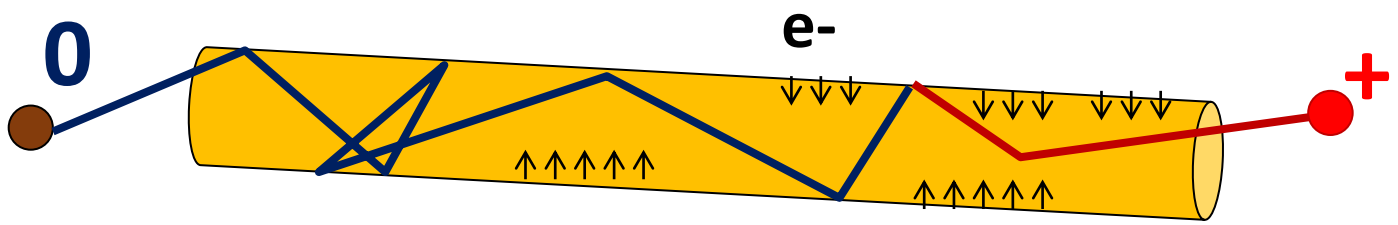
Standard ISOLDE target unit with ***surface*** *ion source*



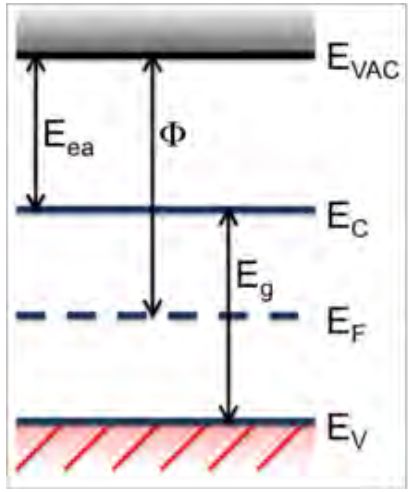


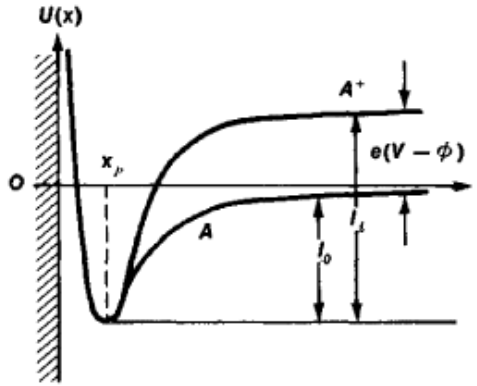
H. Ravn and W. Brian "On-line mass separators. " Treatise on heavy ion science. Springer US, 1989. 363-439.

Surface Ion Sources



Hot tube





Material work function Φ
Isotope 1st Ion. Pot. : Wi

Saha-Langmuir Equation

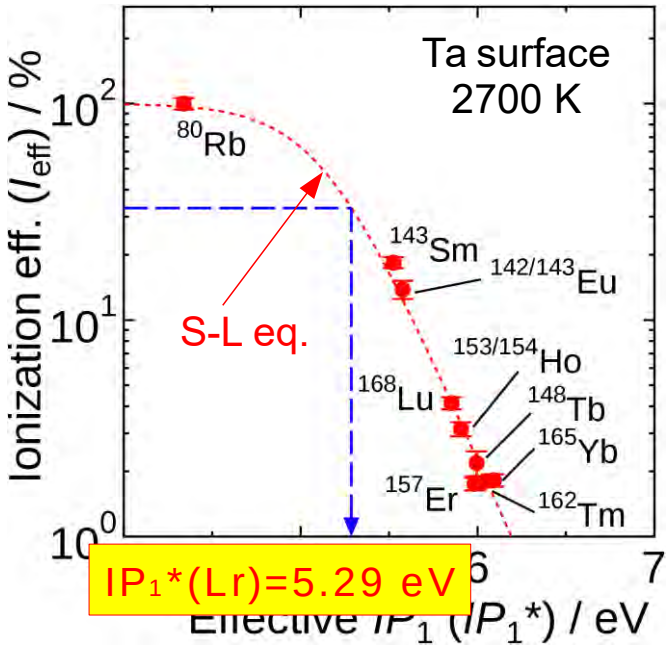
$$\varepsilon_{\text{surface}} = \frac{1}{1 + \frac{g_0}{g_+} \exp\left(\frac{W_i - \Phi}{kT}\right)}$$

For Alkalis,
g_0=2 (2S1/2, degeneracy 2), g+=1

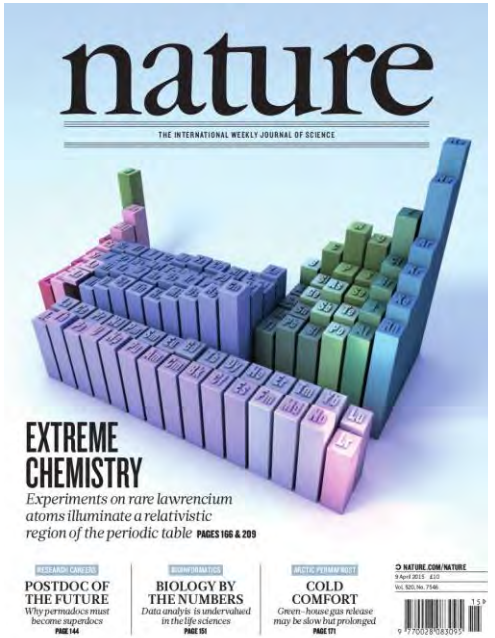
Some additional correction factors such as applied electrical potential or surface coverage

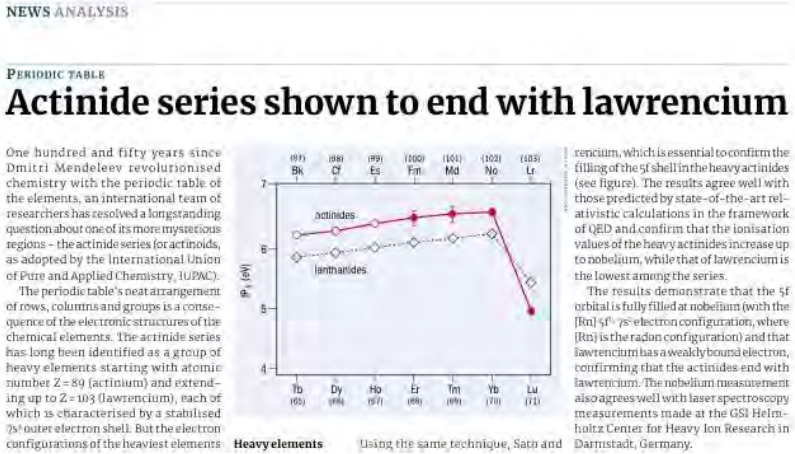
Meghnad Saha, 1920

Clever use of Surface Ion Sources



2015





NEWS ANALYSIS

PERIODIC TABLE

Actinide series shown to end with lawrencium

One hundred and fifty years since Dmitri Mendeleev revolutionised chemistry with the periodic table of the elements, an international team of researchers has resolved a longstanding question about one of its more mysterious regions – the actinide series (or actinoids, as adopted by the International Union of Pure and Applied Chemistry, IUPAC).

The periodic table's neat arrangement of rows, columns and groups is a consequence of the electronic structures of the chemical elements. The actinide series has long been identified as a group of heavy elements starting with atomic number Z = 89 (actinium) and extending up to Z = 103 (lawrencium), each of which is characterised by a stabilised $7s^2$ outer electron shell. But the electron configurations of the heaviest elements

Heavy elements

Using the same technique, Sato and

rencium, which is essential to confirm the filling of the 5f shell in the heavy actinides (see figure). The results agree well with those predicted by state-of-the-art relativistic calculations in the framework of QED and confirm that the ionisation values of the heavy actinides increase up to nobelium, while that of lawrencium is the lowest among the series.

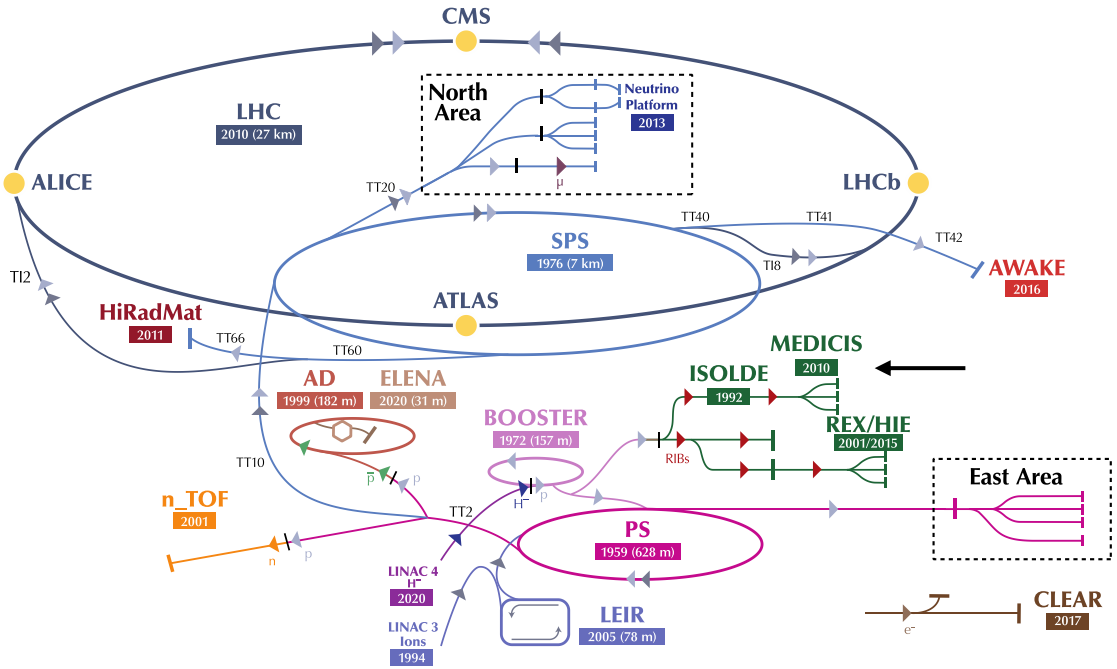
The results demonstrate that the 5f orbital is fully filled at nobelium (with the [Rn] $5f^{14}$ $7s^2$ electron configuration, where [Rn] is the radon configuration) and that lawrencium has a weakly bound electron, confirming that the actinides end with lawrencium. The nobelium measurement also agrees well with laser spectroscopy measurements made at the GSI Helmholtz Center for Heavy Ion Research in Darmstadt, Germany.

T. K. Sato et al., *J. Am. Chem. Soc.* 2018, 140, 44, 14609–146132018

Ideas to measure Ionization potential on element Z=104 have started

The PRISMAP Consortium

The CERN accelerator complex
Complexe des accélérateurs du CERN



H⁻ (hydrogen anions) · p (protons) · ions · RIBs (Radioactive Ion Beams) · n (neutrons) · $\bar{p}$ (antiprotons) · e^- (electrons) · μ (muons)

LHC - Large Hadron Collider // SPS - Super Proton Synchrotron // PS - Proton Synchrotron // AD - Antiproton Decelerator // CLEAR - CERN Linear Electron Accelerator for Research // AWAKE - Advanced WAKefield Experiment // ISOLDE - Isotope Separator OnLine // REX/HIE - Radioactive EXperiment/High Intensity and Energy ISOLDE // MEDICIS // LEIR - Low Energy Ion Ring // LINAC - LINear ACcelerator // n_TOF - Neutrons Time Of Flight // HiRadMat - High-Radiation to Materials // Neutrino Platform

27 EU PRISMAP Medical Radionuclides

MEDICIS
European organization for nuclear research - CERN

PSI
Paul Scherrer Institut – PSI

Hevesy Laboratory
Danmarks Tekniske Universitet – DTU

BR2
Belgian Nuclear Research Centre — SCK CEN

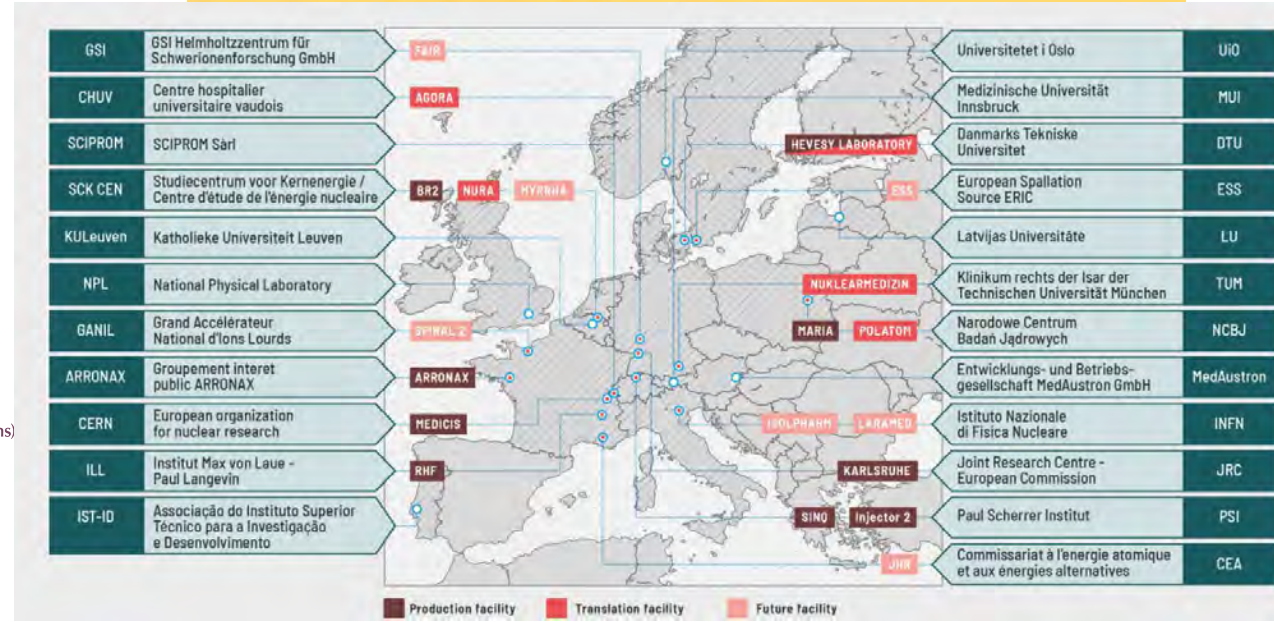
ARRONAX
Groupement interet public ARRONAX — ARRONAX

RHF
Institut Max von Laue - Paul Langevin – ILL

JRC Karlsruhe
Joint Research Centre - European Commission – JRC

NCBJ
Narodowe Centrum Badań Jądrowych — NCBJ

GSI	GSI Helmholtzzentrum für Schwerionenforschung GmbH	Universitetet i Oslo	UiO
CHUV	Centre hospitalier universitaire vaudois	Medizinische Universität Innsbruck	MUI
SCIPROM	SCIPROM Sàrl	Danmarks Tekniske Universitet	DTU
SCK CEN	Studiecentrum voor Kernenergie / Centre d'étude de l'énergie nucleaire	European Spallation Source ERIC	ESS
KULeuven	Katholieke Universiteit Leuven	Latvijas Universitāte	LU
NPL	National Physical Laboratory	Klinikum rechts der Isar der Technischen Universität München	TUM
GANIL	Grand Accélérateur National d'Ions Lourds	Narodowe Centrum Badań Jądrowych	NCBJ
ARRONAX	Groupement interet public ARRONAX	Entwicklungs- und Betriebsgesellschaft MedAustron GmbH	MedAustron
CERN	European organization for nuclear research	Istituto Nazionale di Fisica Nucleare	INFN
ILL	Institut Max von Laue - Paul Langevin	Joint Research Centre - European Commission	JRC
IST-ID	Associação do Instituto Superior Técnico para a Investigação e Desenvolvimento	Paul Scherrer Institut	PSI
		Commissariat à l'energie atomique et aux énergies alternatives	CEA



Equation to express production and mass separation yields

RIB intensity [s^{-1} μA^{-1}]

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

Avogadro Numb.

Diffusion+ Effusion Efficiency

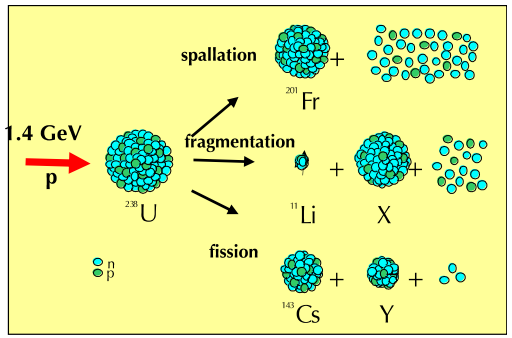
$$I = \int \sigma(E)\ \Phi(E, x)\ \rho(x)\ N/A\ dx\ \varepsilon_{diff+eff}\ \varepsilon_{ion}$$

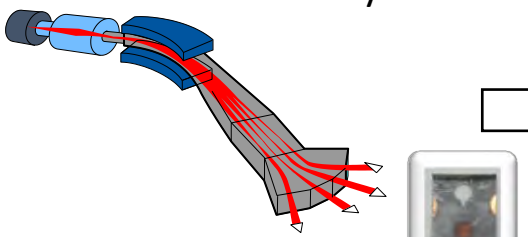
Cross section [cm^2]

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

Target Atomic Mass [g]

Ionization Efficiency

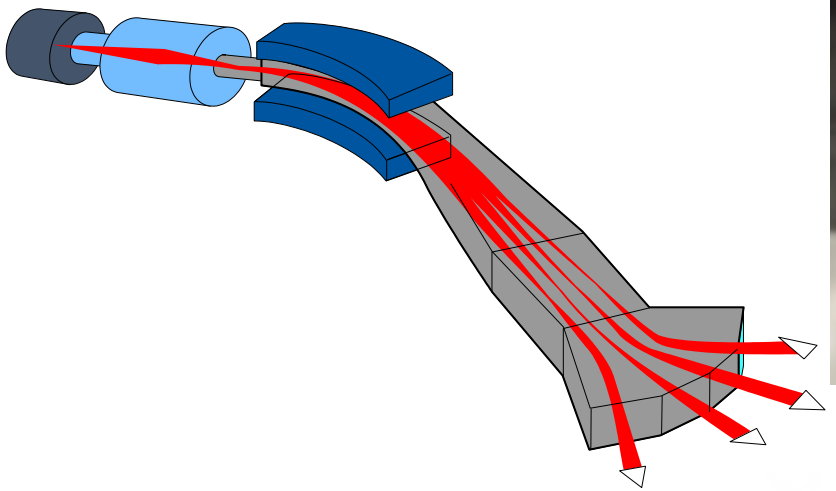


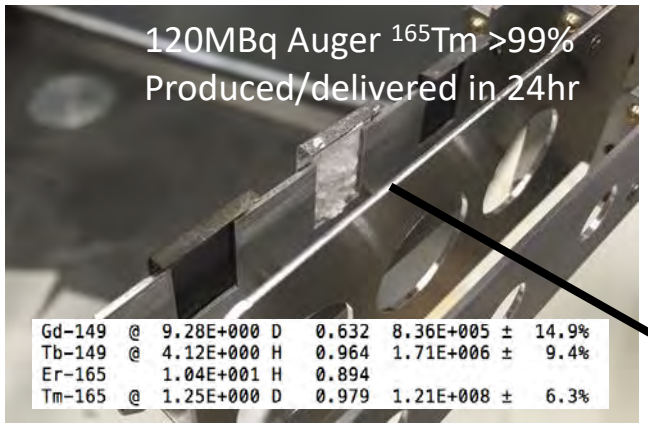


Low specific activity
Impurities

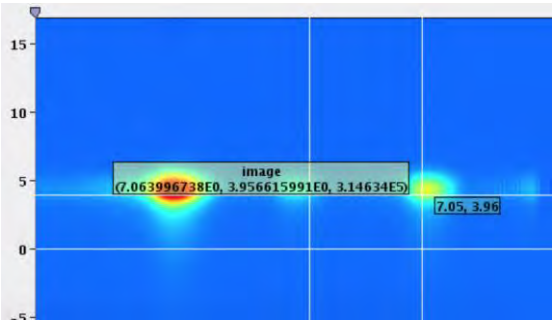
High specific activity
And purity

From CERN- MEDICIS to the lab/Hospital
1st results from MEDICIS operation in 2018





1st Production of 20MBq of non carrier added ^{169}Er (pure β^- emitter)



1000+ isotopes of 70+ chemical elements

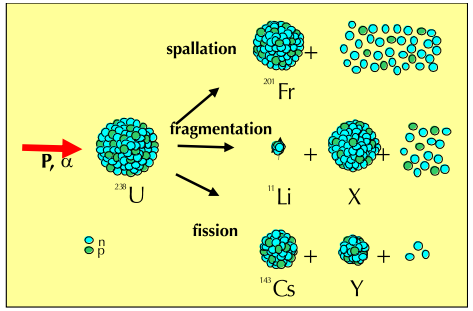
MELISSA (Laser Ion Source) started in 2019

MED011 : R. Formento Cavaier et al, “Very high specific activity Er-169 production at MEDICIS from external ILL target”, $^{168/169}Er_2O_3$ http://cds.cern.ch/record/2632033

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.

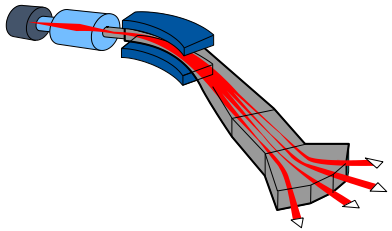
Accelerator



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

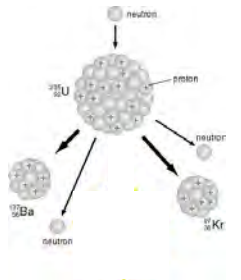
10^{10}pps 100μA (6.10^{14}) 1mbarn 1g/cm² for A_{target}=30g/mol

Isotope mass separation



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

Research reactor



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

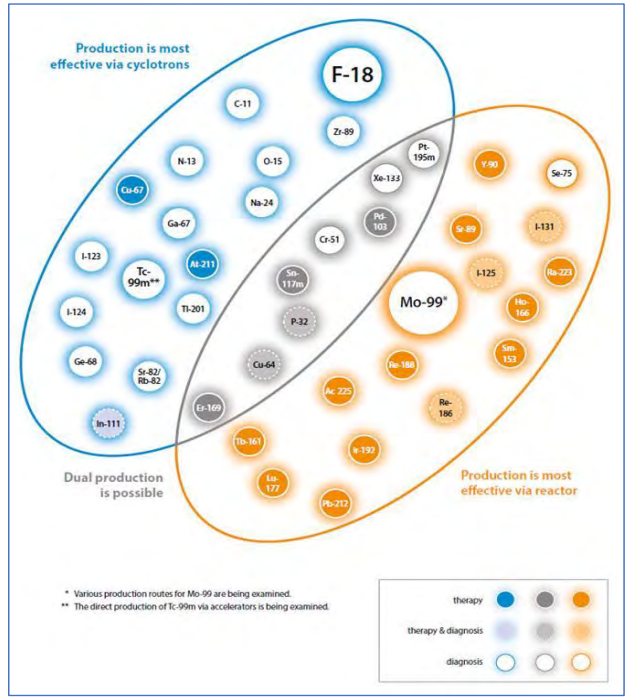
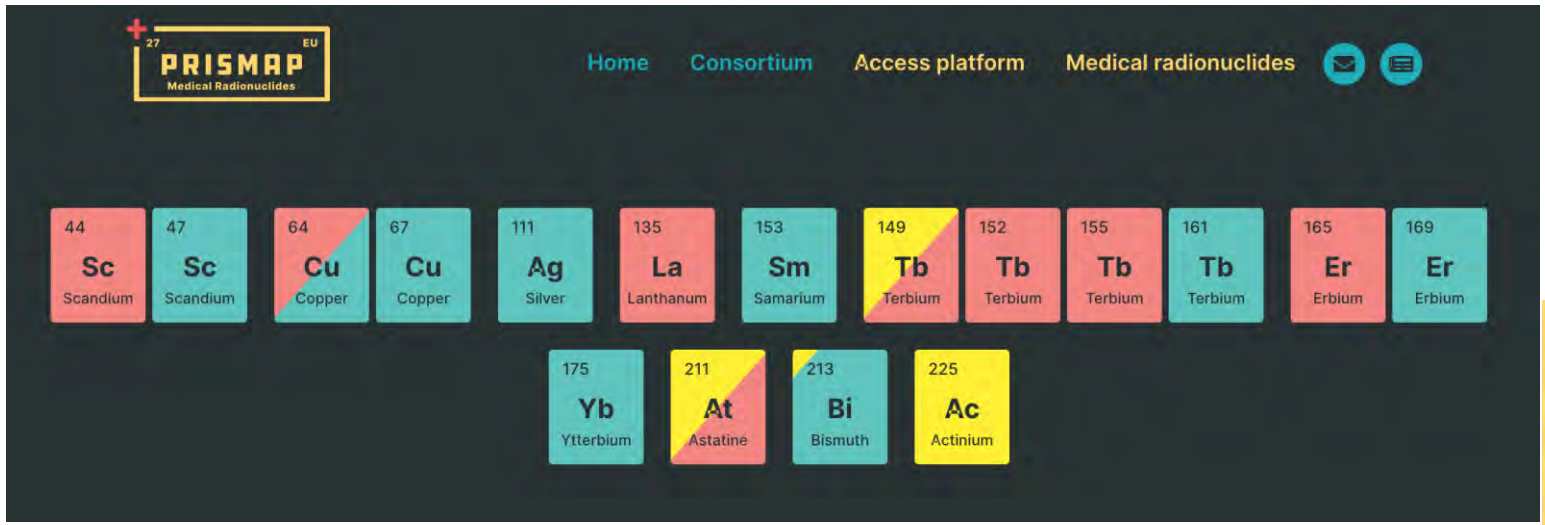


Figure 31 : Main medical radioisotopes production process

European Commission ENER/17/NUCL/SI2.755660 (2018)

Day-1 radionuclides from PRISMAP



specification sheet for Er-169

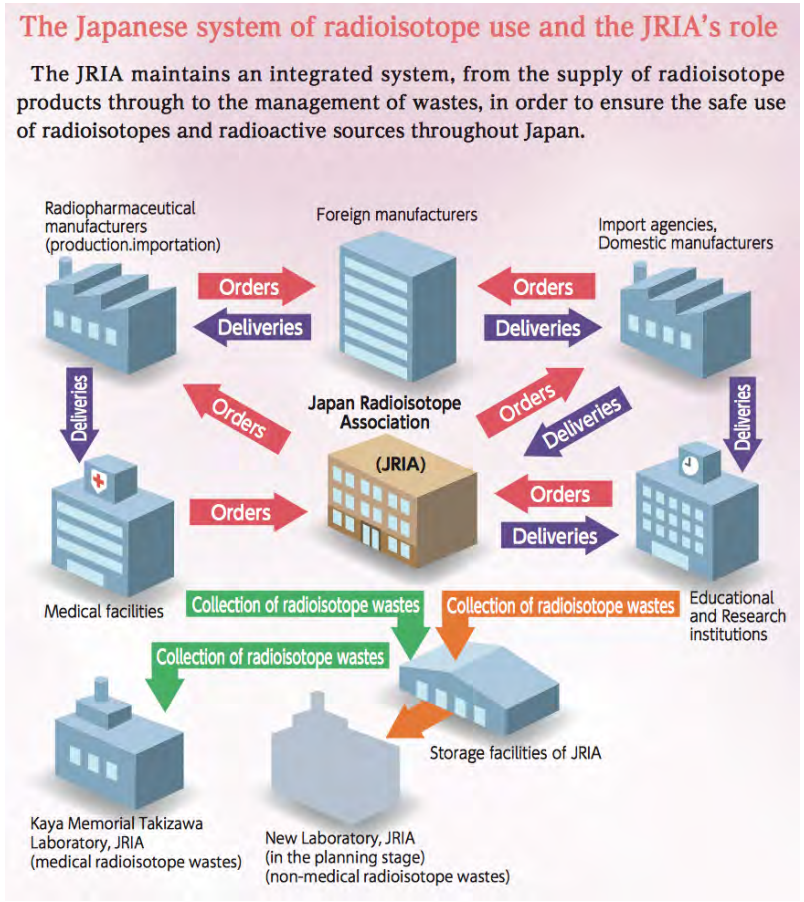
Parameter	Specifications
Half-life	9.39 d
Daughter	Stable Tm-169
Branching Ratio/Decay	100% β^-
Production	Er-168(n,γ) Er-169
Purification	Off-line mass separation + 2-step column separation
Chemical Form	In 0.05 M HCl
Specific Activity	n.a.
Radionuclidic Purity	>99%
Radiochemical Purity	n.a.
Chemical Purity	n.a.
Identification	Presence of 109.8 keV gamma line
Appearance	Clear solution
pH	1-2
Activity available	100 MBq
Availability	Few times per year (planning in advance), depends on reactor and MEDICIS schedule
Grade	preclinical, n.c.a.
Other information	Research grade implanted in Al, Zn or NaCl layer on Au foil also possible

Half-life determination of ^{155}Tb from mass-separated samples produced at CERN-MEDICIS

S. M. Collins et al, in preparation

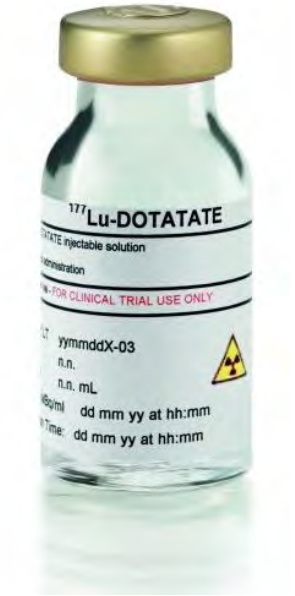
(Some more information at www.prismap.eu)

Other examples of isotope supply



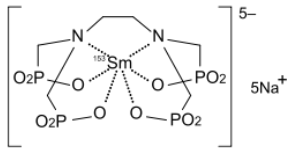
From low to high specific activity radiobioconjugates

$^{223}RaCl_2$



^{177}Lu-DOTATATE

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



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

M. van Voorde et al., European Journal Of Nuclear Medicine And Molecular Imaging; 2021; Vol. 48; pp. S410

^{153}Sm-DOTATATE or other ?

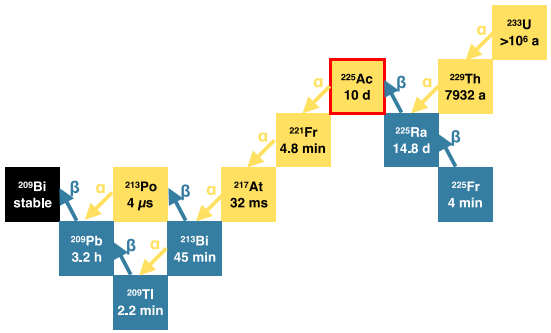
Expected scope of projects to be received in the consortium

- 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

Field of Application	Radiation	Chemical elements	Half lives
PET	β^+	Alkaline earth Halogen Lanthanide Transition metals …	Hours Days Months
SPECT	γ		
TAT	α		
Beta therapy	β^-		
Auger therapy	e^-		

- Studies on cells, animals « preclinical », *possibly pilot clinical phases*

Where are the needs ? Example of Targeted Alpha Therapy

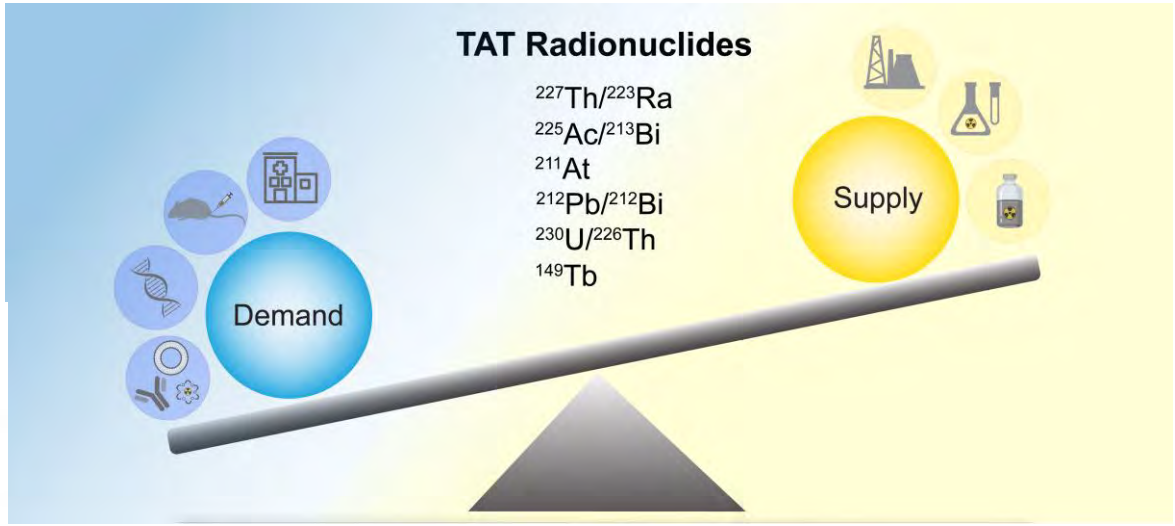


JNM
The Journal of Nuclear Medicine

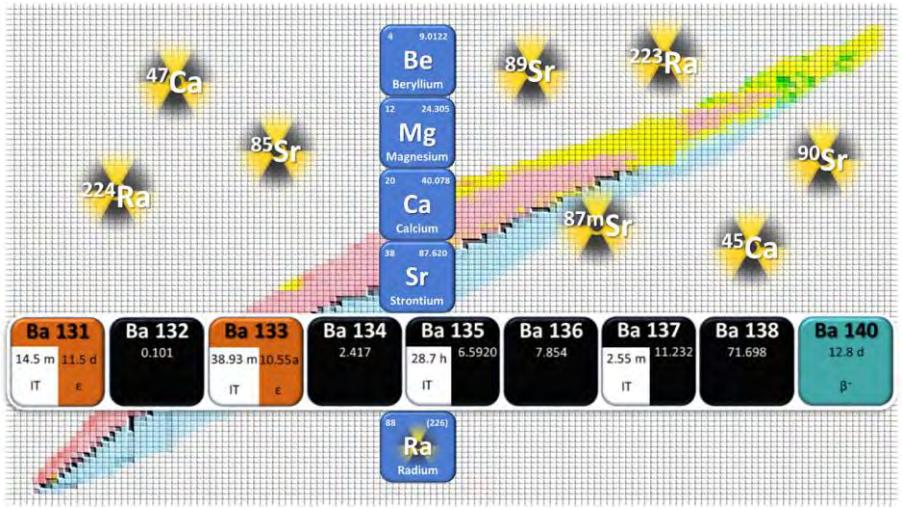
Production and supply of alpha particles emitting radionuclides for Targeted Alpha Therapy (TAT).

Valery Radchenko, Alfred Morgenstern, Amirreza Jalilian, Caterina Ramogida, Cathy S Cutler, Charlotte Duchemin, Cornelia Hoehr, Ferrid Haddad, Frank Bruchertseifer, Haavar Gausemel, Hua Yang, Joao Alberto Osso, Kohshin Washiyama, Kenneth Czerwinski, Kristen Leufgen, Marek Pruszynski, Olga Valzdorf, Patrick Causey, Paul Schaffer, Randy Perron, Maxim Samsonov, D. Scott Wilbur, Thierry Stora and Yawen Li

Journal of Nuclear Medicine July 2021, jnumed.120.261016; DOI: https://doi.org/10.2967/jnumed.120.261016



Earth alkali in nuclear medicine



MED-028 :

Study of the 128Ba/128Cs in vivo generator in a preclinical model of osteosarcoma

D. Viertl et al, CHUV

https://medicis.cern/approved-projects

https://www.frontiersin.org/research-topics/16233/
(advances in radioactive ion beams for nuclear medicine)

https://www.prismap.eu/radionuclides/user-forum/
https://www.prismap.eu/news/events-feed/2022-public-event/

15th June

Thank You !!!

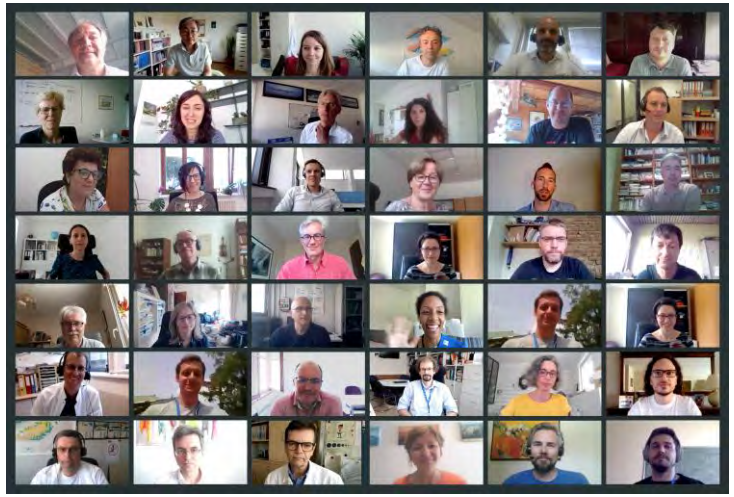
Question ?!*

- Do you need some new isotopes ?

•1667 The first human blood transfusion is administered
•Jean-Baptiste Denys, physician to King Louis XIV of France, transfused sheep blood into a 15-year-old boy. He survived!
•1844 Charles Goodyear patents vulcanization
•1954 The Union of European Football Associations is founded
•1977 Spain holds the first free elections since 1936
•1991 Mount Pinatubo explodes
•most violent eruption of the 20th century

•2022 : PRISMAP Public Event (hybrid)
1st projects received
in the European Medical Radionuclide programme

https://www.prismap.eu/news/events-feed/2022-public-event/



https://www.prismap.eu/radionuclides/user-forum/