

Life, the Universe and Everything

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12 November 2019



Institut Max von Laue – Paul Langevin



Max von Laue
(1879-1960)
Nobel Prize 1914
Diffraction of X-rays

Paul Langevin
(1872-1946)
Langevin dynamics
Magnetism, etc.

An international user facility: \approx 13 member states

ILL Associate countries

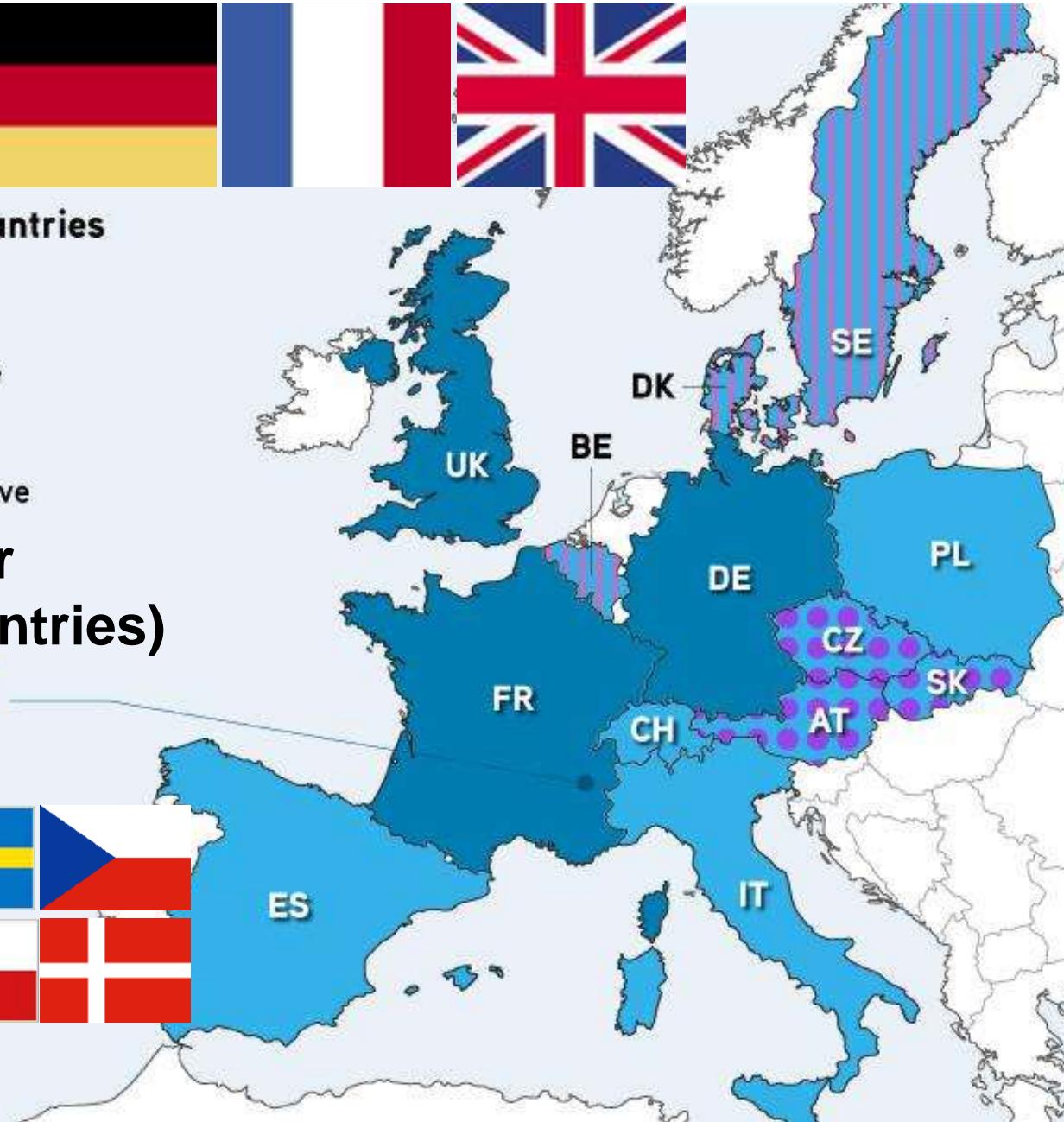


ILL Scientific Member countries

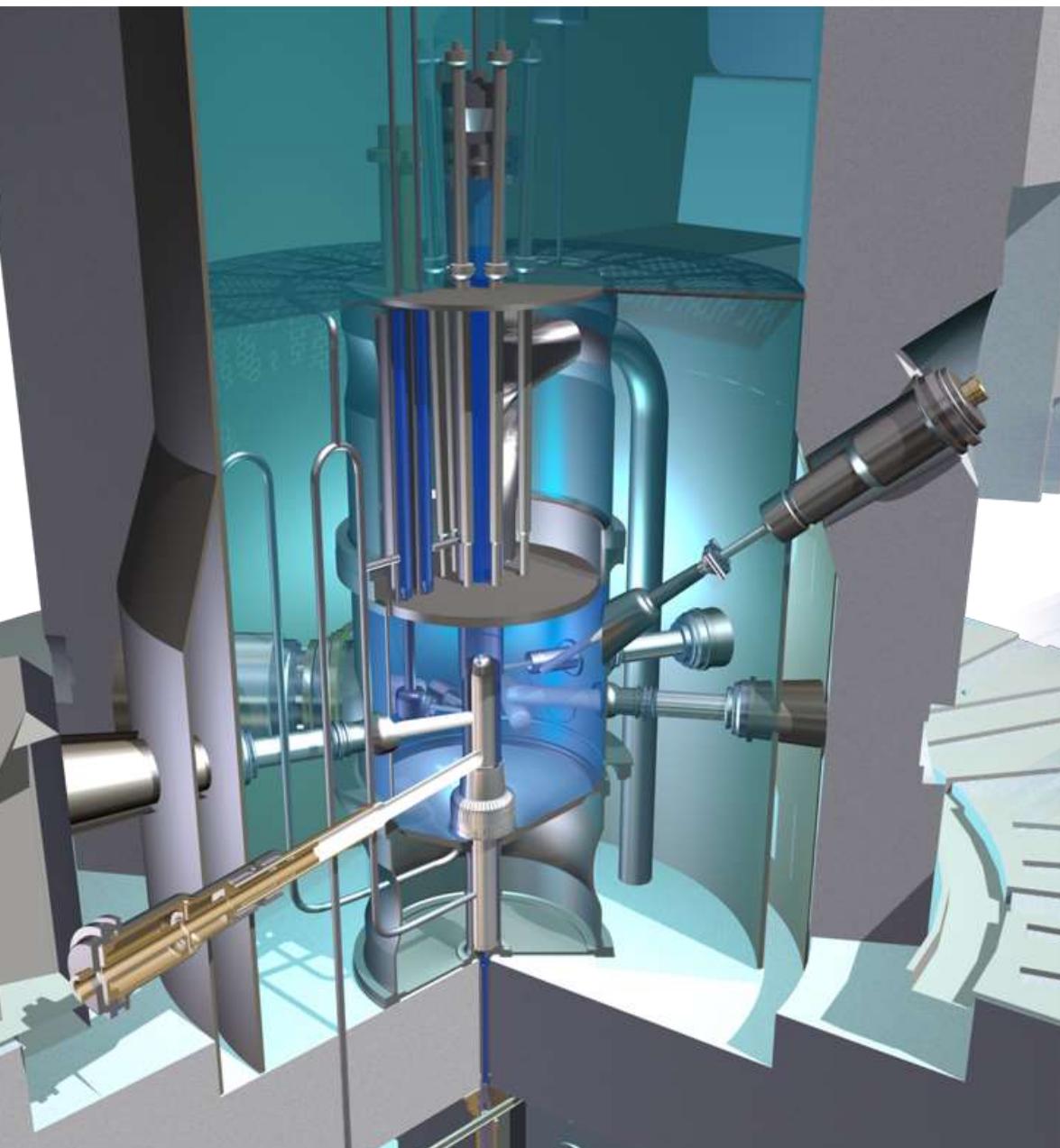
TRANSNI :
TRANSnational Neutron Initiative

CENI :
Central European Neutron Initiative

\approx 1600 users per year
(from \approx 42 countries)

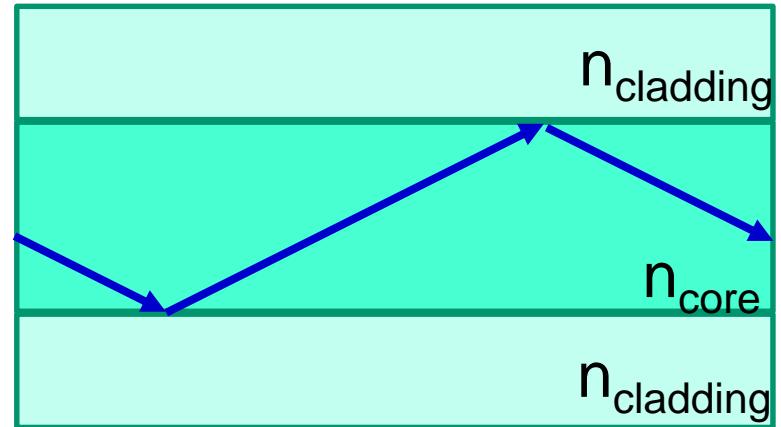
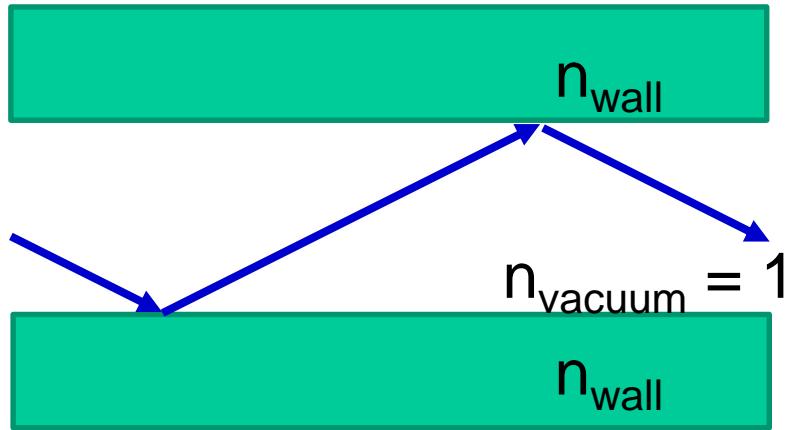


The ILL Reactor



**$5 \cdot 10^{18}$ neutrons/s
generated at 57 MW**

Neutron guides vs. light guides



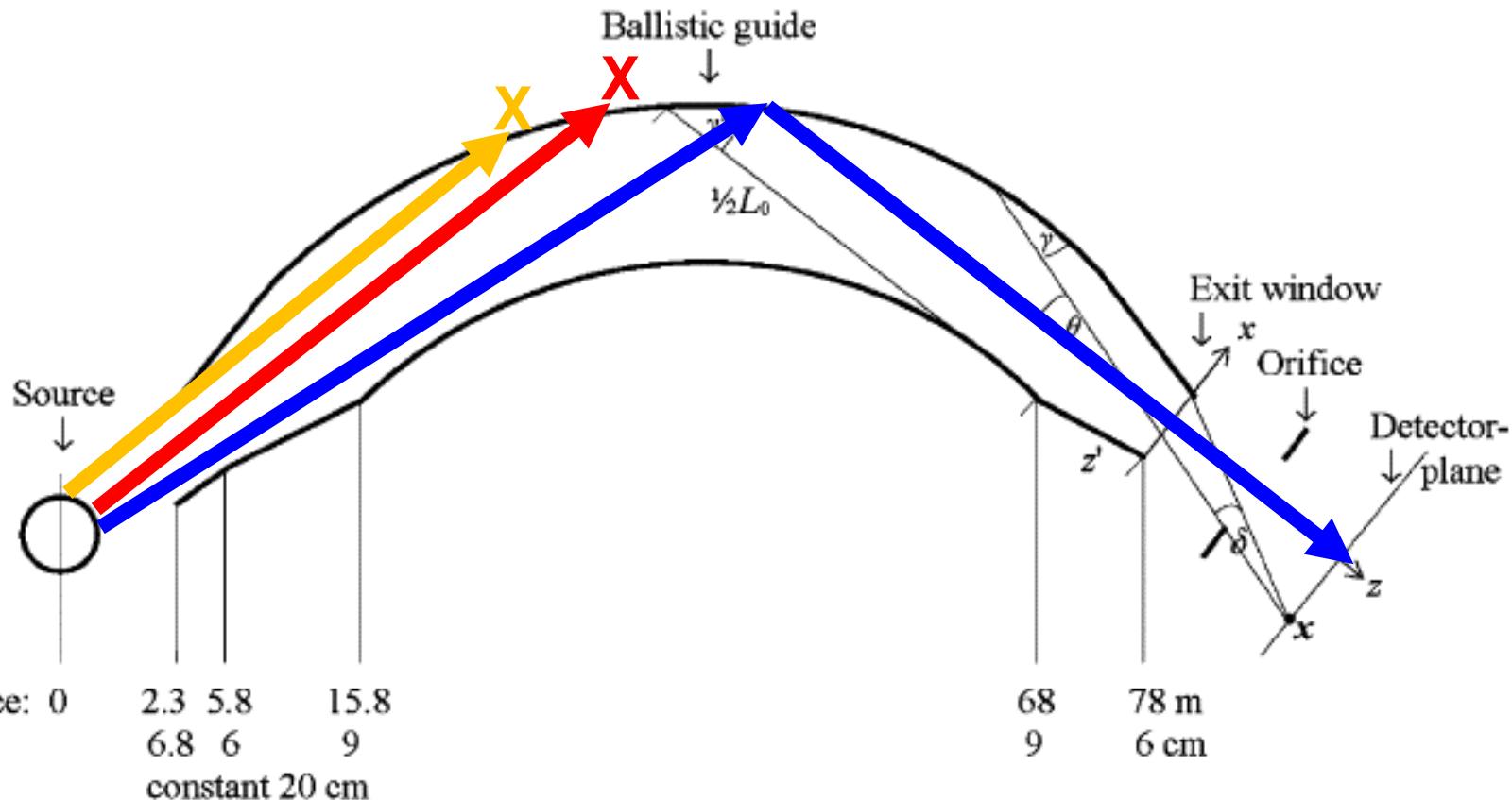
Neutron guide:

$$n_{\text{wall}} < n_{\text{vacuum}} = 1$$

Light guide:

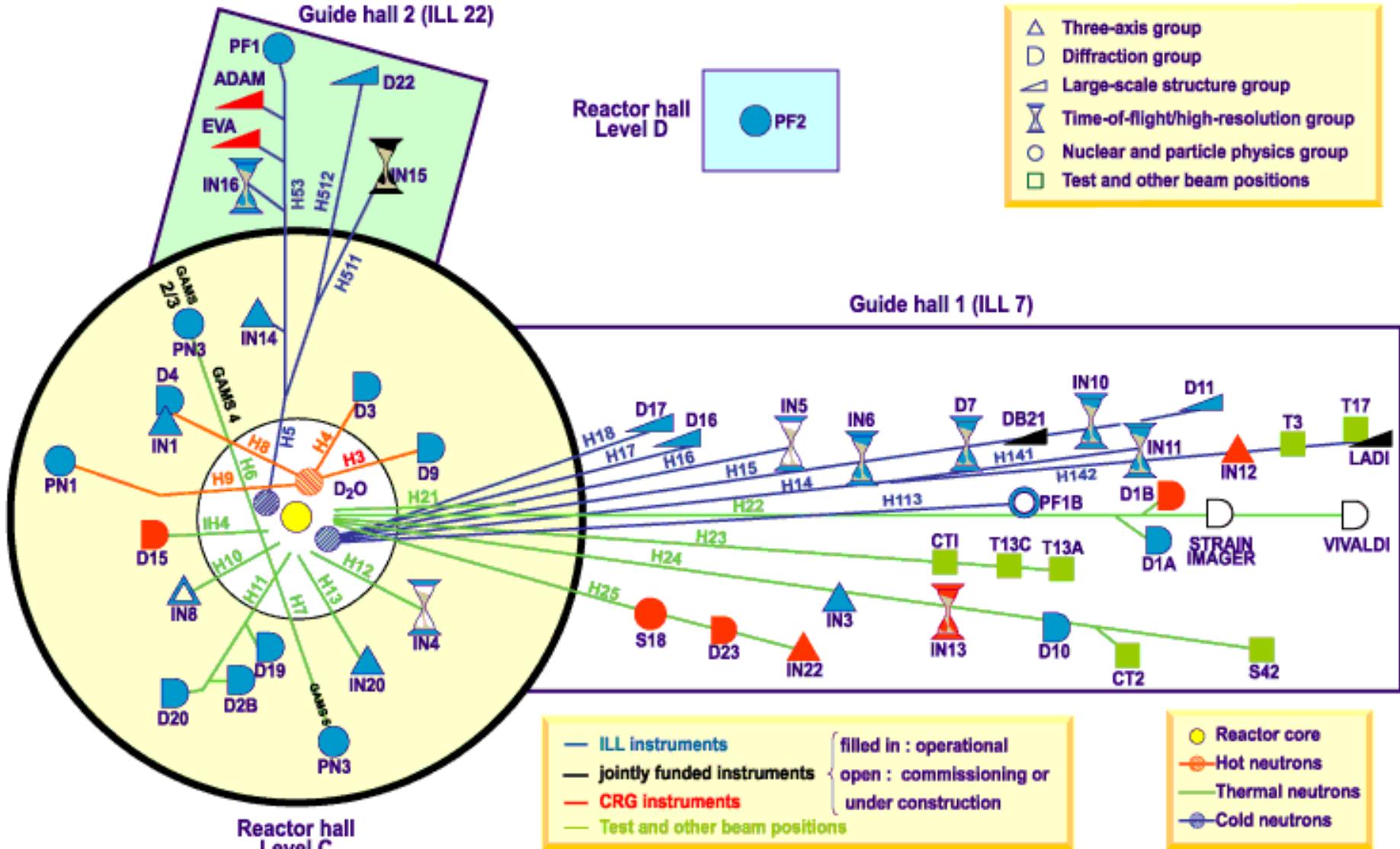
$$n_{\text{core}} > n_{\text{cladding}} > 1$$

Guided neutron beams are “clean”



Fast neutrons and gamma rays are not transported.

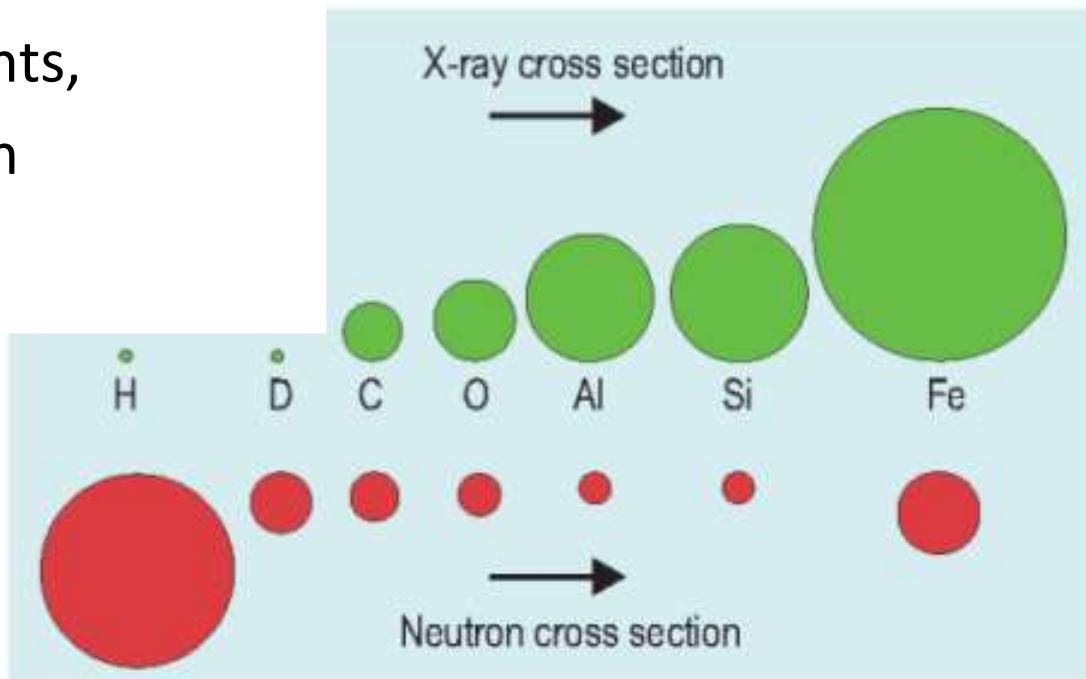
ILL instruments

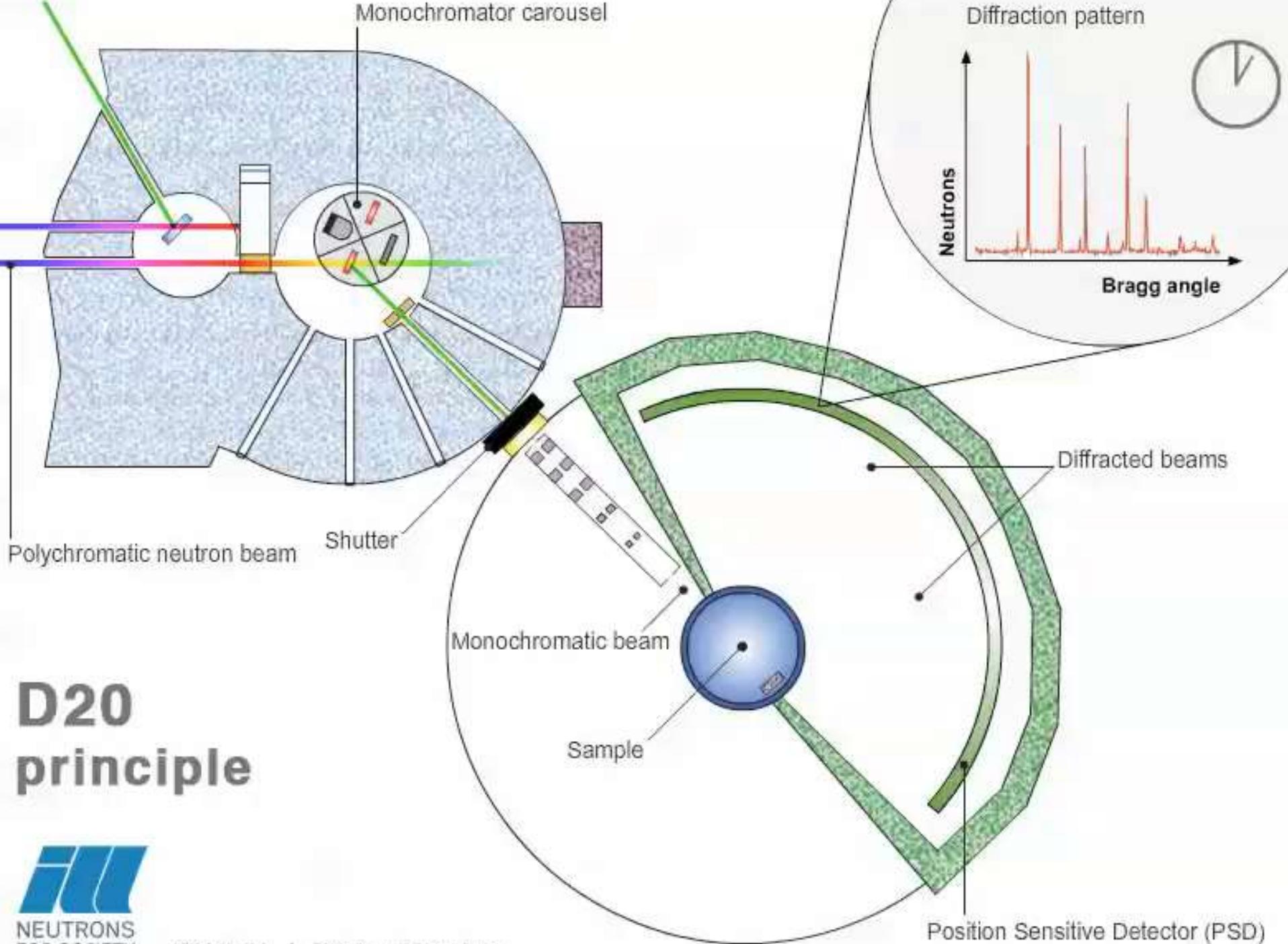


>40 instruments running simultaneously for 150-200 days per year
 Neutron beams with up to $2 \cdot 10^{10} \text{ n.cm}^{-2}\text{s}^{-1}$ flux and up to 320 cm² area

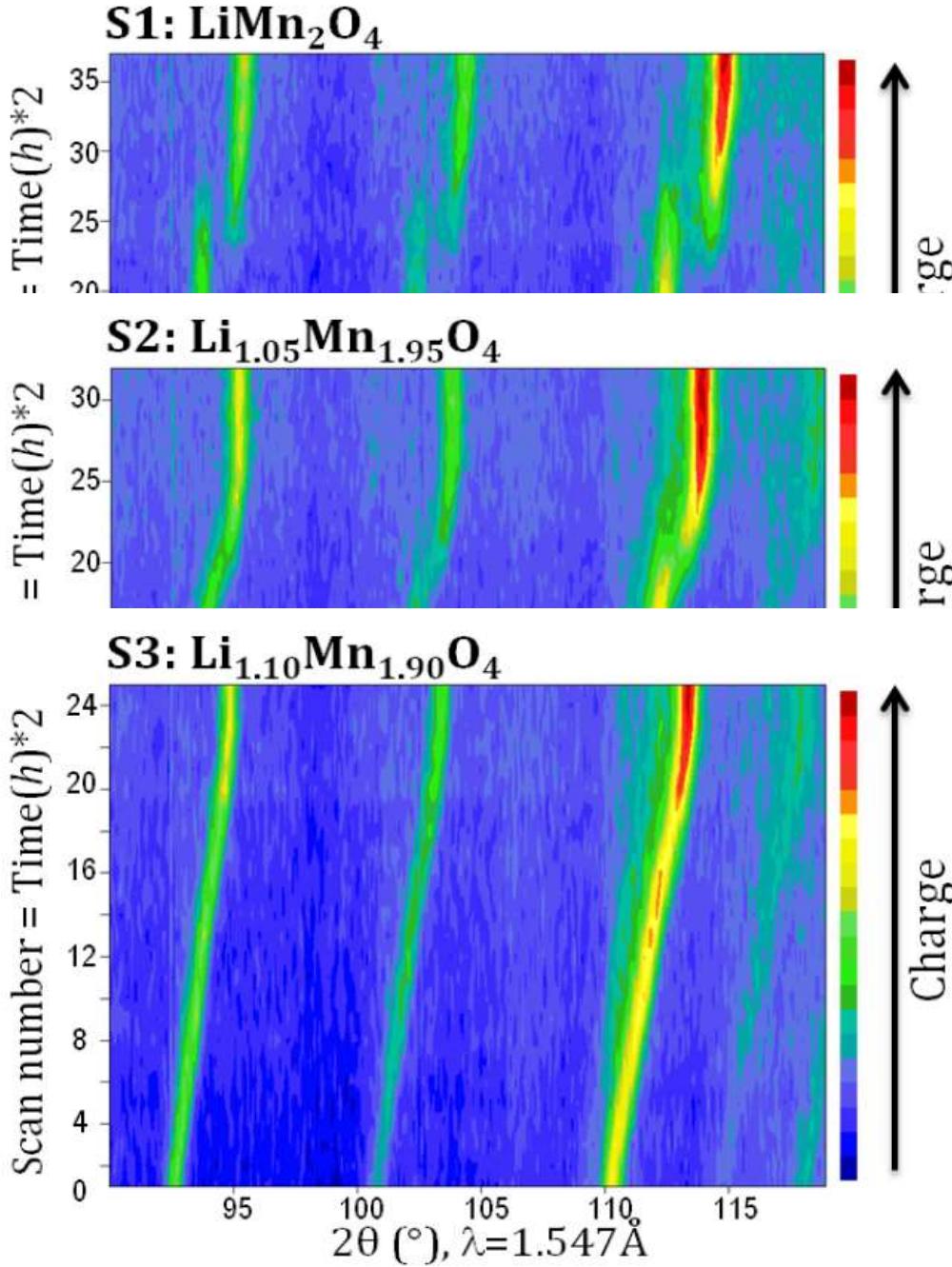
Why neutrons ?

- wavelength of thermal neutrons \approx interatomic distances (sol., liq.)
 \Rightarrow good for scattering
- neutron mass \approx atom mass
 \Rightarrow large momentum transfer possible
- weakly interacting \Rightarrow good penetration (thicker samples...)
- good to “see” light elements,
in particular hydrogen
- magnetic moment
 \Rightarrow magnetic scattering





In operando study of lithium batteries

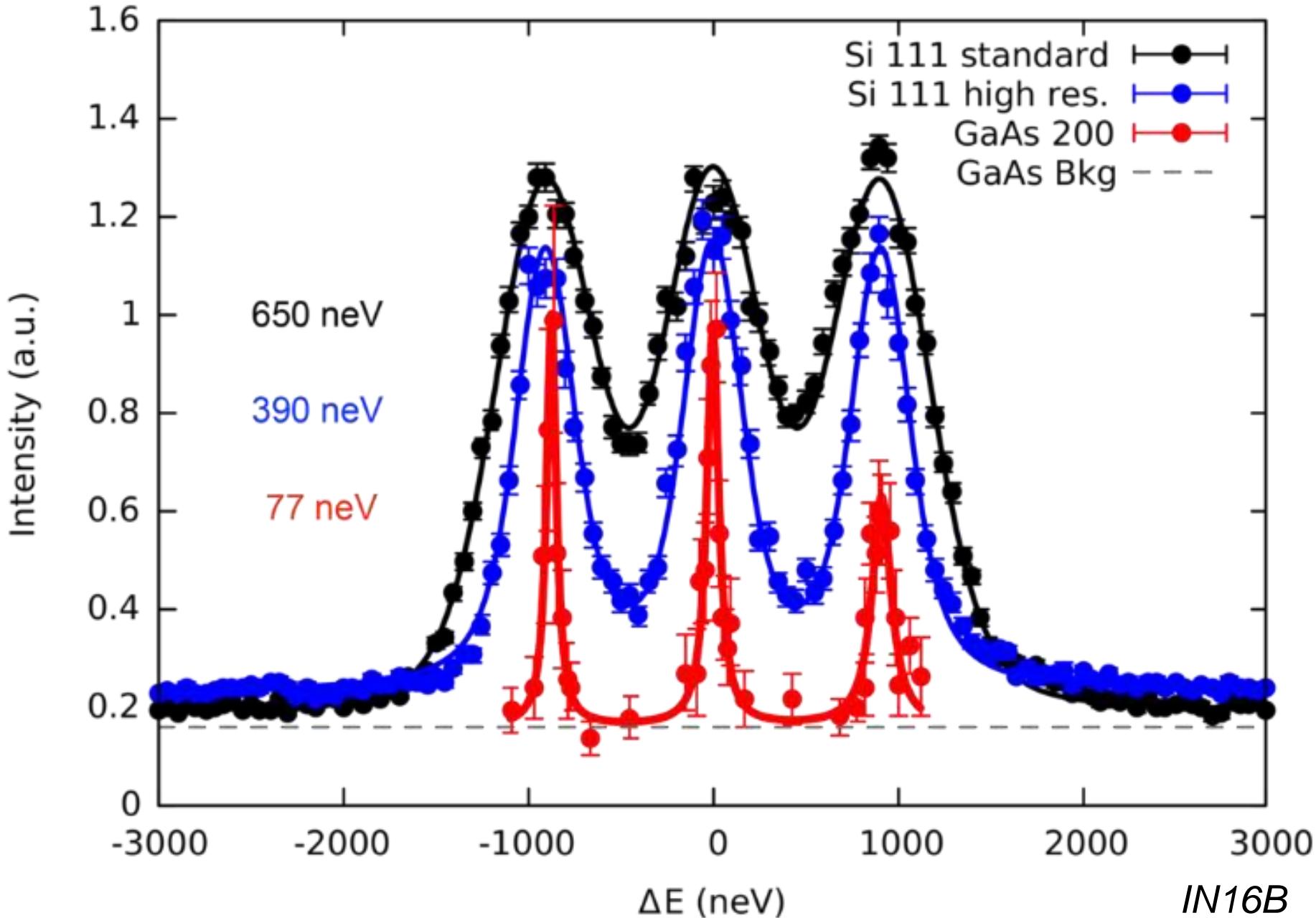


Also:

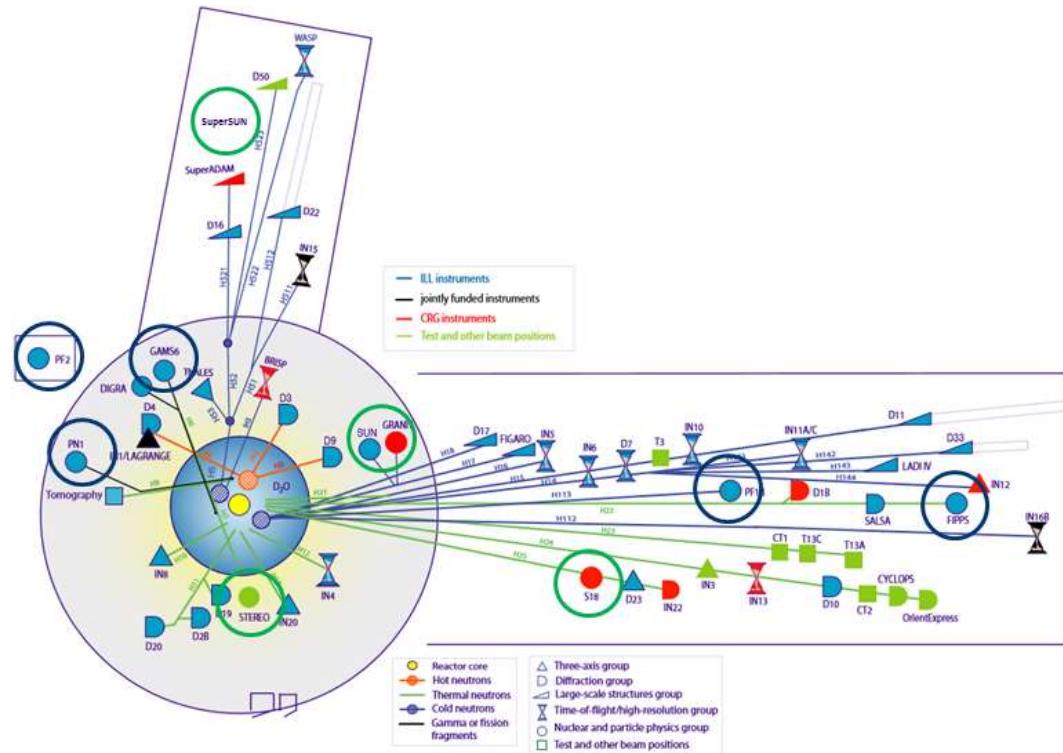
- hydrogen (biological samples !)
- magnetism
- reflectometry
- SANS
- inelastic neutron scattering

M. Bianchini et al.
JPC C 2014;118:25947.

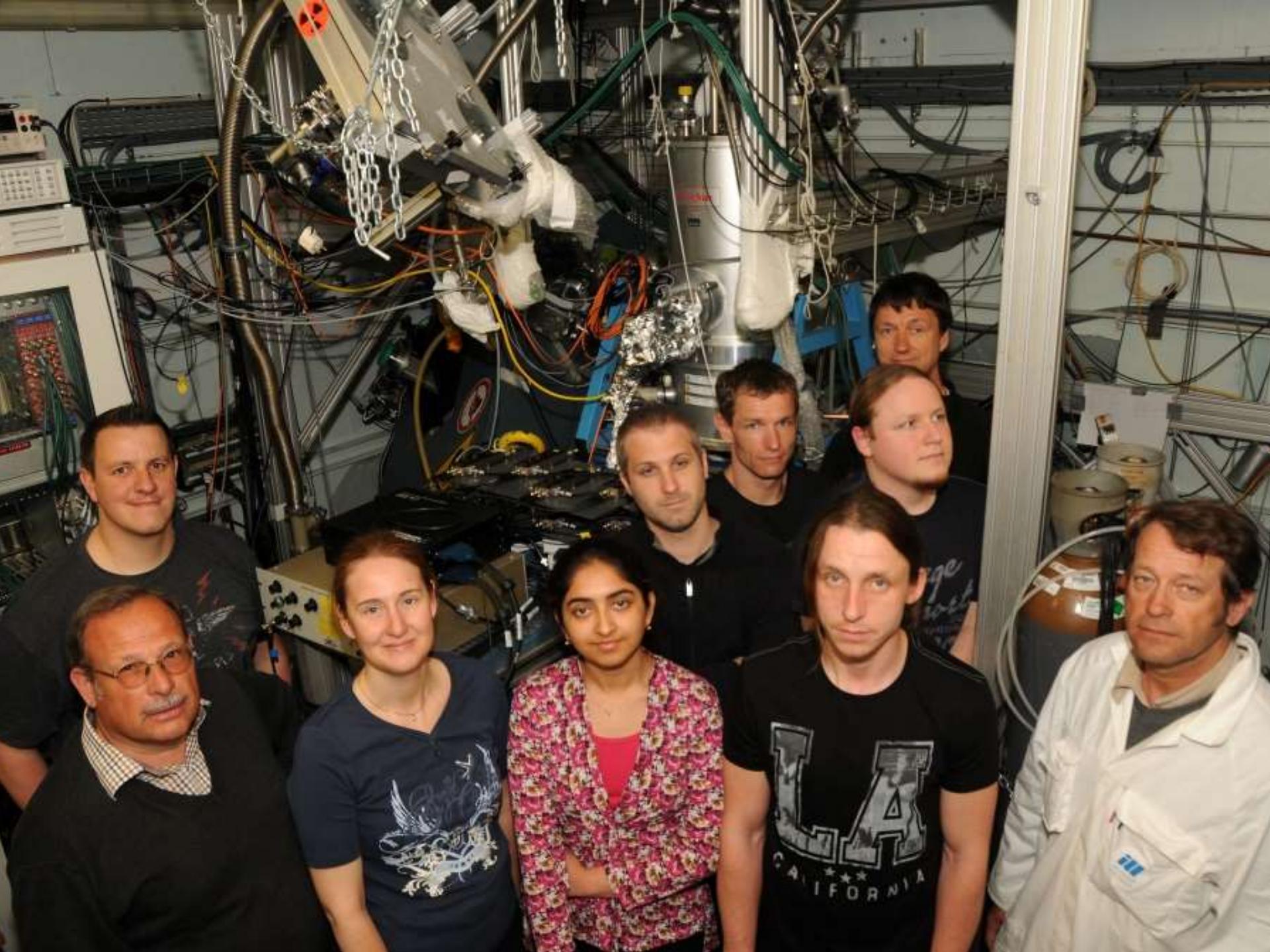
High resolution inelastic neutron spectroscopy



The LOHENGRIN fission fragment recoil separator



P. Armbruster et al.,
Nucl Instr Meth 1976;39:213.



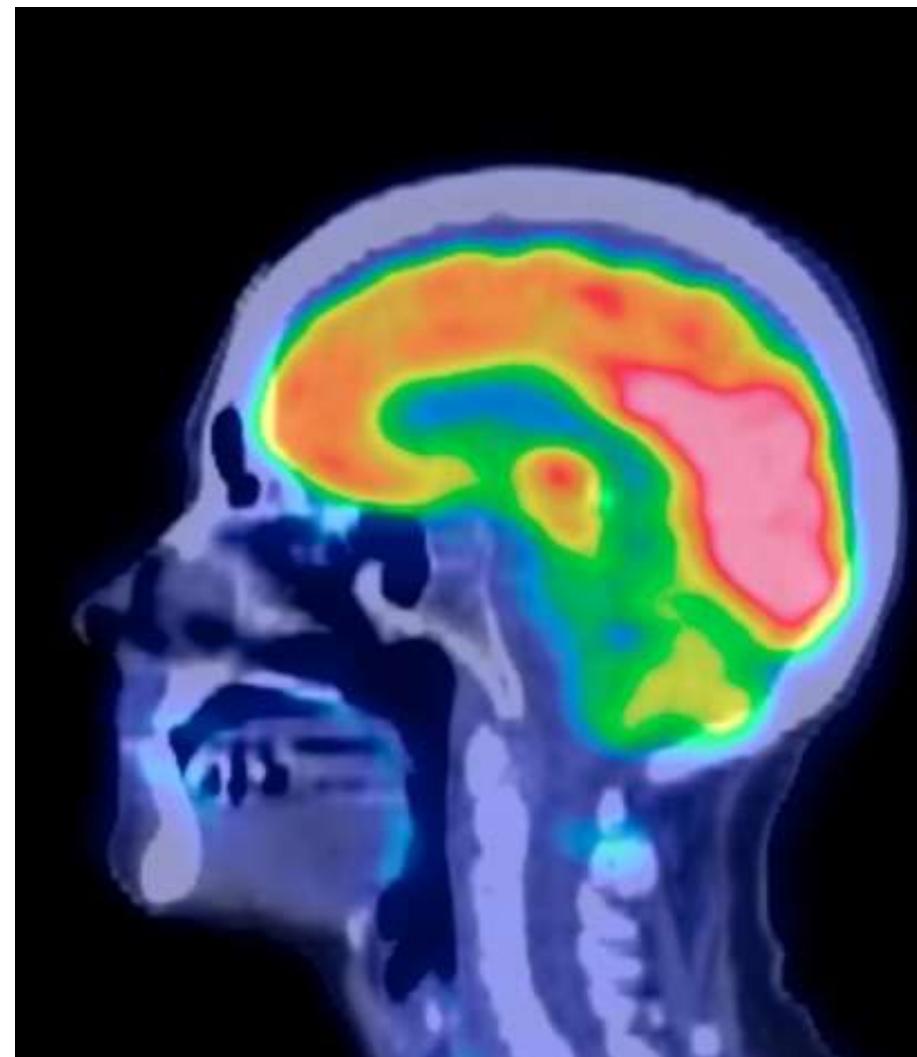
Life, the Universe and Everything

The background image depicts a dark, intricate mechanical or industrial setting. It features several glowing blue rectangular panels arranged in a grid pattern, possibly representing windows or control panels. These panels are set against a dark, metallic background with various pipes, gears, and structural elements visible. A single bright blue light source, resembling a star or a distant planet, is positioned in the center of the frame, casting a glow through the translucent panels.

Structural imaging versus functional imaging molecular imaging

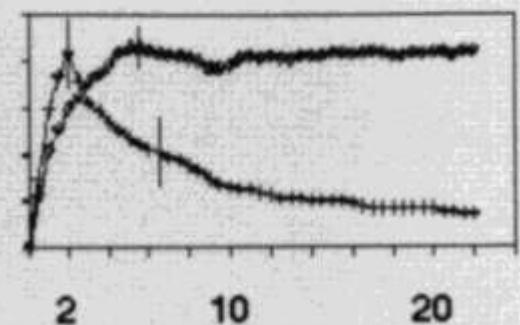
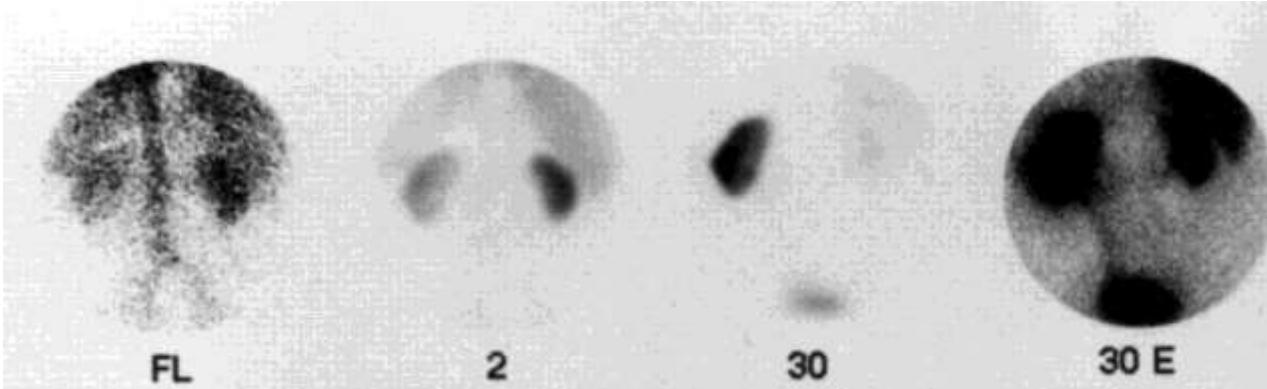
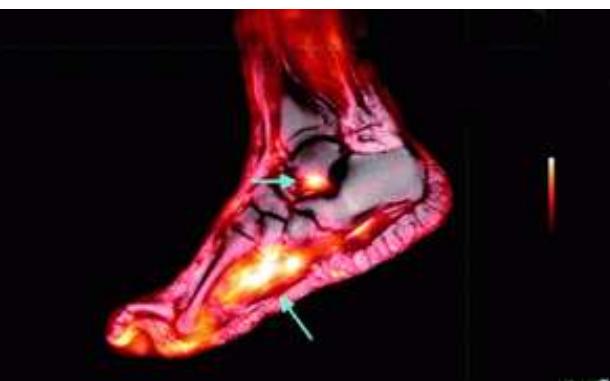
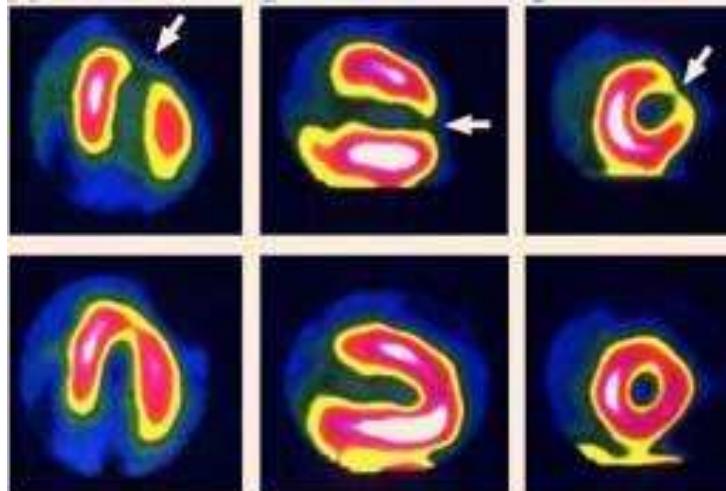
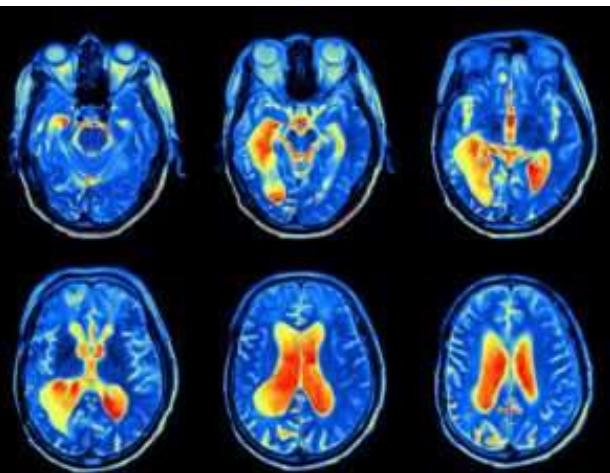


Radiology



Nuclear Medicine

Molecular imaging



What is Theranostics ?

Therapy based on **diagn**ostics
personalized medicine, stratified medicine



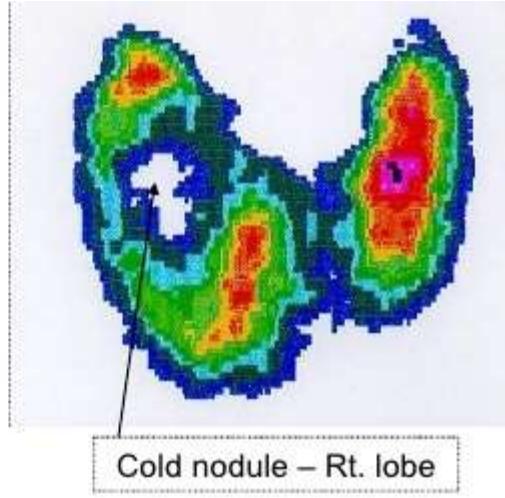
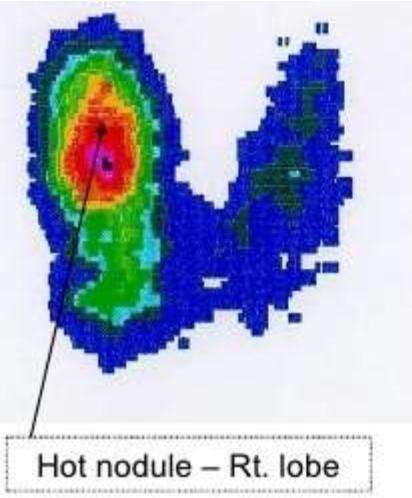
Saul Hertz (Massachusetts General Hospital):

1936 proposes iodine radiotracer

1937 rabbit studies with ^{128}I

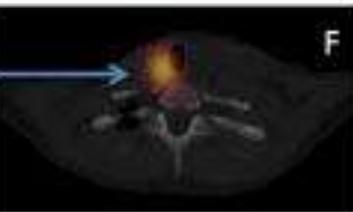
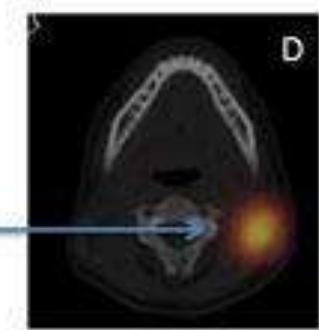
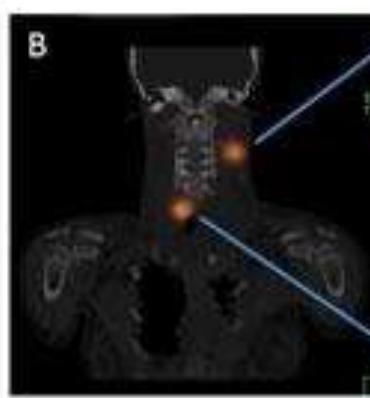
1941 clinical therapy studies with ^{130}I

Thyroid scintigraphy and therapy



I 123
13.2 h
 ε
no β^+
 γ 159

I 131
8.0 d
 β^- 1.0, 1.8,...
 γ 364, 637...



123I-, 131I- or 99mTcO₄- for scintigraphy
131I- for therapy

(Papillary) thyroid cancer has the **highest survival** of all malignant cancers!

How can one treat such patients?

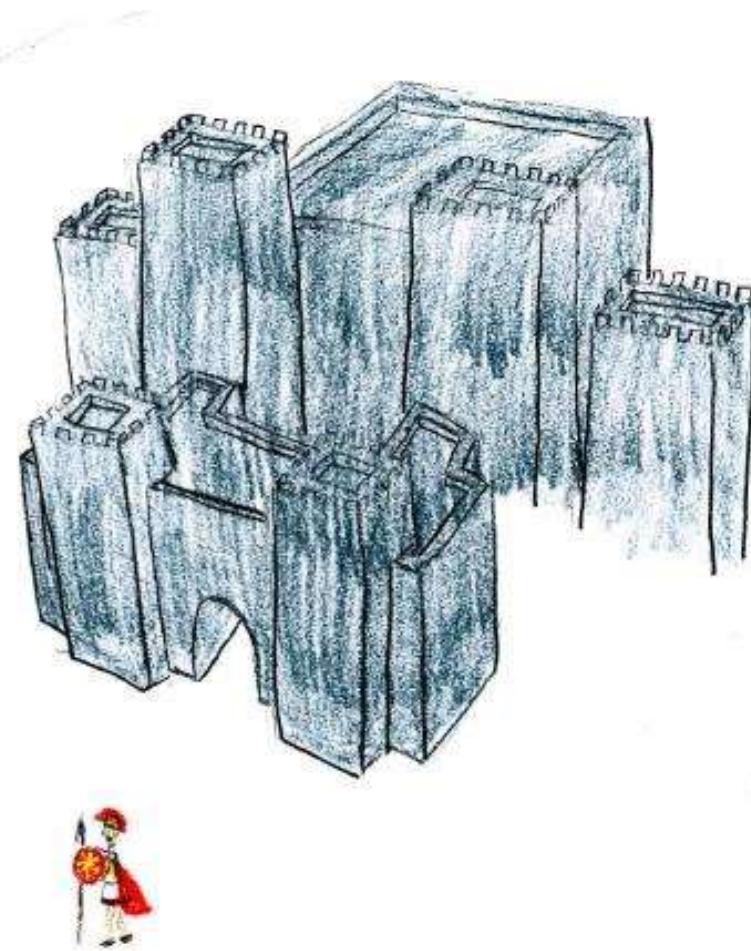
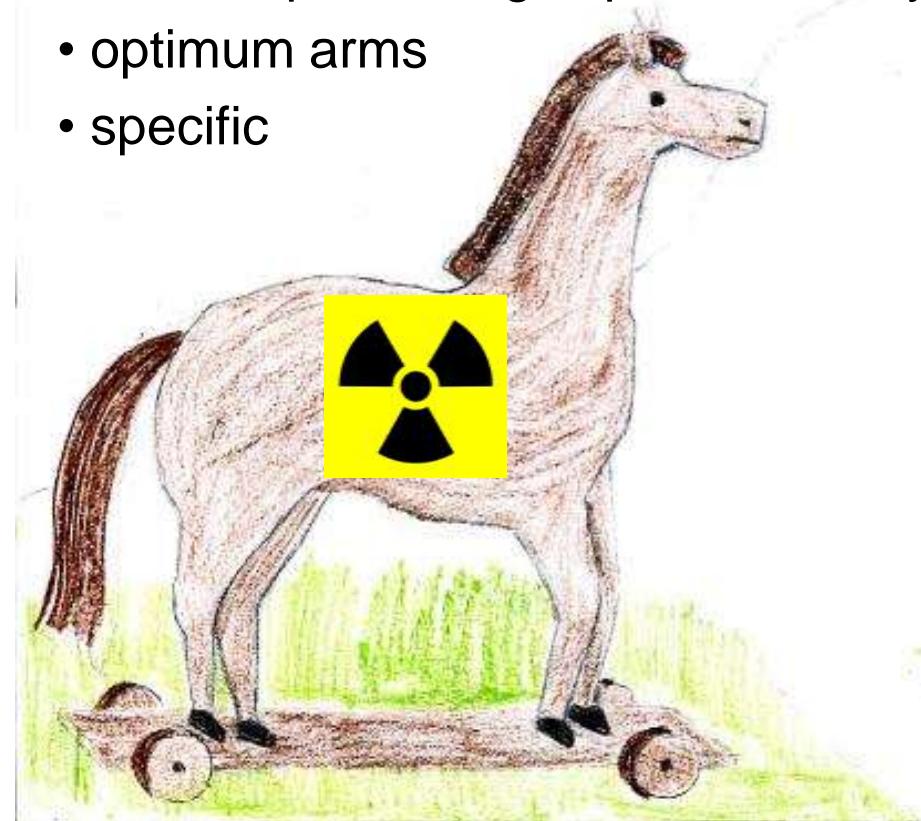


Learning from history

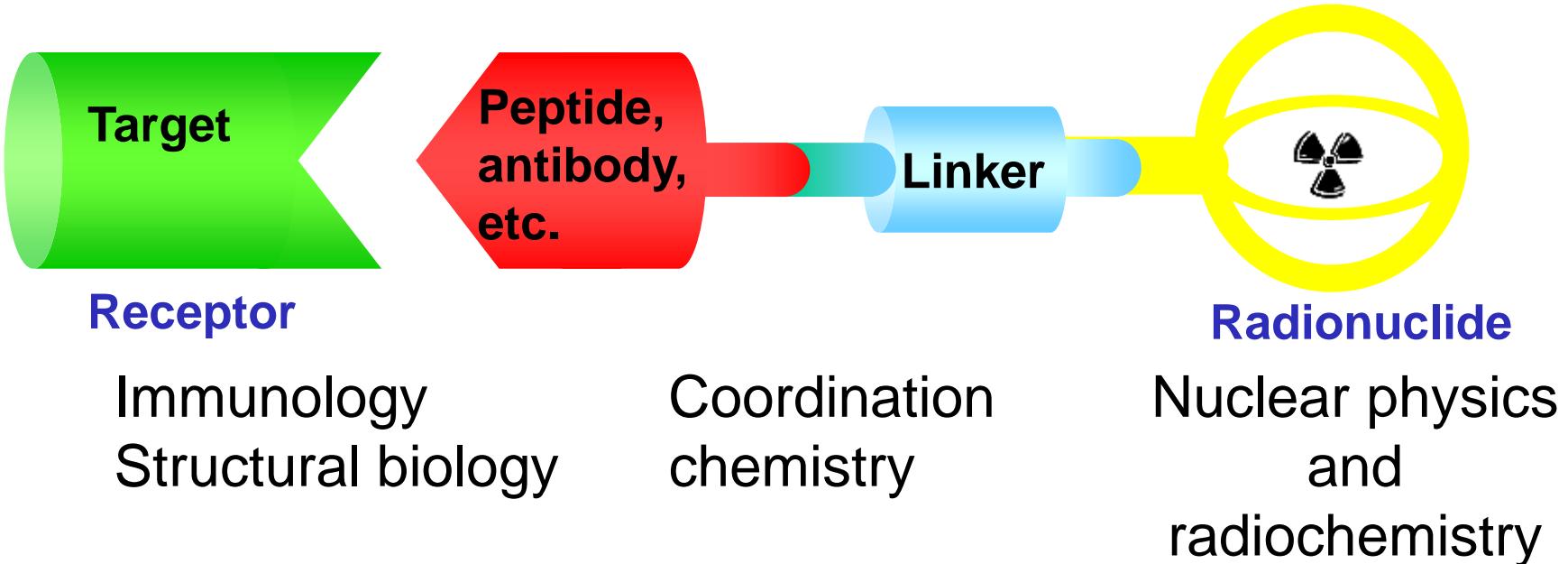


The principle of targeted therapies

- “attractive” vector > high uptake by the target
- transportable
- good in-vivo stability
- warriors “not visible”
- delayed uptake > suitable half-life
- limited space > high specific activity
- optimum arms
- specific

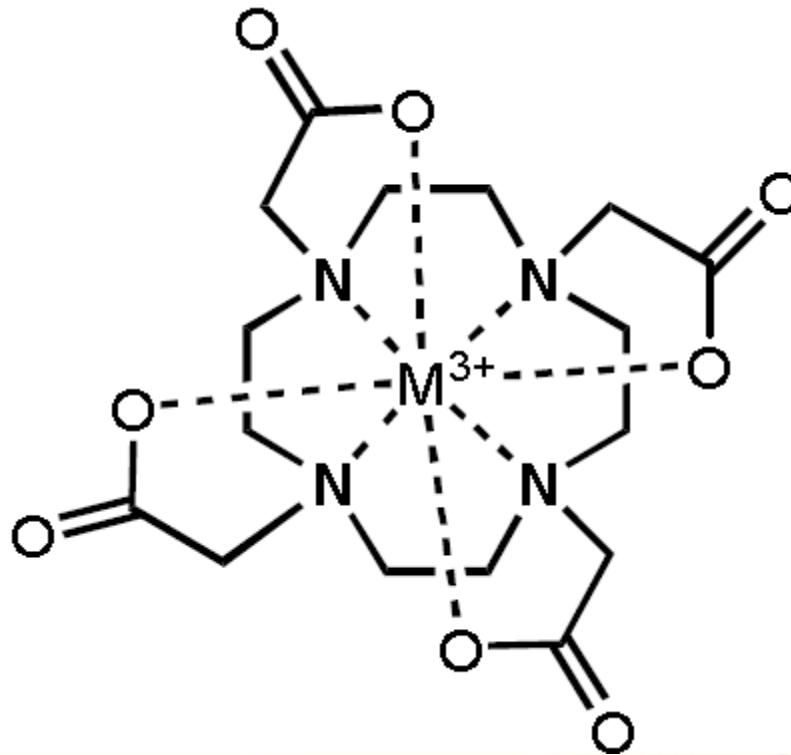


Multidisciplinary collaboration to fight cancer

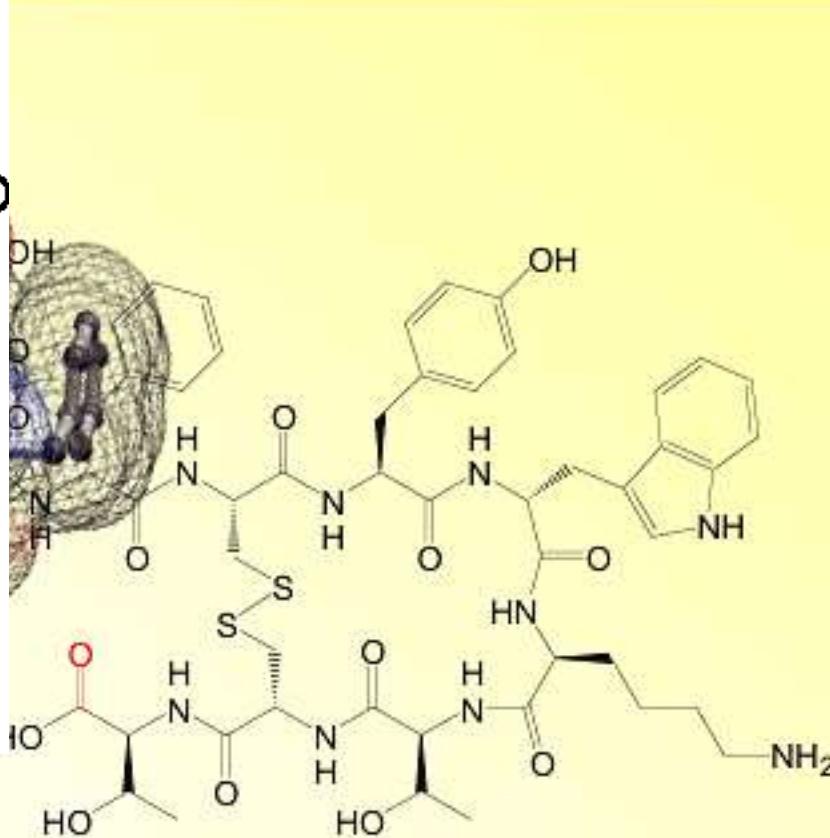


Nuclear medicine and medical physics

Structural Formula of DOTA-TOC/TATE



DOTA-TATE



1,4,7,10-tetraazacyclododecane tetraacetate

^{111}In

^{90}Y

^{67}Ga

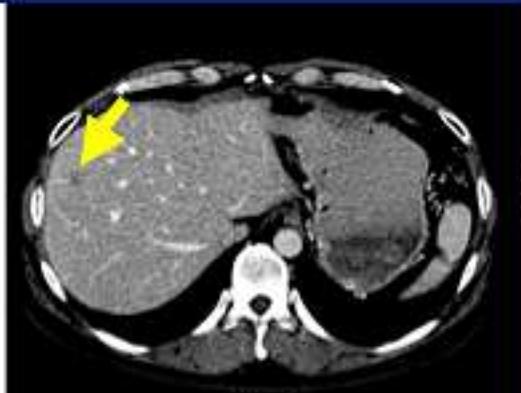
^{177}Lu

^{68}Ga

^{213}Bi

$\text{IC}_{50} (\text{Y}^{\text{III}}) = 1.6 \pm 0.4 \text{ nM}$

Helmut Maecke, EANM-2007.



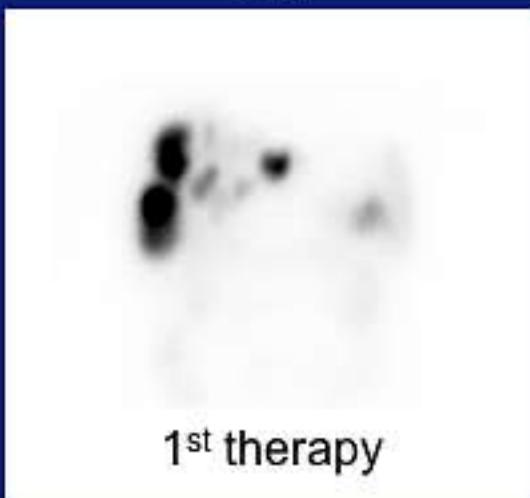
Male

36 years of age

Small cell pancreatic
neuroendocrine
tumour

Liver metastases

Ki-67 index 10-15%
(liver biopsy)



1st therapy



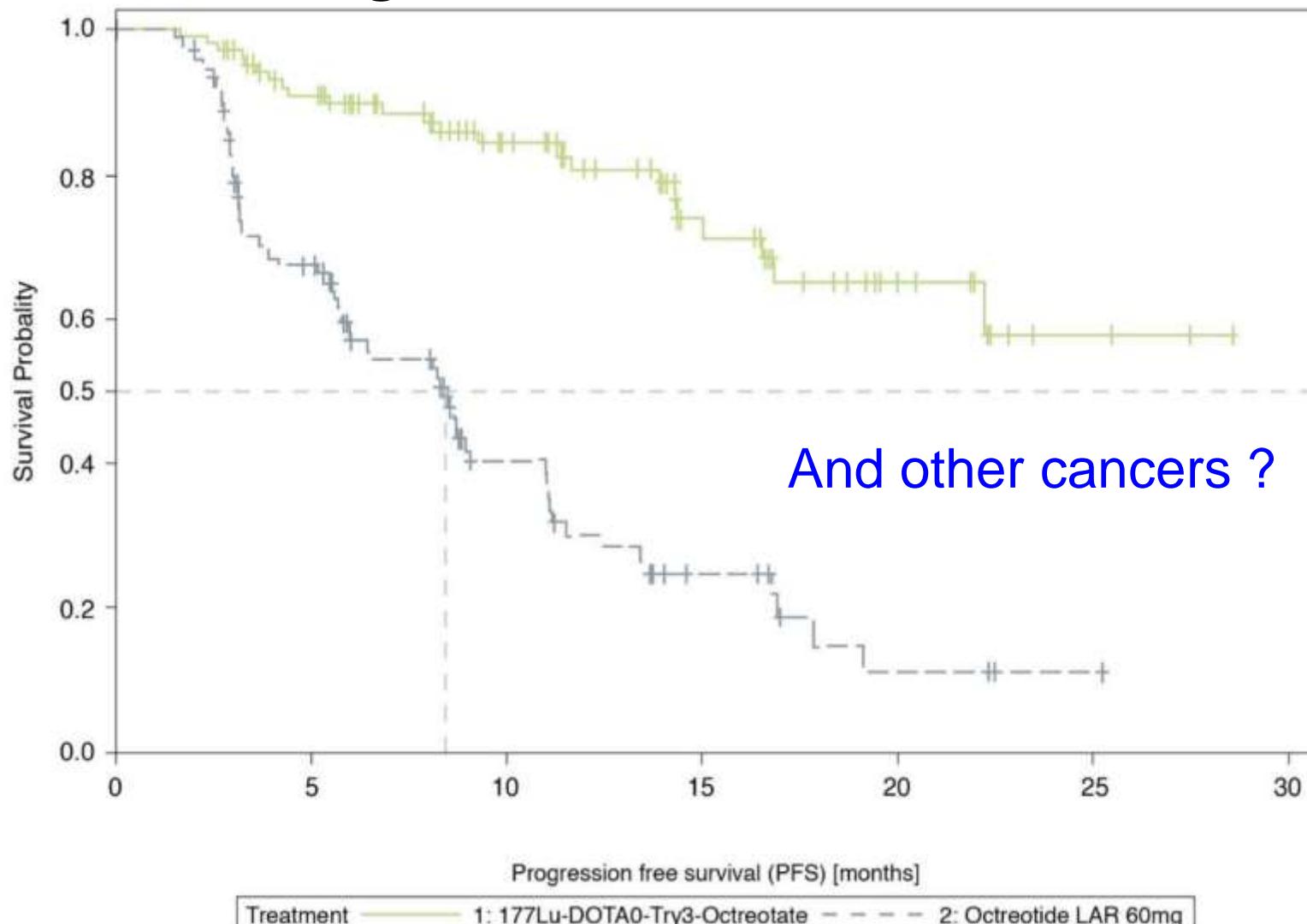
4th therapy

4 cycles with ^{177}Lu -
octreotate and
capecitabine

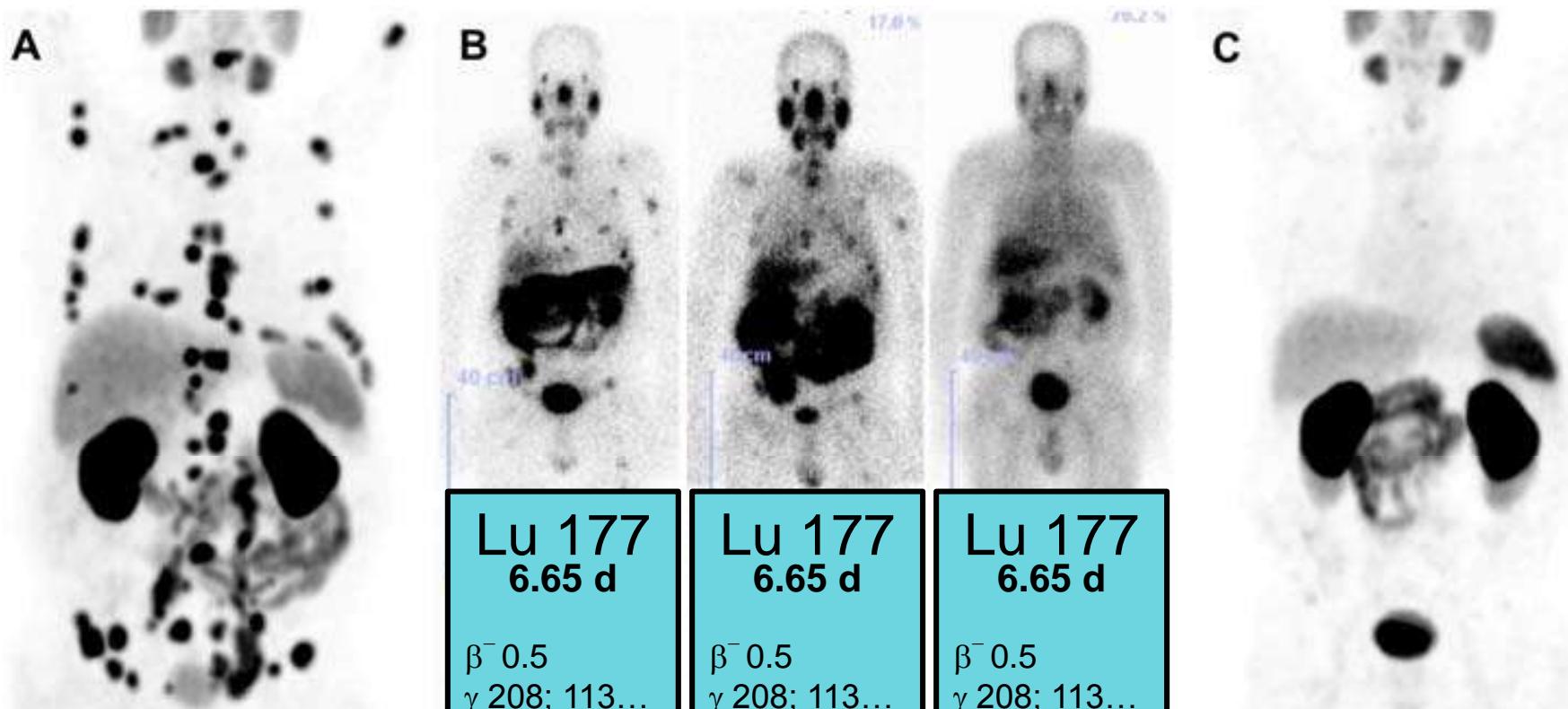
Partial remission

Roelf Valkema, EANM-2008.

^{177}Lu -Peptide Receptor Radionuclide Therapy of midgut neuroendocrine tumors



^{177}Lu -radioligand therapy of advanced prostate cancer



C. Kratochwil et al., *Eur J Nucl Med Mol Imaging* 2015;42:987.

R.P. Baum et al., *J Nucl Med* 2016;57:1006.

C. Kratochwil et al., *J Nucl Med* 2016;57:1170.

K. Rahbar et al., *J Nucl Med* 2017;58:85.

M.S. Hofman et al., *Lancet Oncol* 2018;19:825.

M.M. Heck et al., *Eur Urol* 2019;75:920.

T.W. Barber et al., *J Nucl Med* 2019; 60:955.

The “gold standard” for radionuclide therapy

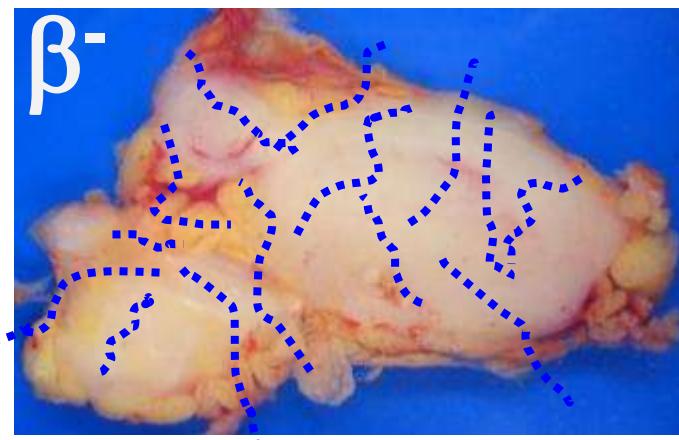


Institut Laue-Langevin 2018:
≈ 1600 scientific users came to ILL
≈ 4000 patients got ^{177}Lu from ILL



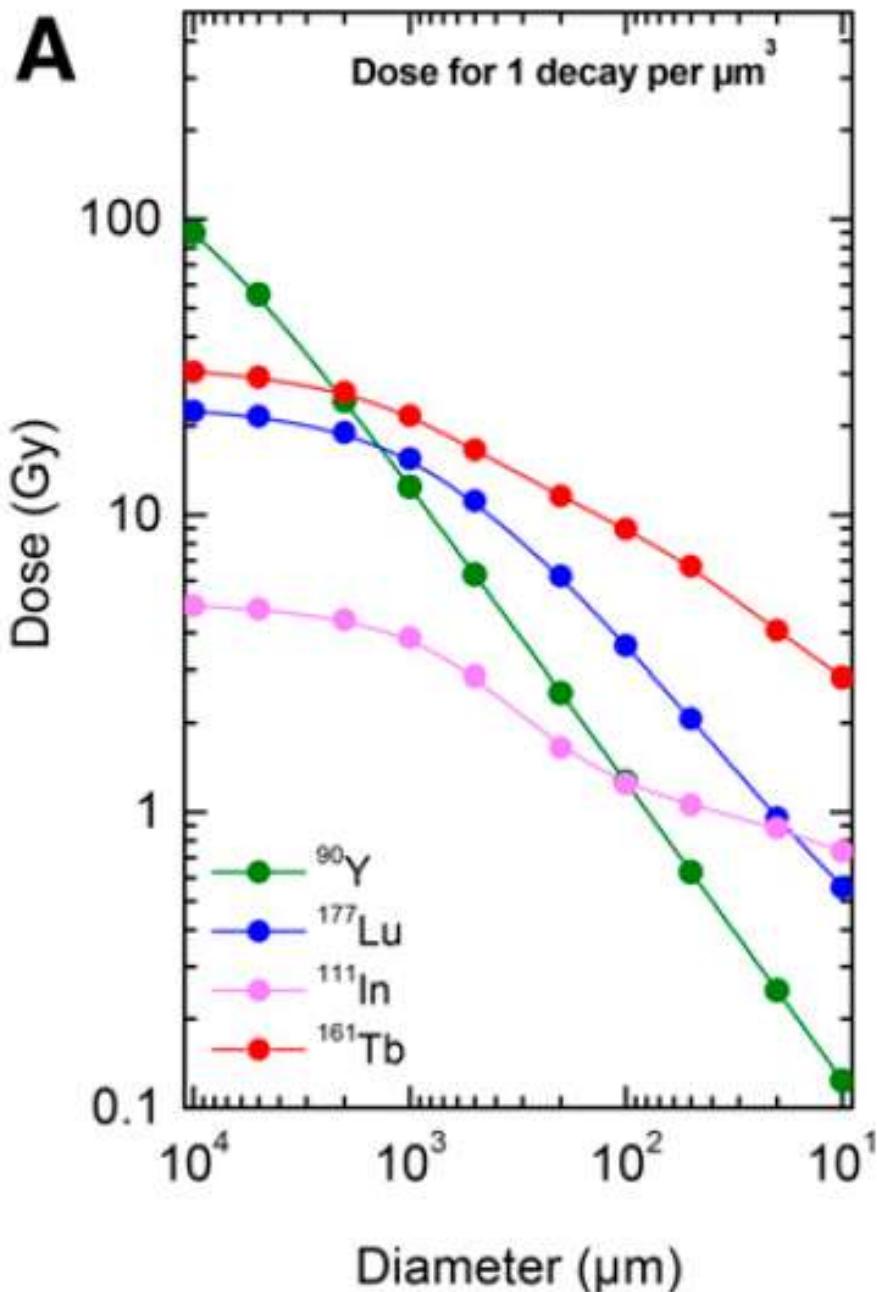
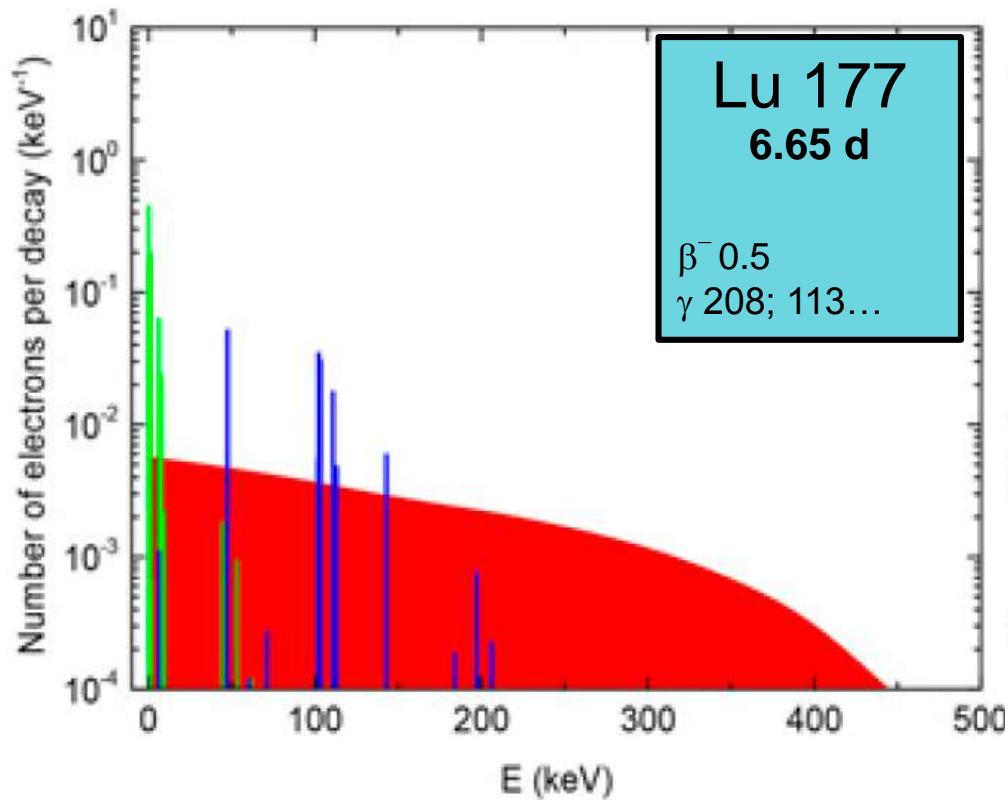
Radionuclides for Radioligand Therapy

Radio-nuclide	Half-life	E mean (keV)	E γ (B.R.) (keV)	Range	
Y-90	2.67 d	934 β	-	12 mm	cross-fire
I-131	8.02 d	182 β	364 (82%)	3 mm	Established isotopes
Lu-177	6.65 d	134 β	208 (10%) 113 (6%)	2 mm	Emerging isotopes

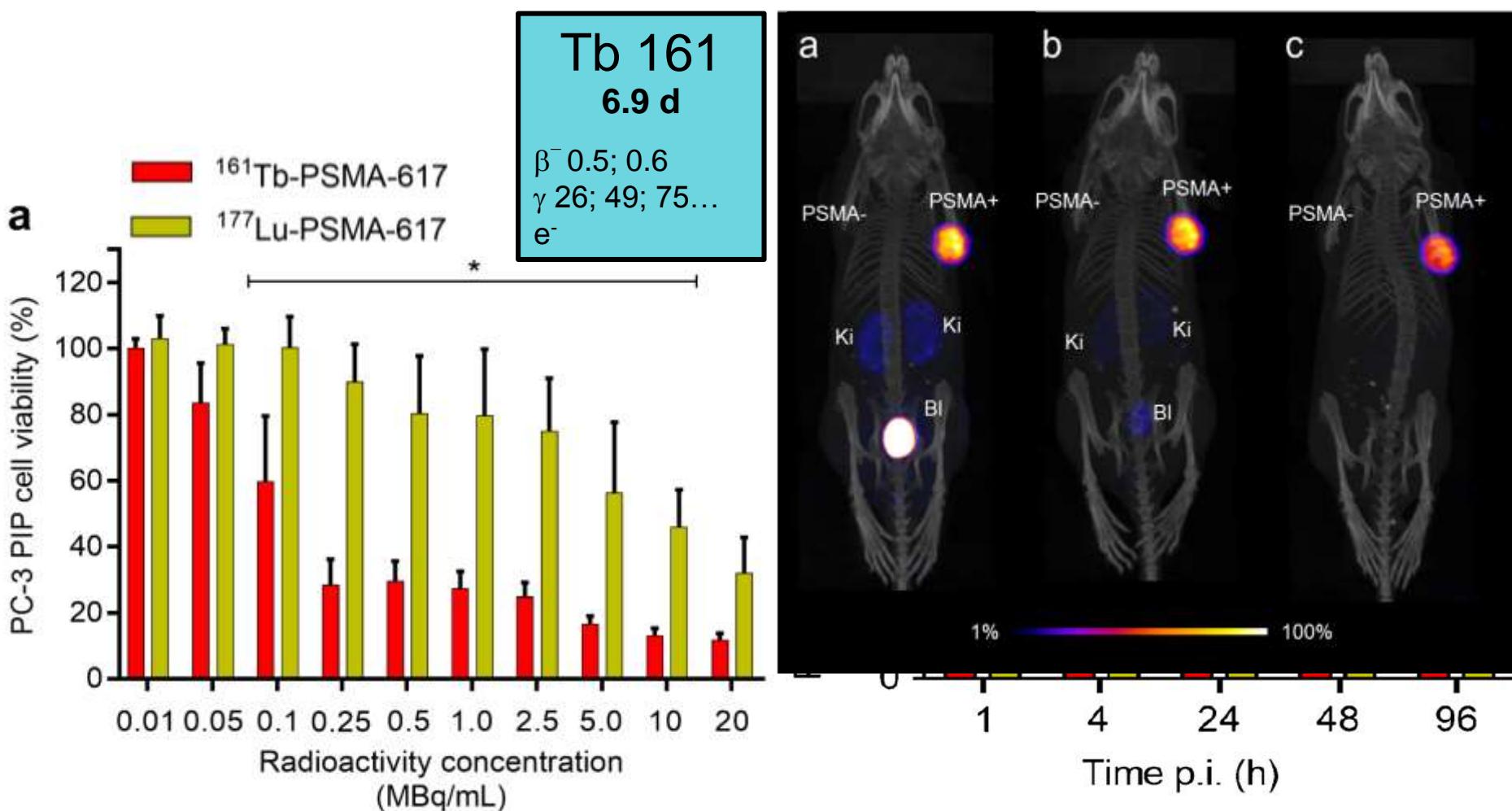


cross-fire
Established isotopes
Emerging isotopes
localized

^{161}Tb versus ^{177}Lu

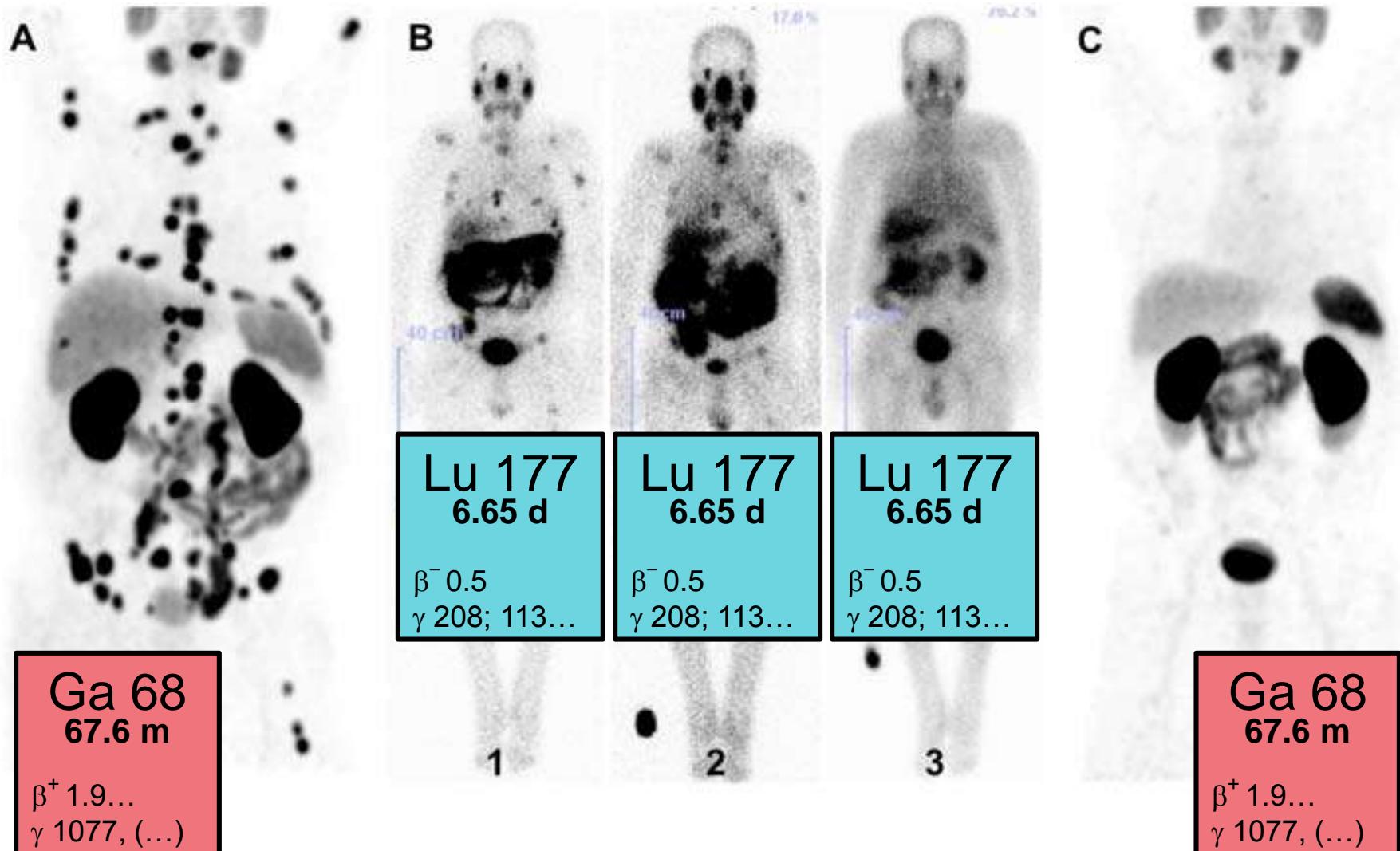


^{161}Tb -PSMA-617 vs. ^{177}Lu -PSMA-617

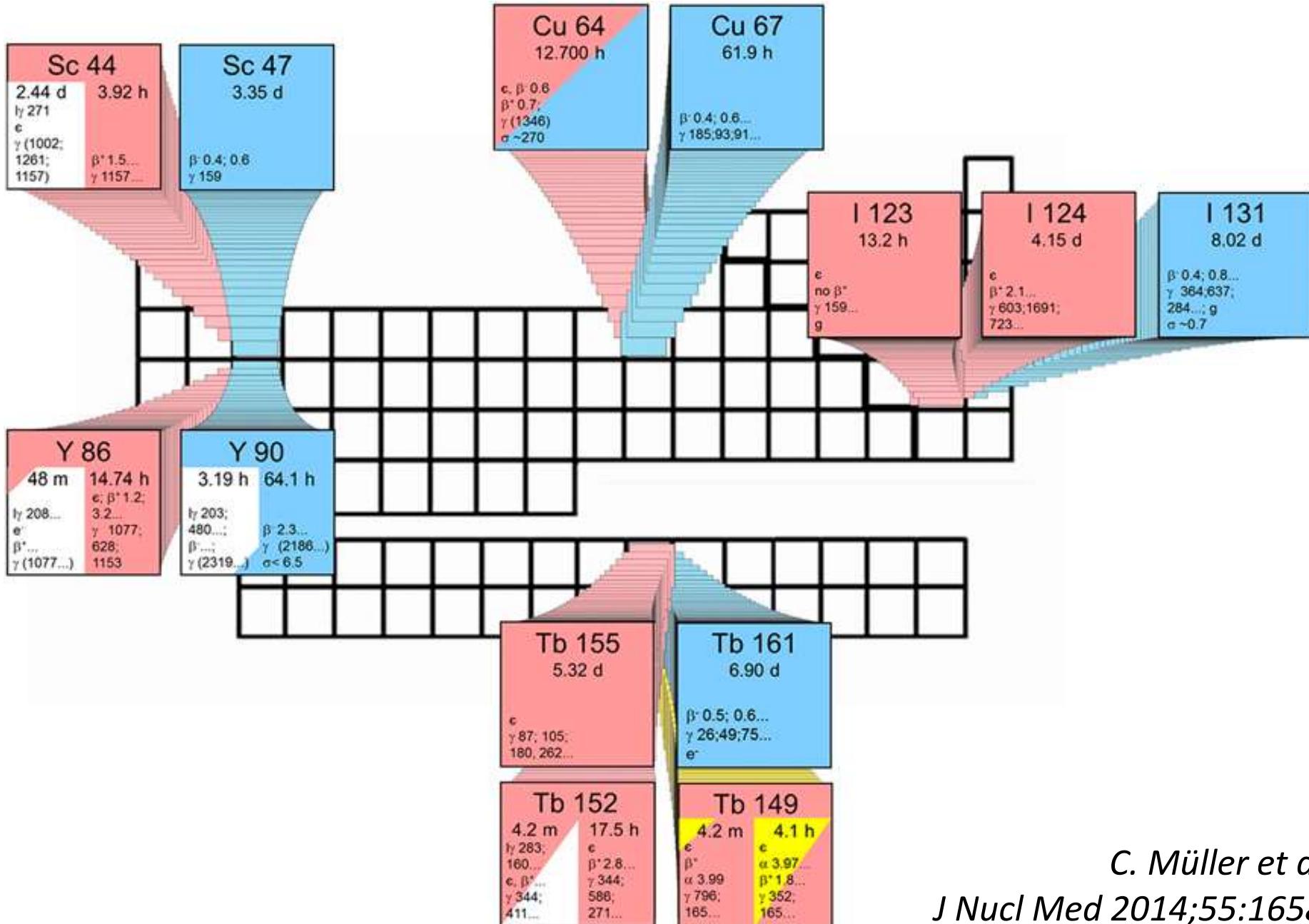


C. Müller et al., Eur J Nucl Med Mol Imaging 2019;46:1919.

^{177}Lu -radioligand therapy of advanced prostate cancer

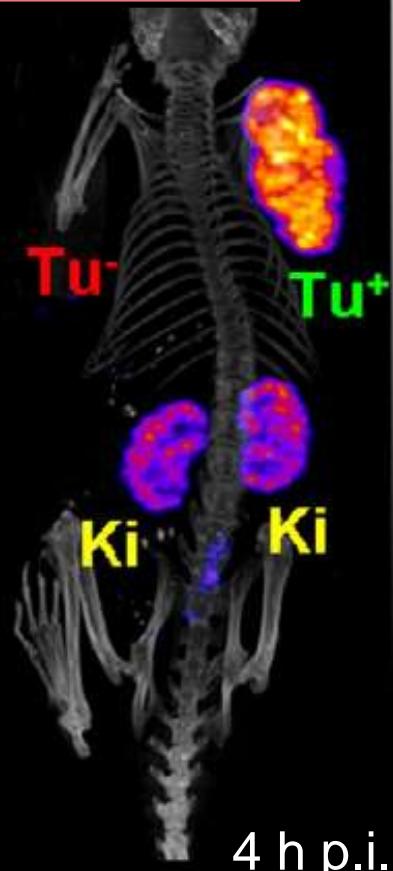


Matched pairs for theranostics



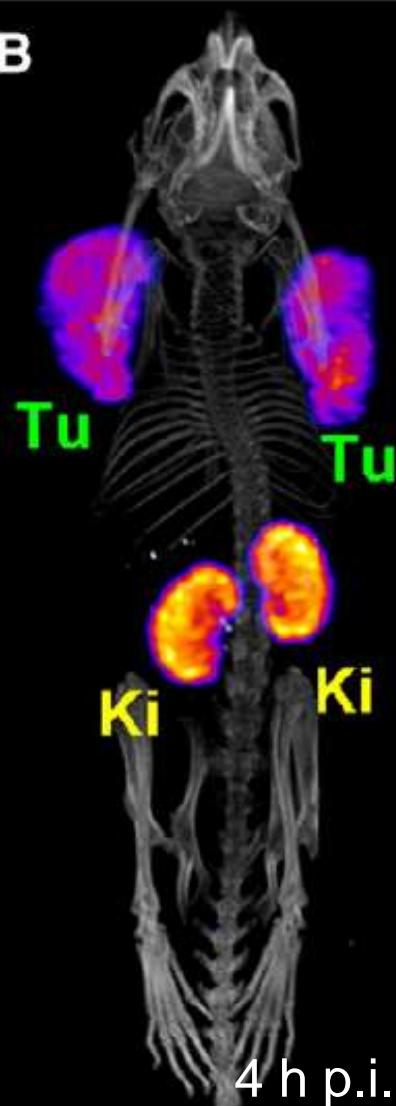
Tb 155
5.3 d

ε
 γ 87; 105; 180...

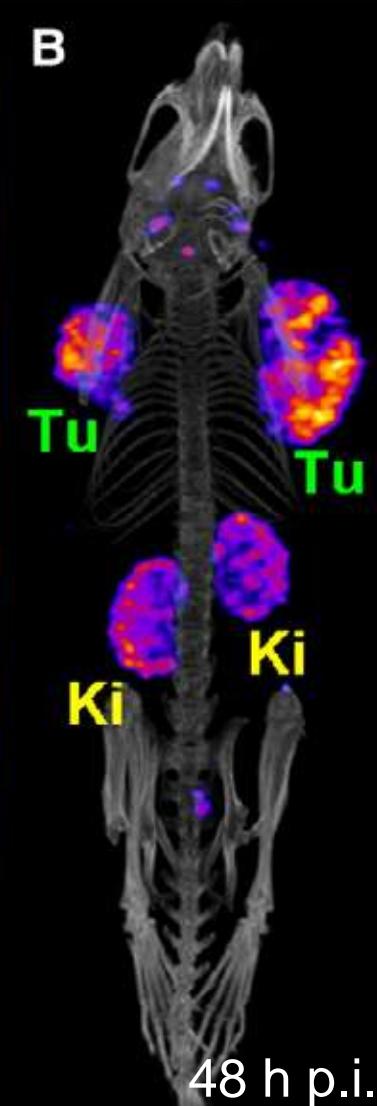


155Tb for SPECT

B



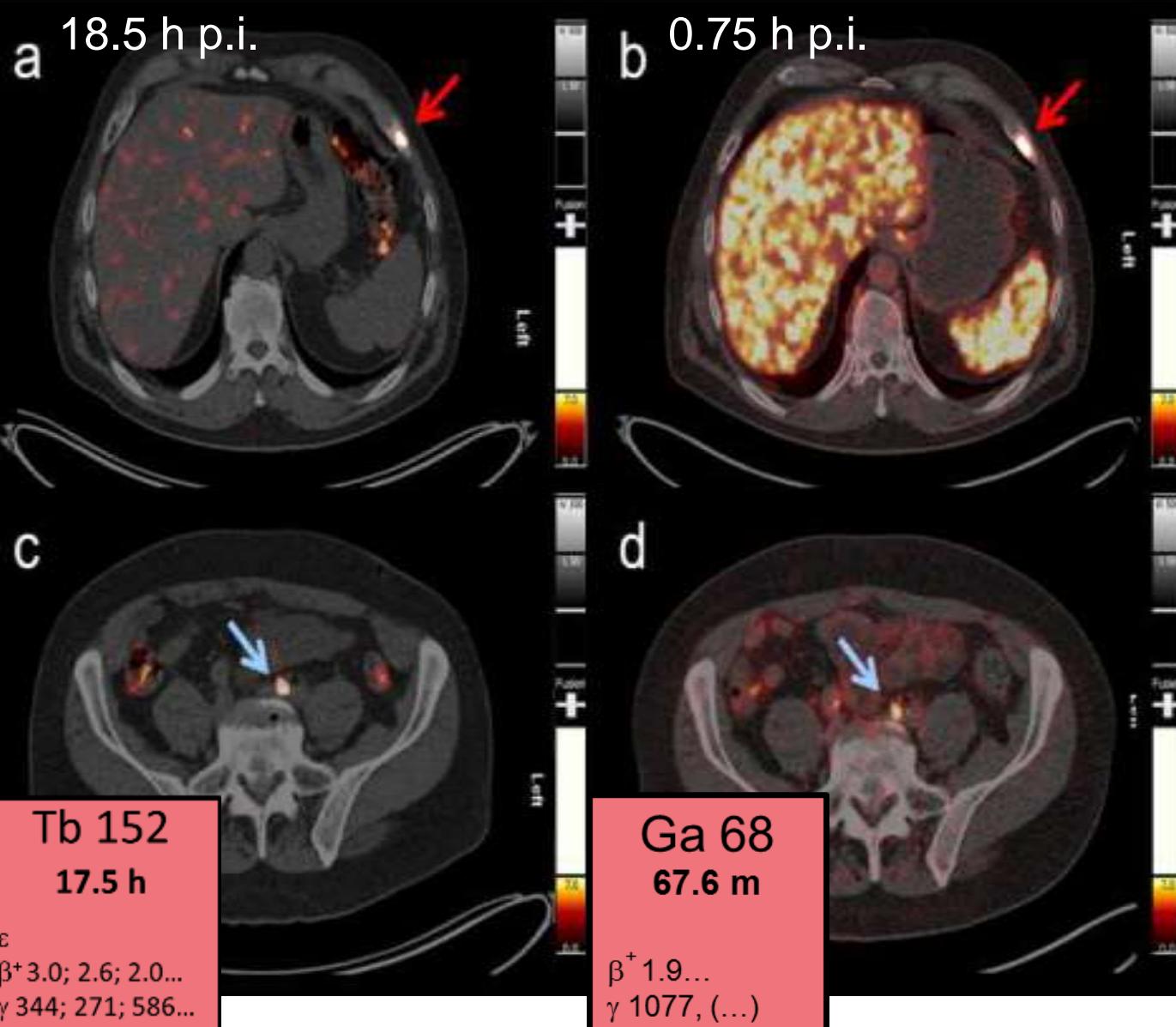
B



72 h p.i.

chCE7
SKOV-3ip tumor

First-in-human study with ^{152}Tb -PSMA-617



Zentrale Bad Berka

PAUL SCHERRER INSTITUT



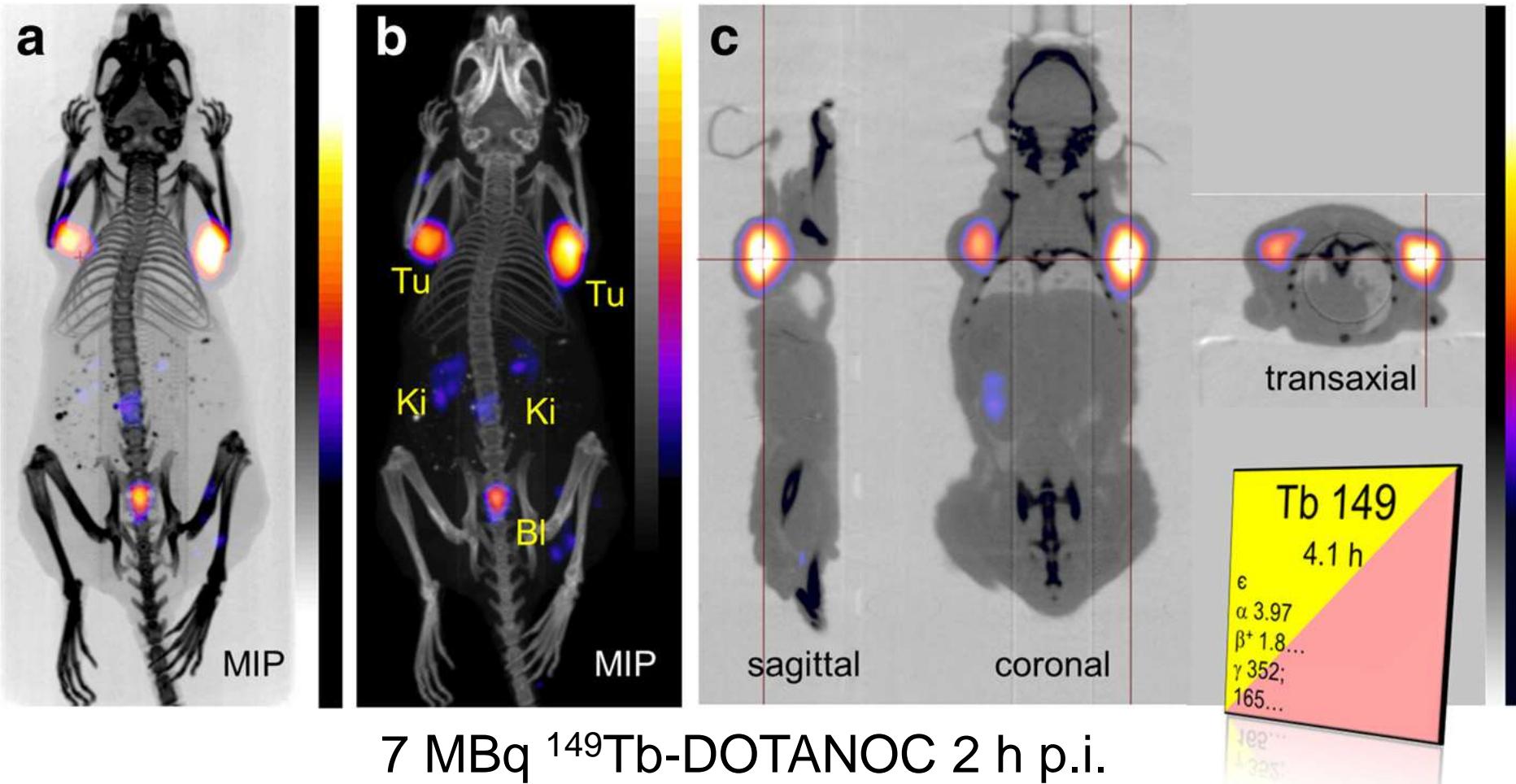
ETH zürich



NEUTRONS
FOR SOCIETY

ENSAR²

Alpha-PET with ^{149}Tb



PAUL SCHERRER INSTITUT

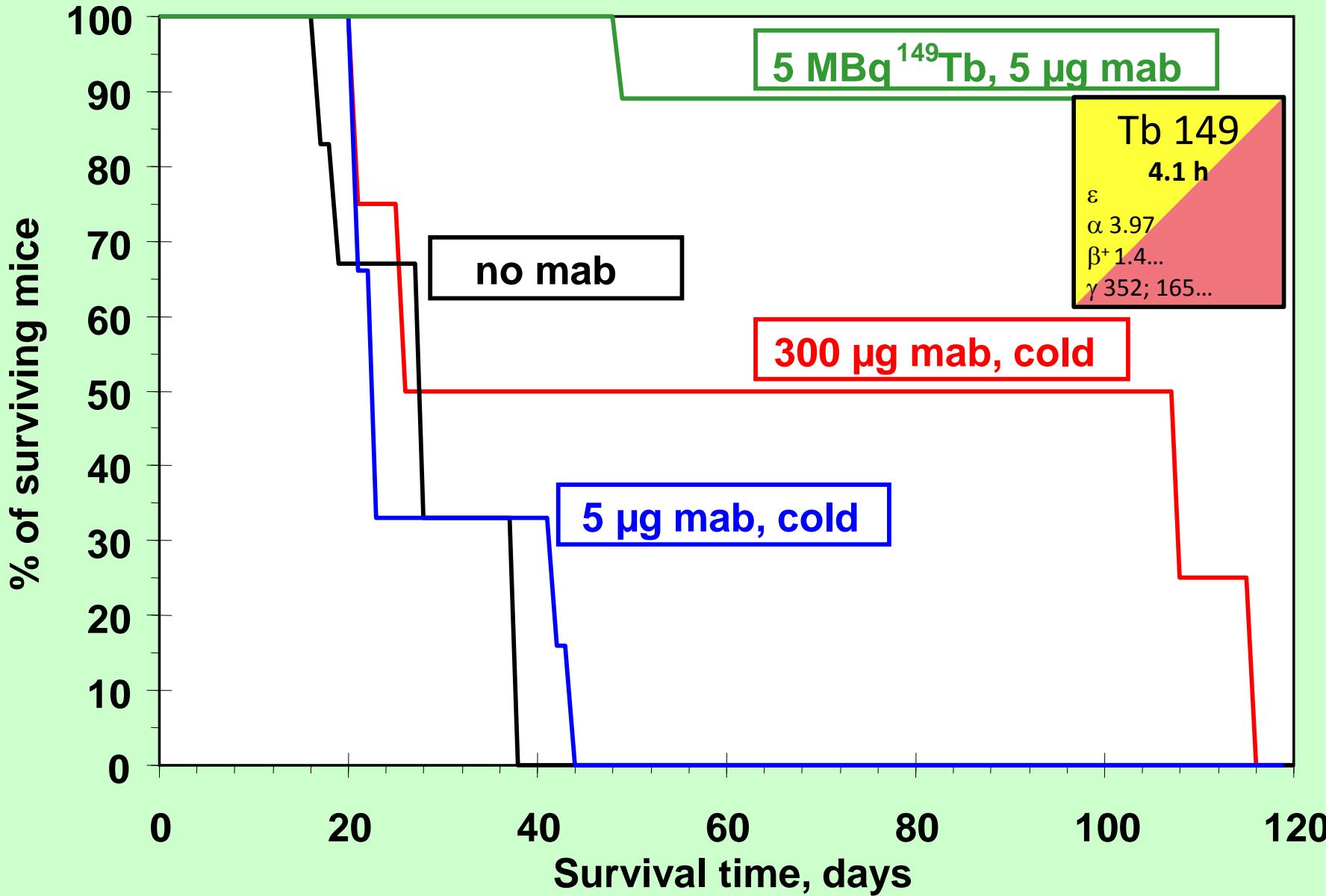


ETH zürich  u^b

NEUTRONS
FOR SOCIETY

UNIVERSITÄT
BERN

^{149}Tb -rituximab in leukemia mouse model



Terbium: the Swiss knife for nuclear medicine

Tb 155

5.3 d

ε

γ 87; 105; 180...

e^-

Tb 152

17.5 h

ε

β^+ 3.0; 2.6; 2.0...

γ 344; 271; 586...

Tb 161

6.9 d

β^- 0.5; 0.6

γ 26; 49; 75...

e^-

Tb 149

4.1 h

ε

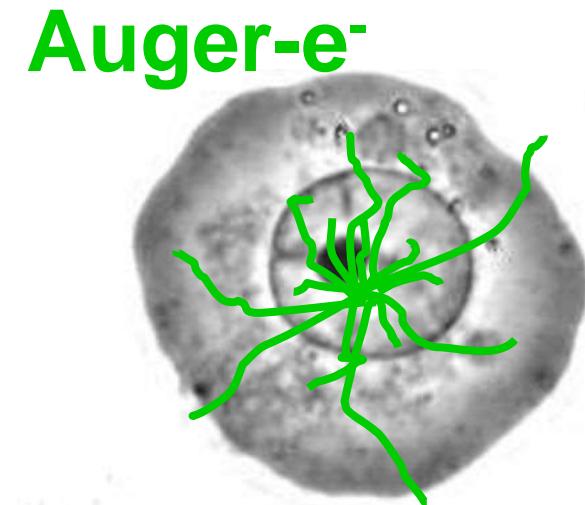
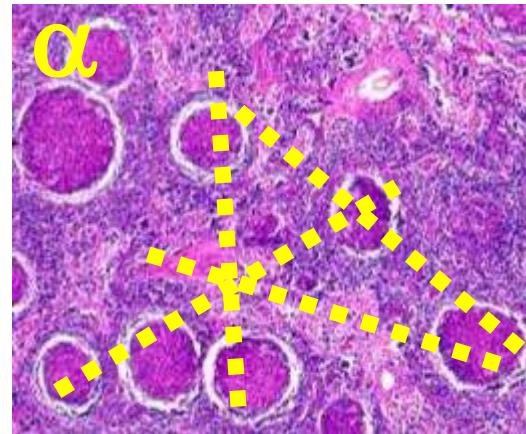
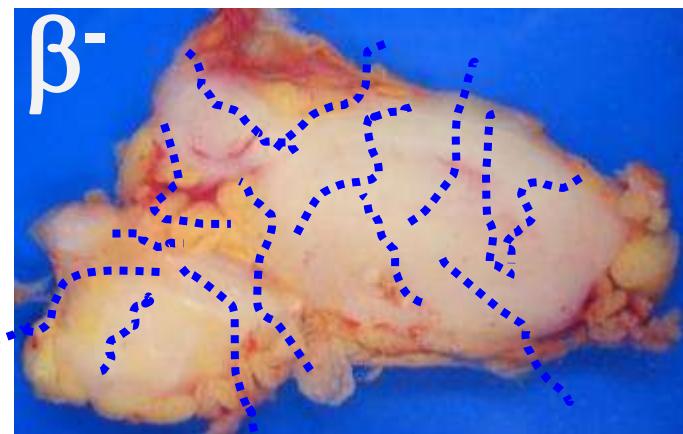
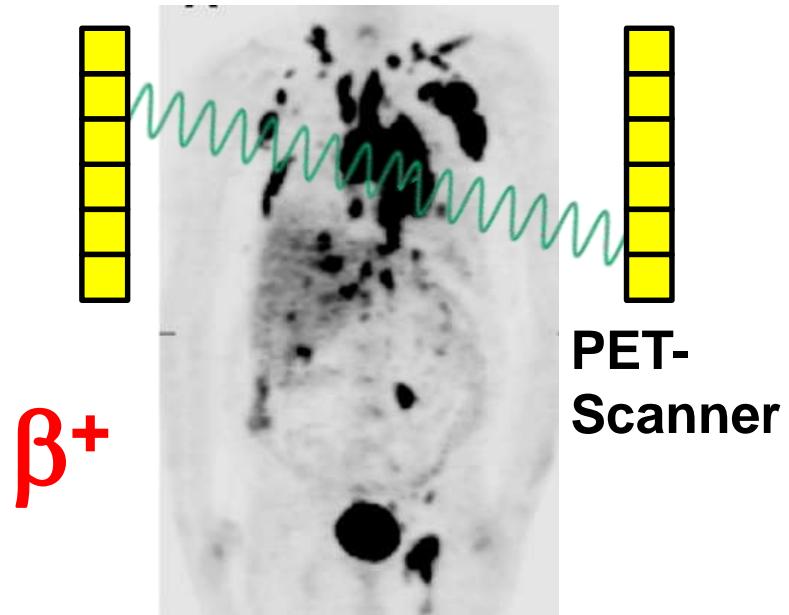
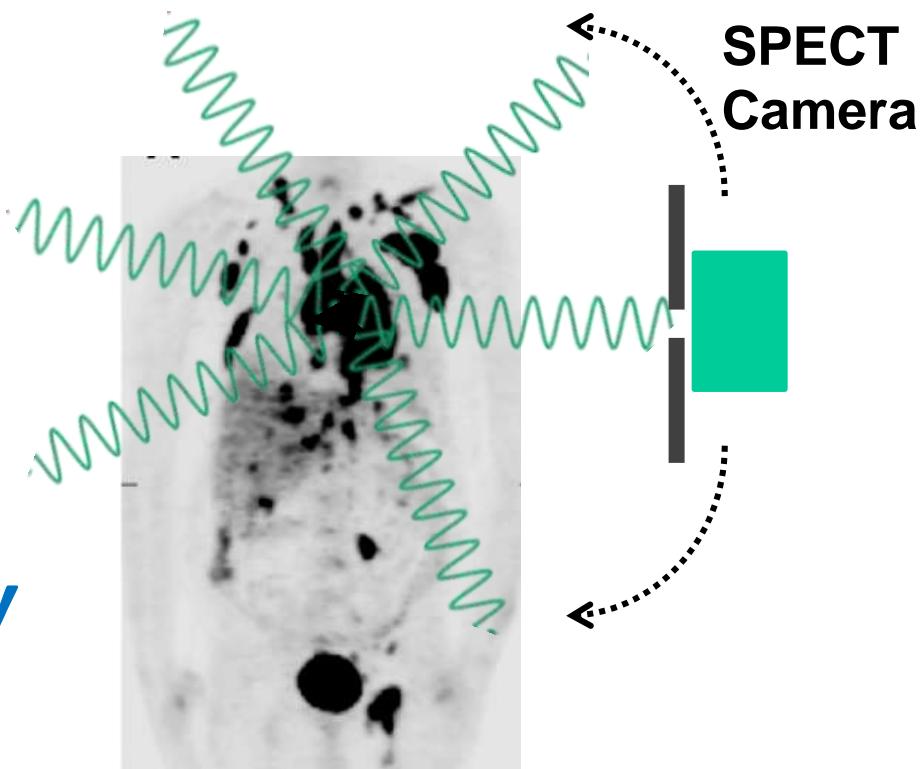
α 3.97

β^+ 1.4...

γ 352; 165...

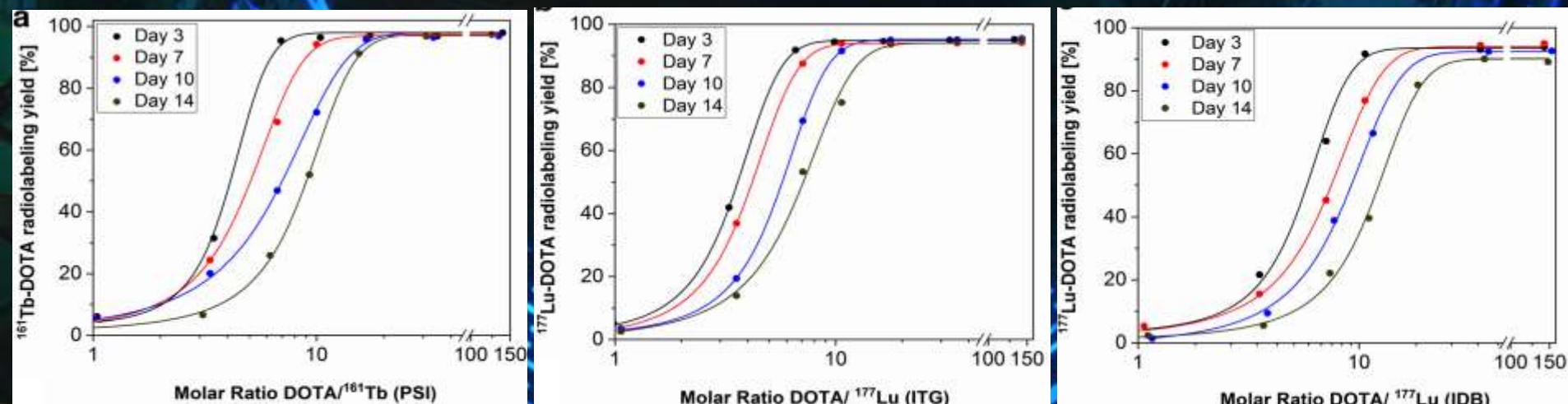
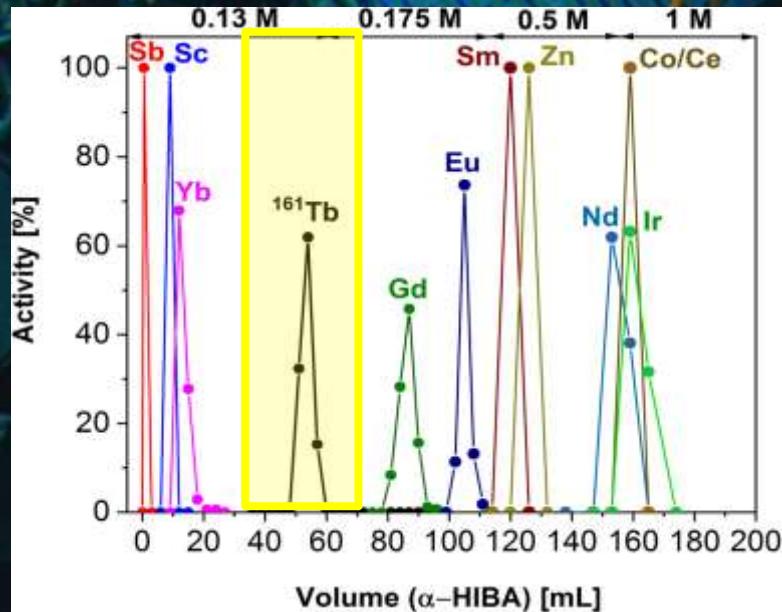


The Nuclear Medicine Alphabet



Production of non-carrier-added ^{161}Tb

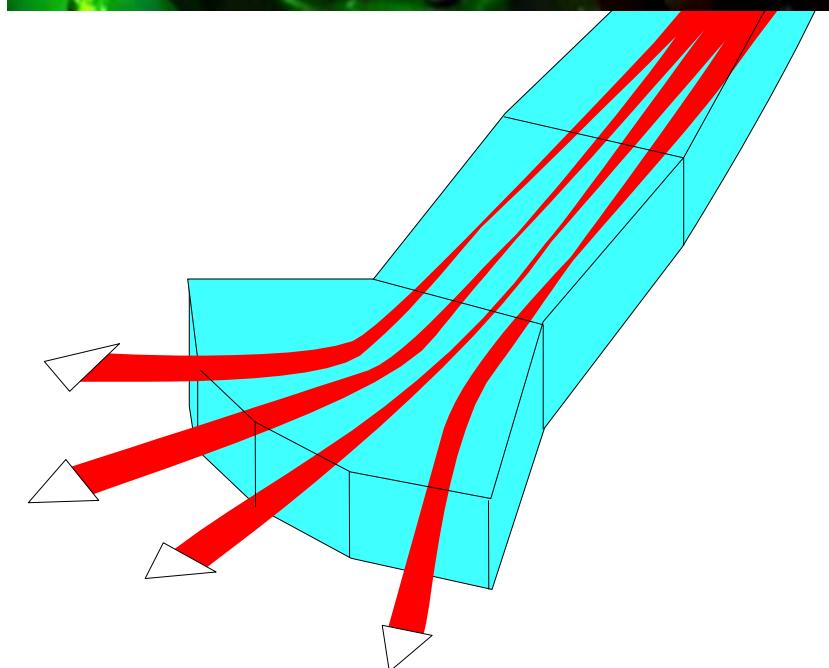
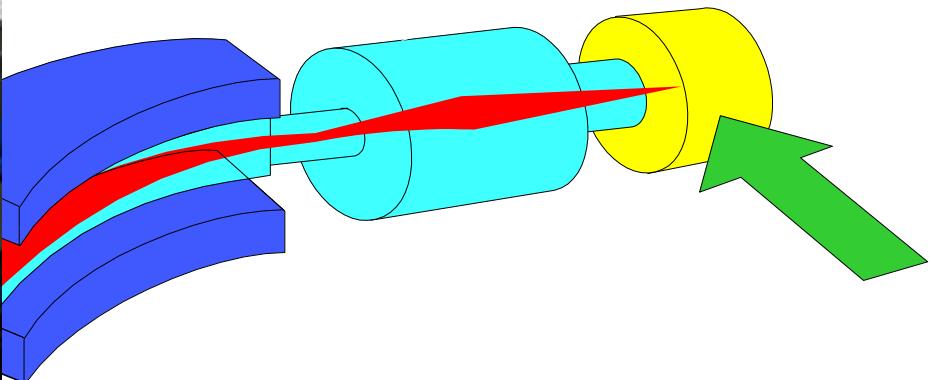
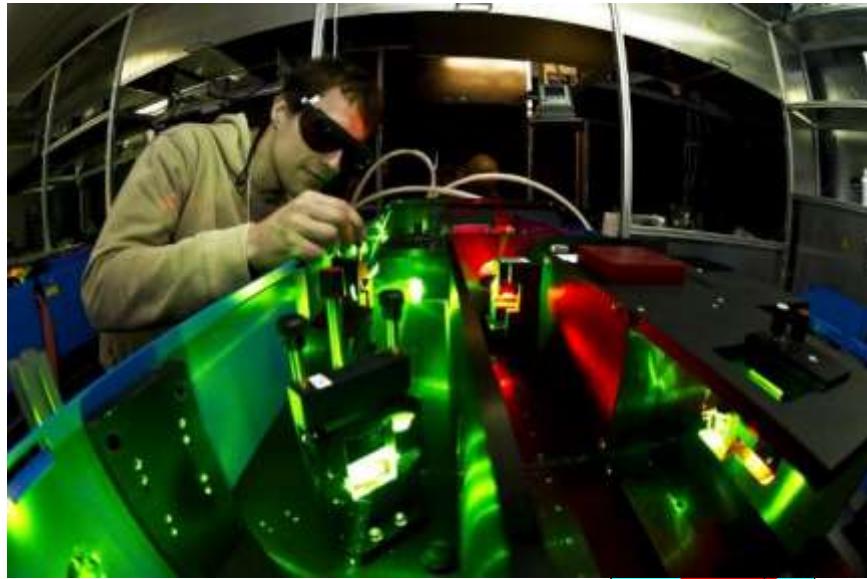
Dy 160 2.329	Dy 161 18.889	Dy 162 25.475	Dy 163 24.896	Dy 164 28.260
σ_{60} $\sigma_{n, \alpha} < 0.0003$	σ_{600} $\sigma_{n, \alpha} < 1\text{E-}6$	σ_{170}	σ_{120} $\sigma_{n, \alpha} < 2\text{E-}5$	$\sigma_{1610} + 1040$
Tb 159 100	Tb 160 72.3 d	Tb 161 6.90 d	Tb 162 7.76 m	Tb 163 19.5 m
$\sigma_{23.2}$	β^- 0.6; 1.7... γ 879; 299; 966... σ_{570}	β^- 0.5; 0... γ 26; 49; 5... e^-	β^- 1.4; 2.4... γ 260; 808; 888...	β^- 0.8; 1.3... γ 351; 390; 494...
Gd 158 24.84	Gd 159 18.48 h	Gd 160 21.86	Gd 161 3.66 m	Gd 162 8.2 m
$\sigma_{2.3}$	β^- 1.0... γ 364; 58...	$\sigma_{1.5}$	β^- 1.6; 1.7... γ 361; 315; 102... σ_{20000}	β^- 1.0... γ 442; 403...



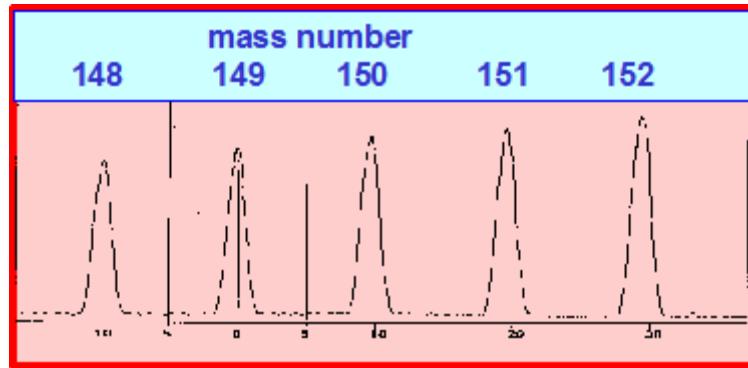
Irradiation at ILL & Necsa, chemical separation at PSI

N. Gracheva et al., EJNMMI Radiopharm Chem 2019;4:12.

Production of ^{149}Tb , ^{152}Tb and ^{155}Tb at ISOLDE



radioactive ion beams



Efficient parallel operation



Transport limitations (ADR, IATA)

BASIC RADIONUCLIDE VALUES FOR UNKNOWN RADIONUCLIDES OR MIXTURES

Radioactive contents	A_1 TBq	A_2 TBq	Activity concentration for exempt material Bq/g
Only beta or gamma emitting nuclides are known to be present	0.1	0.02	1×10^1 20 GBq ^{161}Tb
Alpha emitting nuclides but no neutron emitters are known to be present	0.2	9×10^{-5}	1×10^{-1} 90 MBq ^{149}Tb

Terbium (65)	A ₂ (TBq)
Tb-149	8×10^{-1}
Tb-157	4×10^1
Tb-158	1×10^0
Tb-160	1×10^0
Tb-161	3×10^1

2018 Edition

Specific Safety Requirements

No. SSR-6 (Rev. 1)



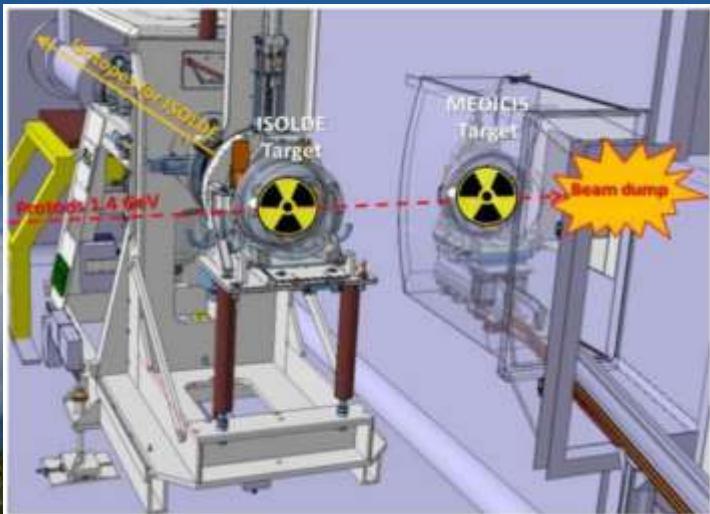
IAEA

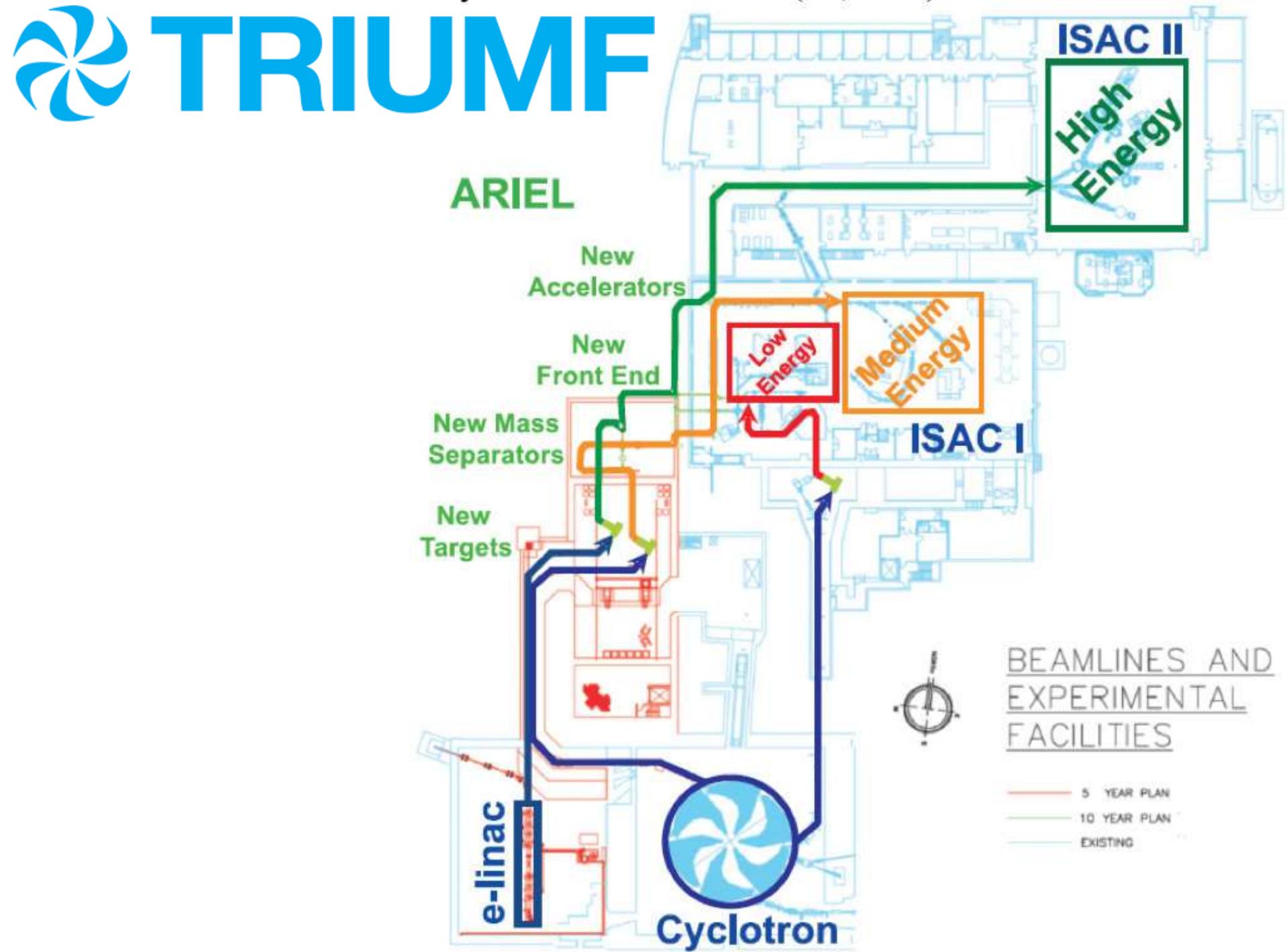
International Atomic Energy Agency



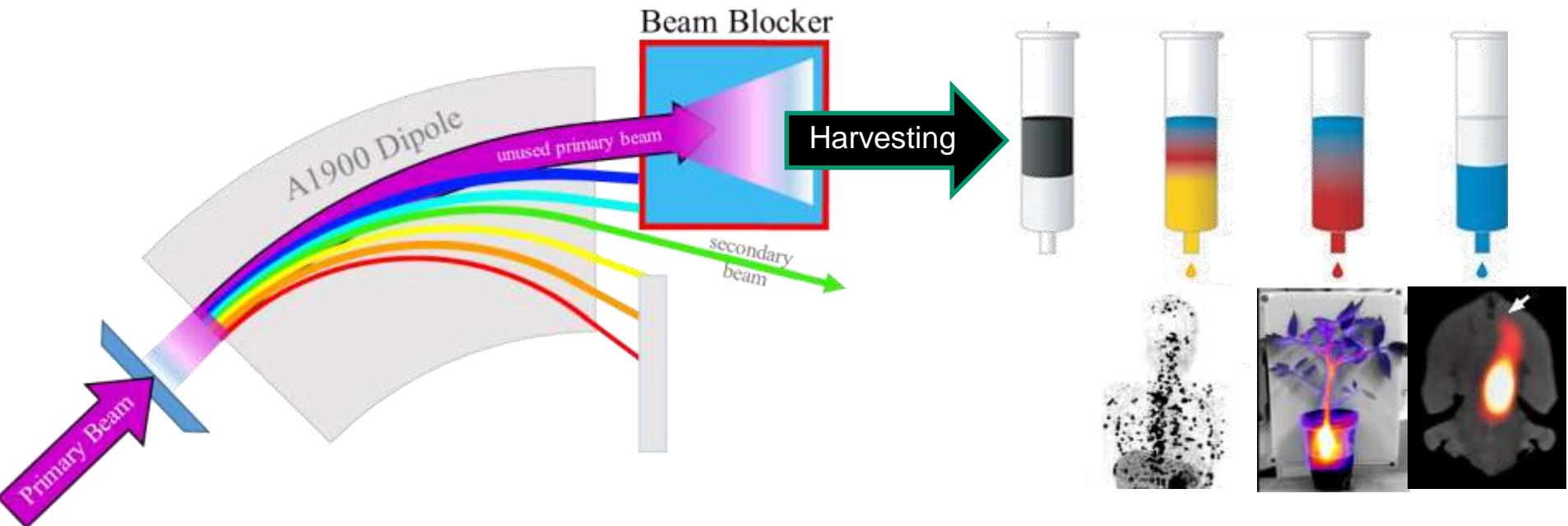
MEDICIS

a very useful beam dump !





Harvesting isotopes at FRIB



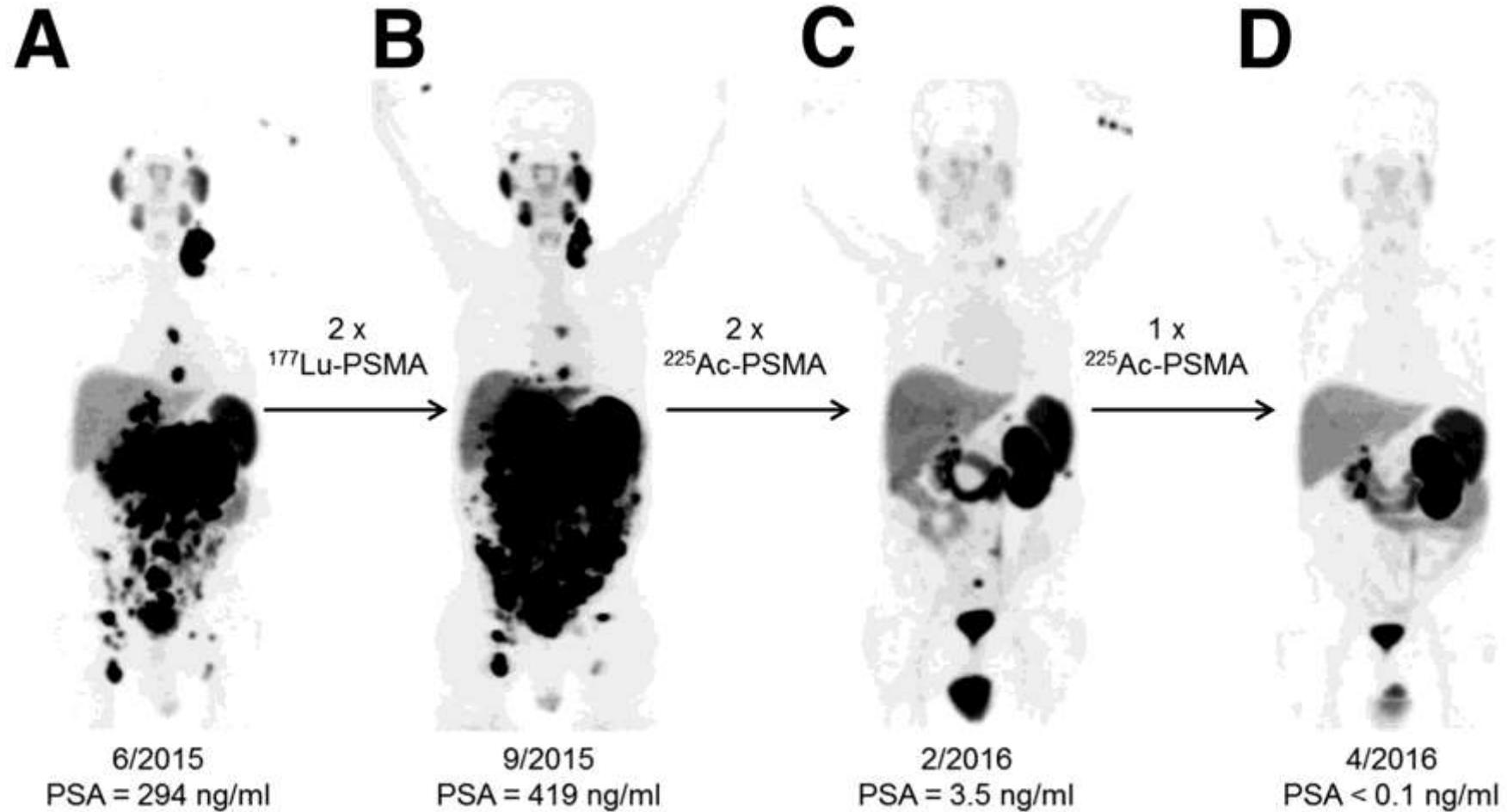
courtesy: Greg Severin (MSU)



U.S. Department of Energy Office of Science
National Science Foundation
Michigan State University

E Paige Abel et al., J. Phys. G 2019;46:100501.

Targeted therapy with ^{225}Ac



Isotopes for targeted alpha therapy

^{211}At production at ARRONAX

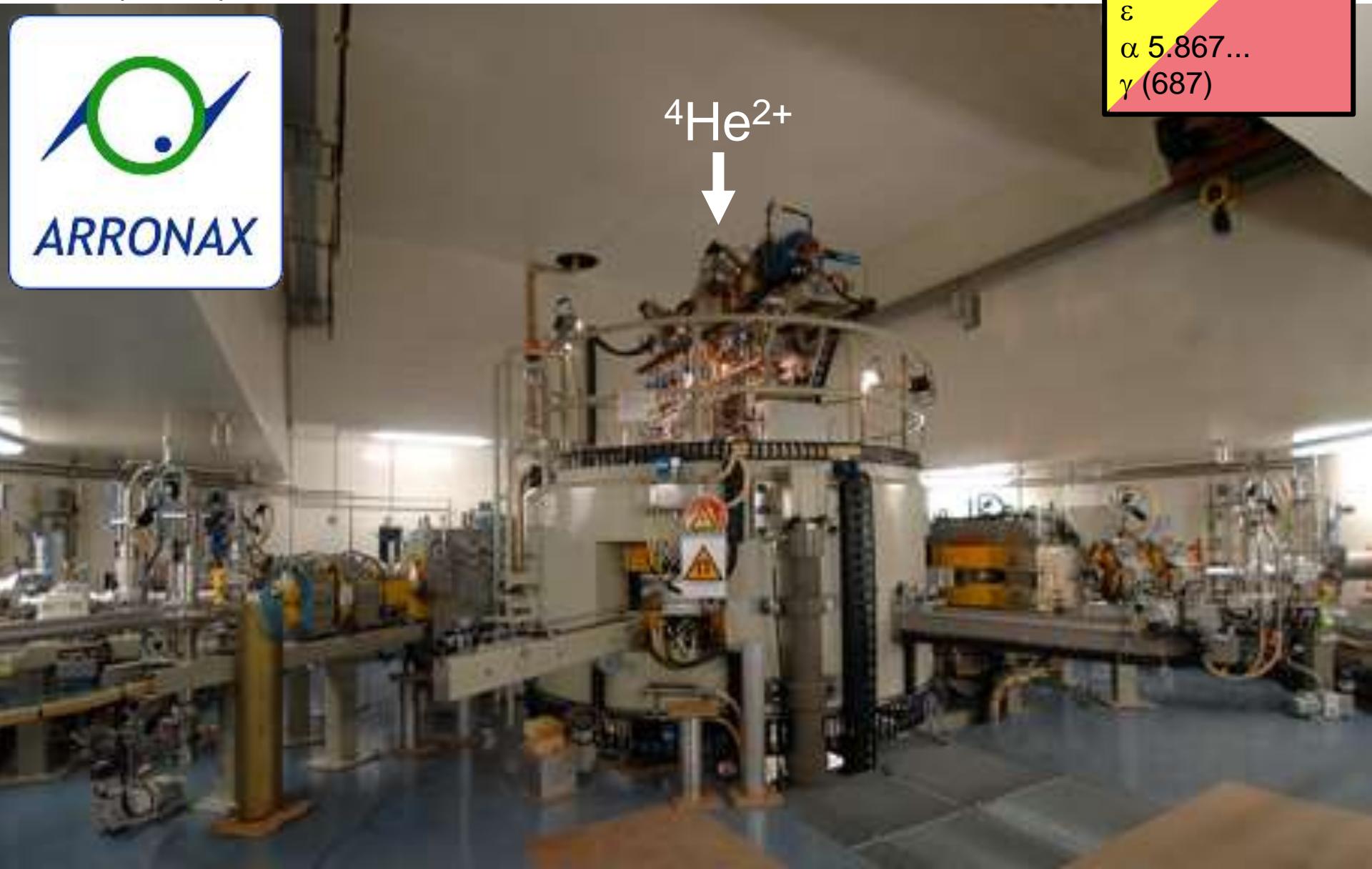
At 211
7.2 h

ε
 α 5.867...
 γ (687)

$^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$ with 28-29 MeV α beams

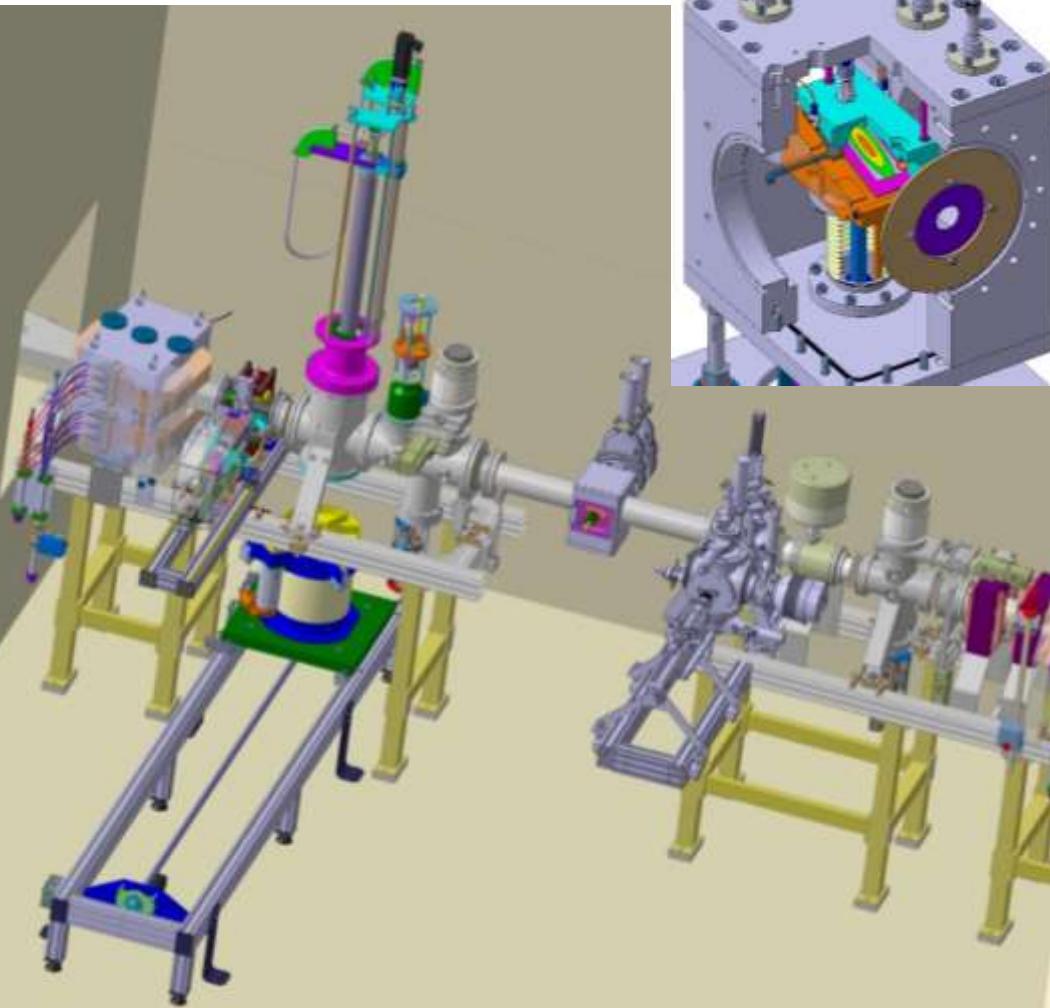
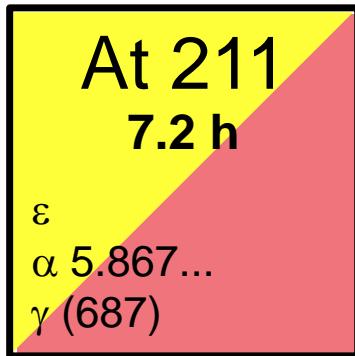


$^4\text{He}^{2+}$
↓



^{211}At production at SPIRAL2

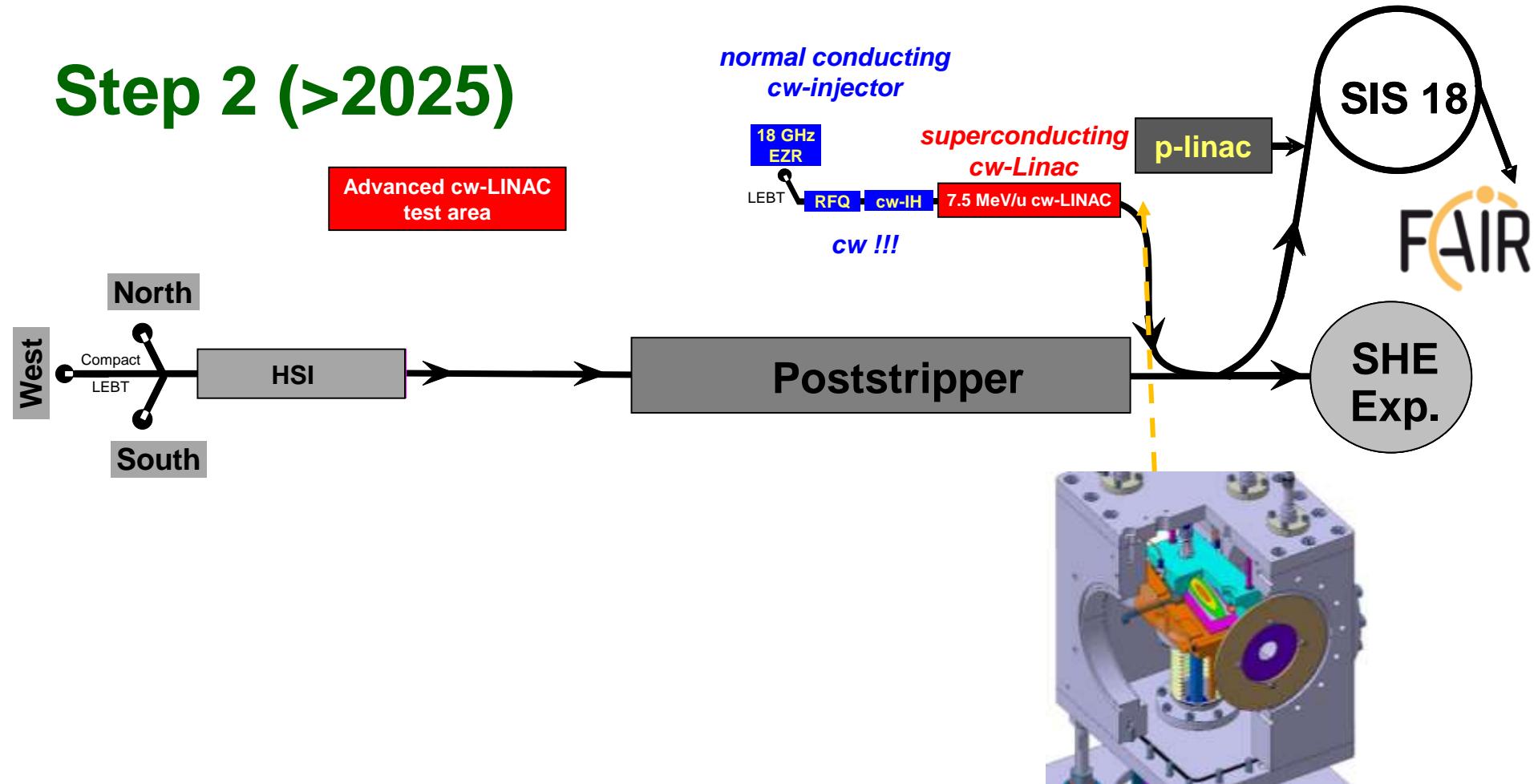
$^{209}\text{Bi}(\alpha, 2\text{n})^{211}\text{At}$ with 28-29 MeV α beams



1. Use of 1 kW station (≈ 10 doses in 4 h) in 2020 once alpha beams are available at SPIRAL2.
2. Design of a 10 kW rotating solid target (≈ 100 doses in 4 h).
3. Design of a liquid Bi target for continuous ^{211}At or ^{211}Rn extraction.

Future superconducting cw-Linac at GSI

Step 2 (>2025)



Radionuclides for Radioligand Therapy

Radio-nuclide	Half-life	E mean (keV)	E γ (B.R.) (keV)	Range
Y-90	2.67 d	934 β	-	12 mm
I-131	8.02 d	182 β	364 (82%)	3 mm
Lu-177	6.65 d	134 β	208 (10%) 113 (6%)	2 mm
Tb-161	6.96 d	154 β 5, 17, 40 e^-	75 (10%)	2 mm 1-30 μm
Tb-149	4.12 h	3967 α	165,..	25 μm
Ge-71	11.4 d	8 e^-	-	1.7 μm
Er-165	10.3 h	5.3 e^-	-	0.6 μm

cross-fire

Established isotopes

Emerging isotopes

future isotopes:
supply-limited!

localized

Better targeted ligands require shorter-range radiation
 ⇒ need for adequate (R&D) radioisotope supply.

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: December 4, 1958

Today 30 million clinical applications per year !

TO: Addressees Below
FROM: Daniel M. Schaeffer, Head *DMS*
BNL Patent Office
SUBJECT: P-701 and P-702 - PREPARATION OF CARRIER-FREE MOLYBDENUM AND OF TECHNETIUM FROM FISSION PRODUCTS

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

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

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

A great model: the US DOE Isotope Program

NIDC: National Isotope Development Center +

https://www.isotopes.gov 110% ⌂ ⌂ ⌂

NIDC NATIONAL ISOTOPE DEVELOPMENT CENTER

the government source of isotopes for science, medicine, security, & other applications

U.S. DEPARTMENT OF ENERGY Office of Science

Product Catalog News Education & Outreach Isotope Production About NIDC

Welcome to the NIDC!

The **National Isotope Development Center (NIDC)** interfaces with the isotope user community and manages the coordination of isotope production across the facilities and business operations involved in the production, sale, and distribution of isotopes. A virtual center, the NIDC is funded by the [U.S. Department of Energy Isotope Program](#) within the [Office of Nuclear Physics](#) in the [Office of Science](#).

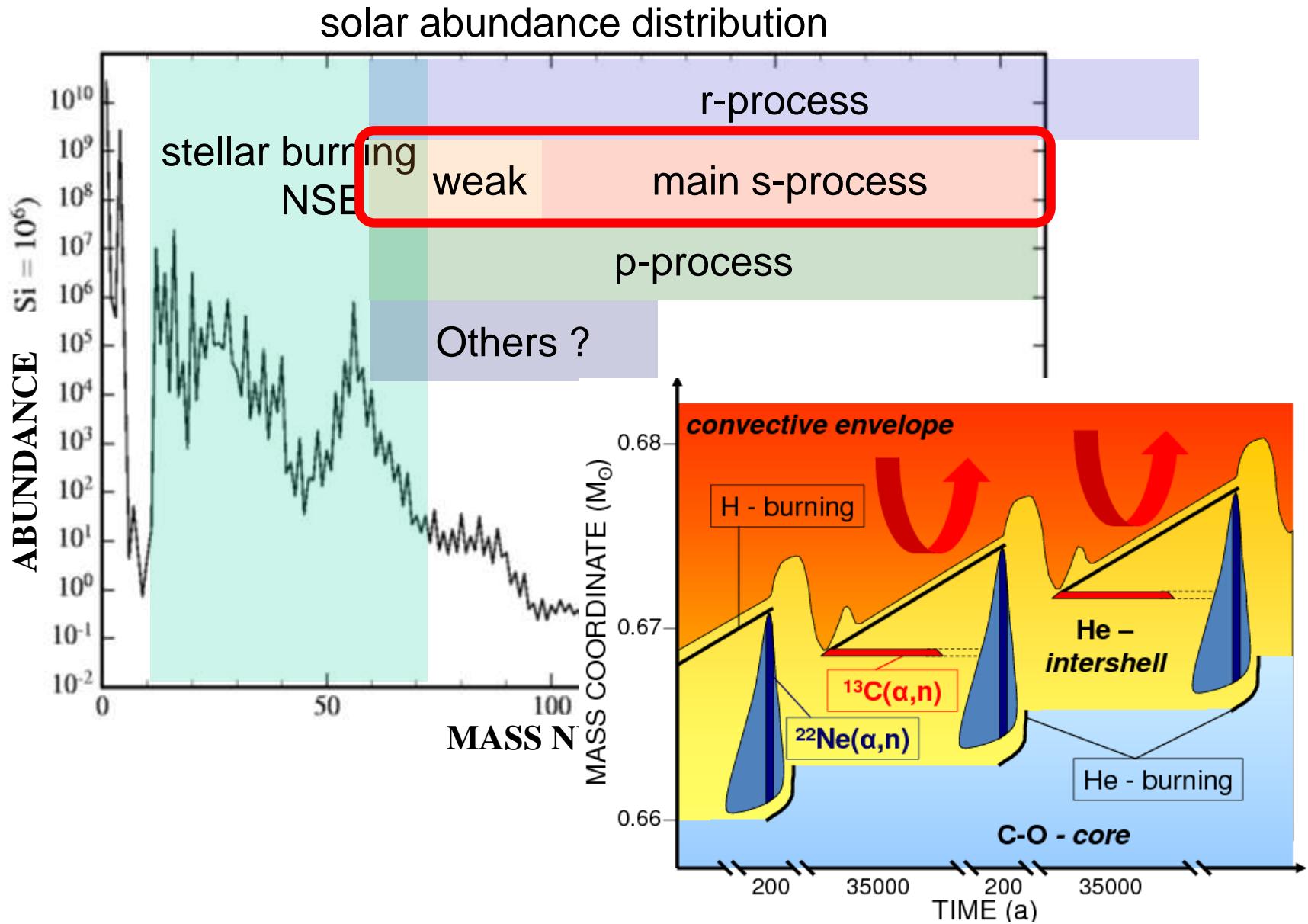
PRISMAS-MAP: improved access to emerging medical radioisotopes



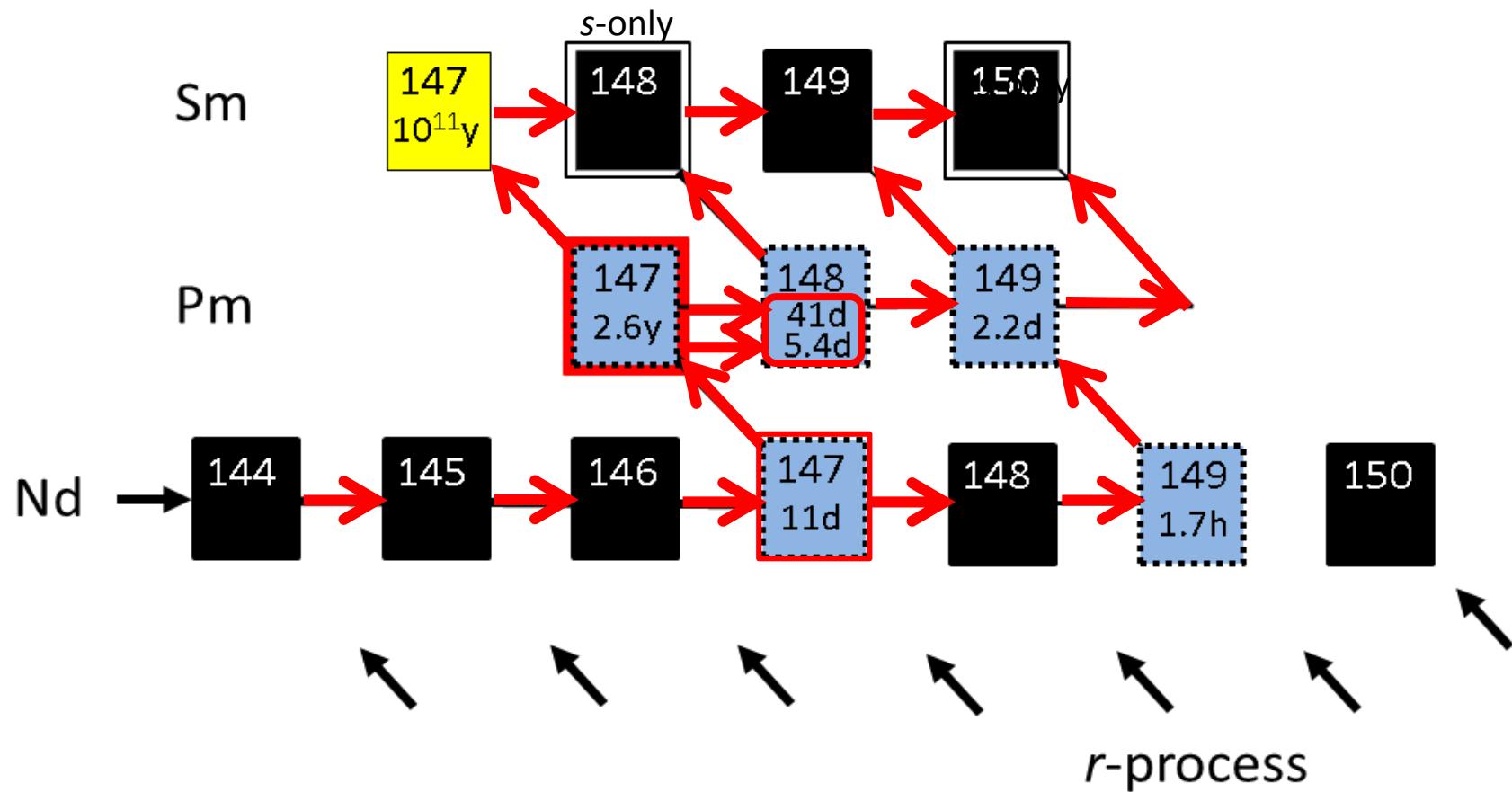
Life, the Universe and Everything

The background image depicts a dark, intricate interior space, likely a corridor or a large room within a futuristic vessel. The walls and ceiling are lined with numerous rectangular panels that emit a bright blue light, creating a glowing effect against the deep shadows. In the center of the frame, there is a large, circular, metallic structure, possibly a hatch or a vent, which also has a blue glow around its perimeter. The overall atmosphere is mysterious and high-tech, with the blue lighting suggesting a cold, metallic environment.

the Universe: nucleosynthesis

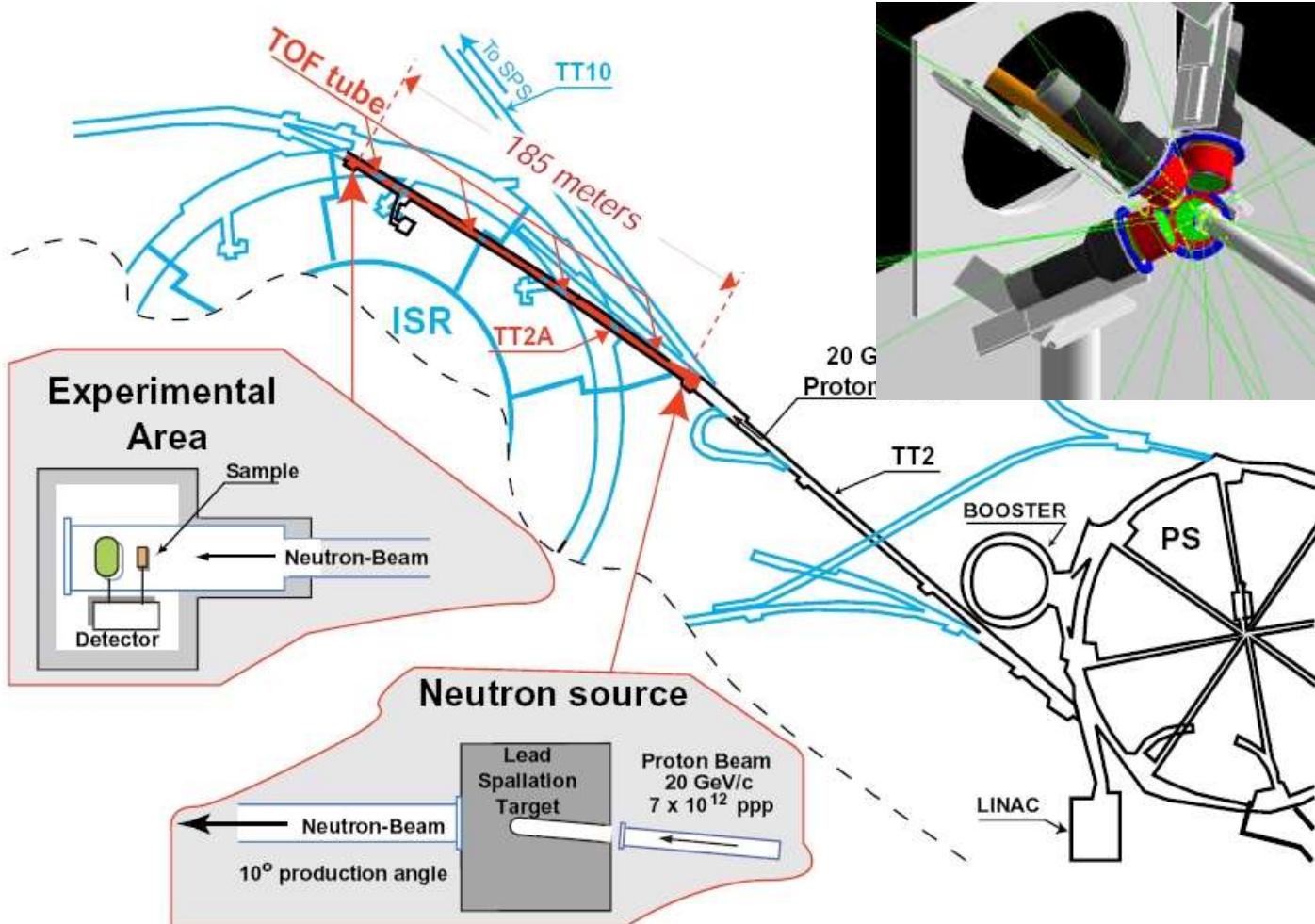


Branching points: example at A=147/148



Neutron capture at s-process branching points

Sm 147 14.99	Sm 148 11.24	Sm 149 13.82	Sm 150 7.38
$\alpha = 1.06 \cdot 10^{-1}$ a $\sigma = 2.235$ $\tau_{1/2} = 56$ days	$\alpha = 7 \cdot 10^{-1}$ a $\sigma = 1.96$ $\tau_{1/2} = 0.8$ days	$\alpha = 40100$ $\sigma = 0.031$ $\tau_{1/2} = 102$ days	
Pm 146 5.53 a $\alpha = 0.8$ $\gamma = 454, 747$ $\tau_{1/2} = 738$ days	Pm 147 2.62 a $\alpha = 0.2$ $\gamma = 121, 123$ $\tau_{1/2} = 54$ days	Pm 148 1.13 a $\alpha = 0.2$ $\gamma = 121, 123$ $\tau_{1/2} = 53.1$ h	Pm 149 0.11 a $\alpha = 0.2$ $\gamma = 121, 123$ $\tau_{1/2} = 1.1$ h
Nd 145 8.293 $\alpha = 47$ $\tau_{1/2} = 126$ days	Nd 146 17.189 $\alpha = 1.5$	Nd 147 10.98 d $\alpha = 0.8$	Nd 148 5.756 $\alpha = 2.4$
Yb 170 2.982 $\sigma = 12$ $\tau_{1/2} < 1.0 \cdot 10^5$	Yb 171 14.09 $\sigma = 53$ $\tau_{1/2} < 1.5$ days	Yb 172 21.68 $\sigma = 1.3$ $\tau_{1/2} < 1 \cdot 10^6$	Yb 173 16.103 $\sigma = 16$ $\tau_{1/2} < 1 \cdot 10^6$
Tm 169 100 $\tau_{1/2} = 108$	Tm 170 127.8 d $\beta^- = 1.0$ $\gamma = 84, \#^-$ $\tau_{1/2} = 92$	Tm 171 1.92 a $\beta^- = 0.1$ $\gamma = 67, 1094$ $\tau_{1/2} = 10$	Tm 172 63.6 h $\beta^- = 0.1$ $\gamma = 79, 1094$ $\tau_{1/2} = 1587, 1530$ days
Er 168 26.978 $\sigma = 2.3$ $\tau_{1/2} < 10^5$	Er 169 9.40 d $\beta^- = 0.3$ $\gamma = 110, \dots$ $\tau_{1/2} = 92$	Er 170 14.910 $\beta^- = 0.3$ $\gamma = 110, \dots$ $\tau_{1/2} = 8$	Er 171 7.52 h $\beta^- = 0.1$ $\gamma = 115, 196, 1112$ $\tau_{1/2} = 15$
Pb 204 67.2 m $\tau_{1/2} = 370$ $\sigma = 0.68$	Pb 205 1.5 $\cdot 10^{-1}$ a $\tau_{1/2} = 370$ $\sigma = 0.5$	Pb 206 24.1 $\tau_{1/2} = 0.027$	
Tl 203 29.52 $\sigma = 11$ $\tau_{1/2} < 0$	Tl 204 3.78 a $\tau_{1/2} = 0.03$ $\sigma = 0.5$	Tl 205 70.48 $\tau_{1/2} = 0.11$	
Hg 200 29.00 $\tau_{1/2} = 4.9$	Hg 203 0.2 $\tau_{1/2} = 279$	Hg 204 6.87 $\tau_{1/2} = 0.4$	



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THE HEBREW UNIVERSITY OF JERUSALEM

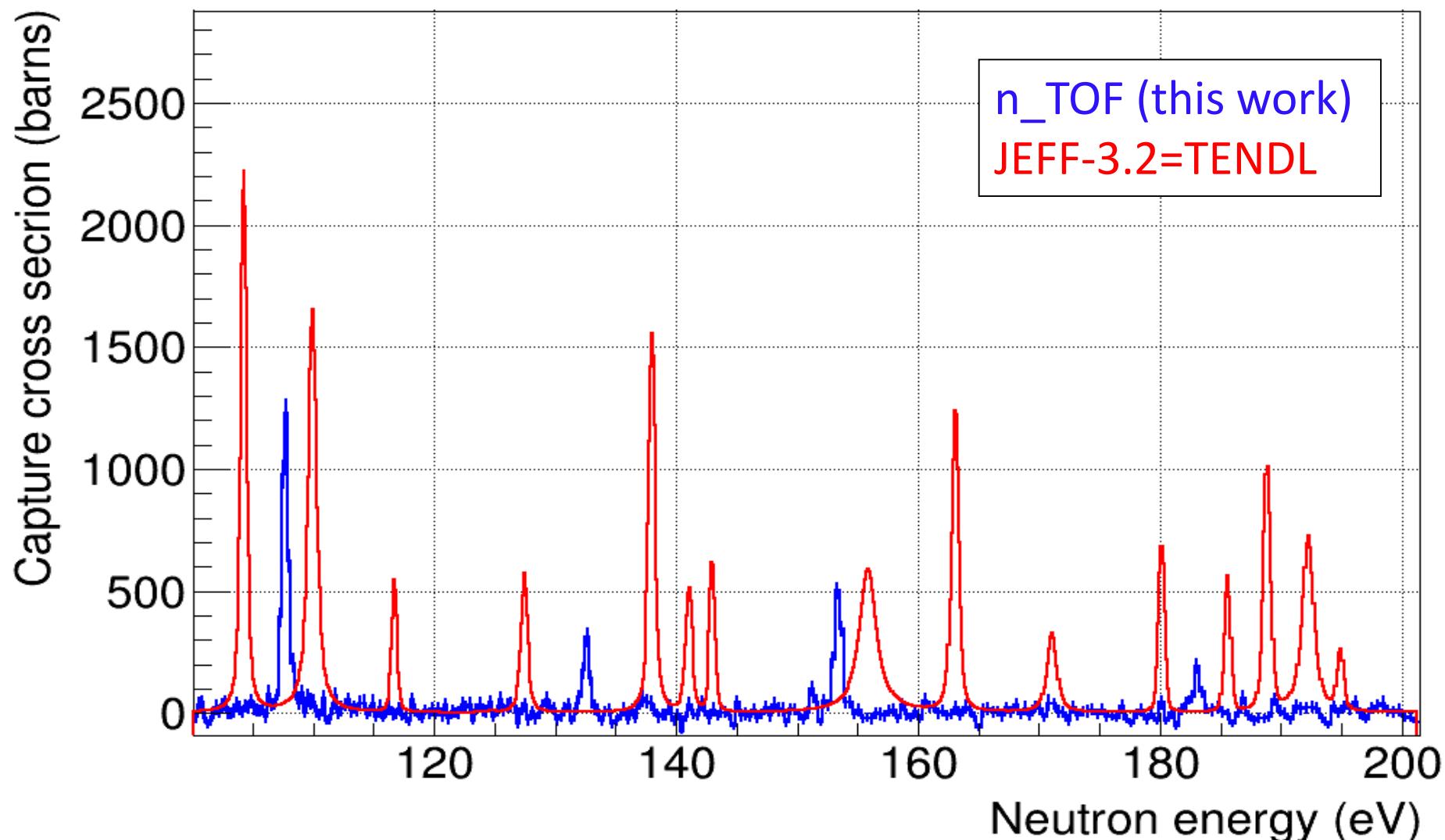


PAUL SCHERRER INSTITUT
PSI

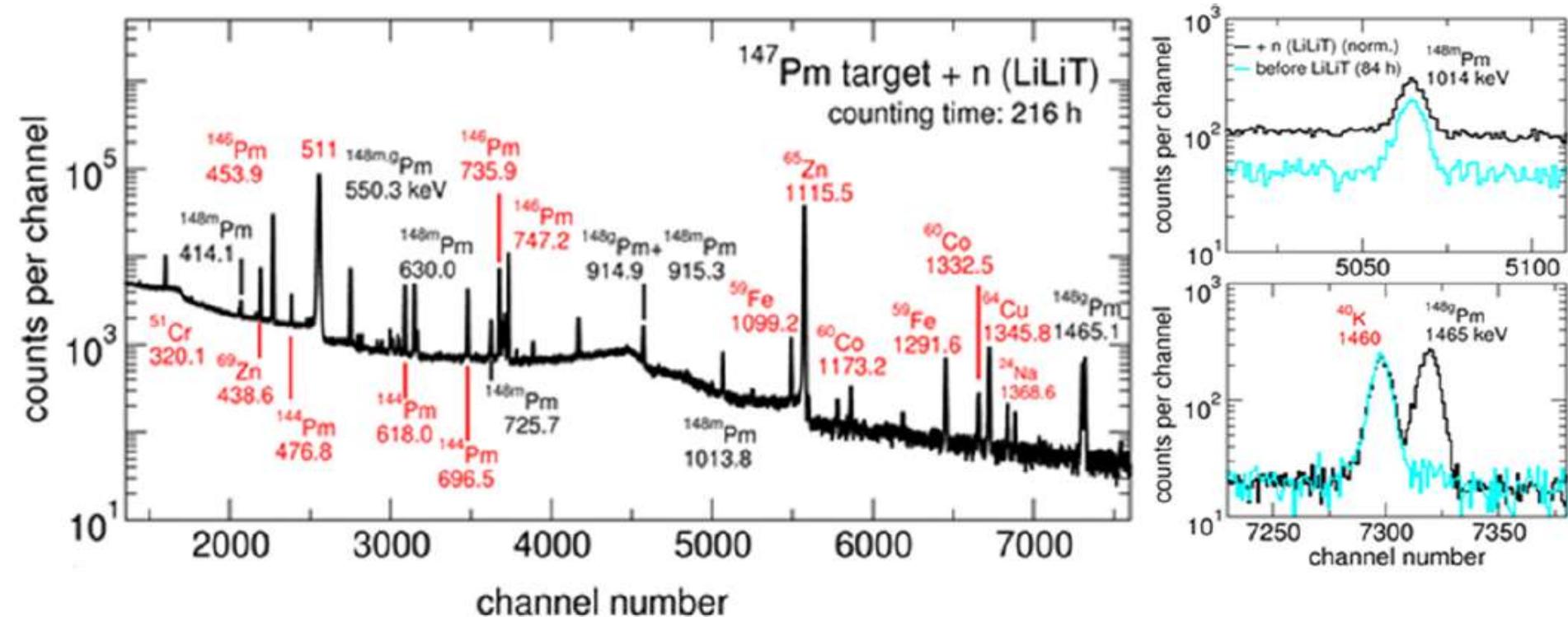
NEUTRONS
FOR SOCIETY

UNIVERSIDAD DE SEVILLA
Soreq Nuclear Research Center

Results for $^{171}\text{Tm}(n,\gamma)$ measured at n_TOF-EAR1



$^{147}\text{Pm}(n,\gamma)^{148g,m}\text{Pm}$ MACS at SARAFLiLiT



$^{147}\text{Pm}(n,\gamma)^{148g}\text{Pm}$

$^{147}\text{Pm}(\text{n},\gamma)^{148\text{m}}\text{Pm}$

$^{147}\text{Pm}(n,\gamma)^{148\text{g,m}}\text{Pm}$

469(50) mb MACS at 30 keV

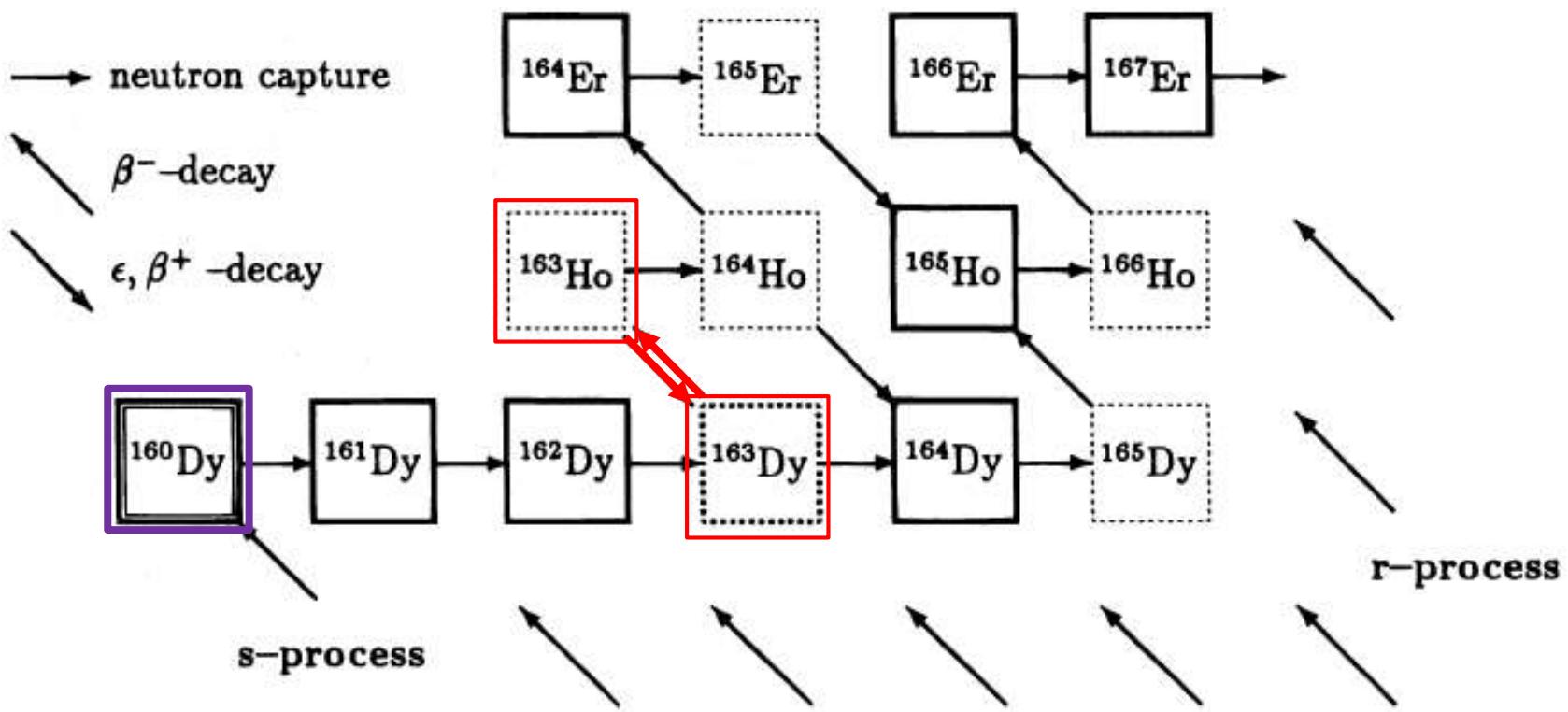
357(27) mb MACS at 30 keV

826(57) mb MACS at 30 keV

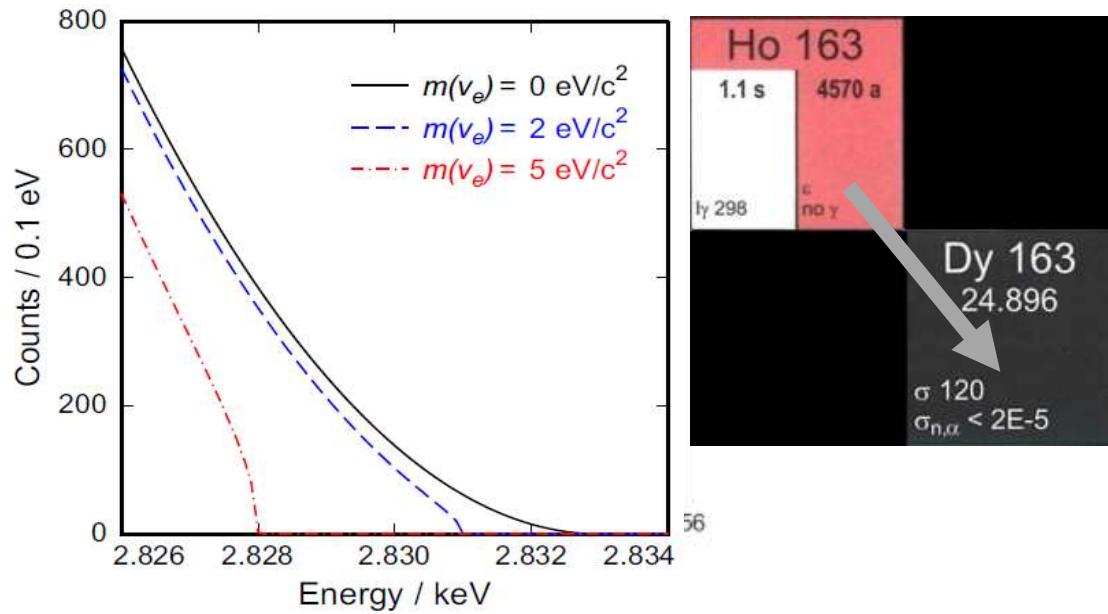
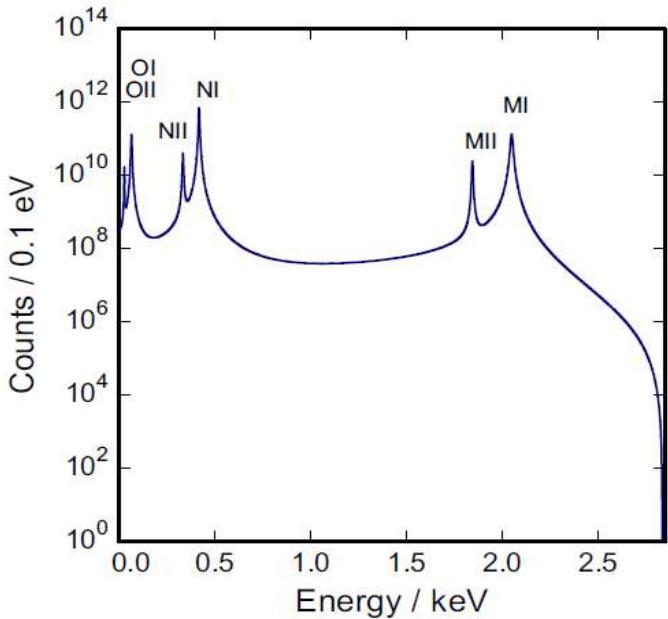
^{163}Ho as part of branching at A=163

^{163}Dy stable, but β^- (47 d) to ^{163}Ho when fully ionized (stellar plasma)

Equilibrium abundance of ^{163}Ho (from ^{163}Dy) produces ^{164}Ho via (n,γ) .
The equilibrium abundance of ^{163}Ho is determined by the temperature
and electron density in the star.



^{163}Ho for Neutrino Mass Measurements



L. Gastaldo et al. Eur Phys J Spec Top 2017;226:1623.

^{163}Ho for Neutrino Mass Measurements



DFG

Deutsche
Forschungsgemeinschaft

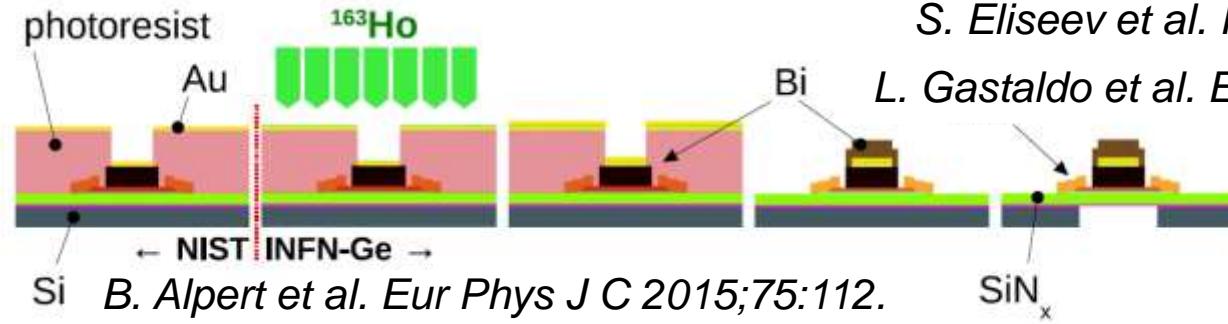
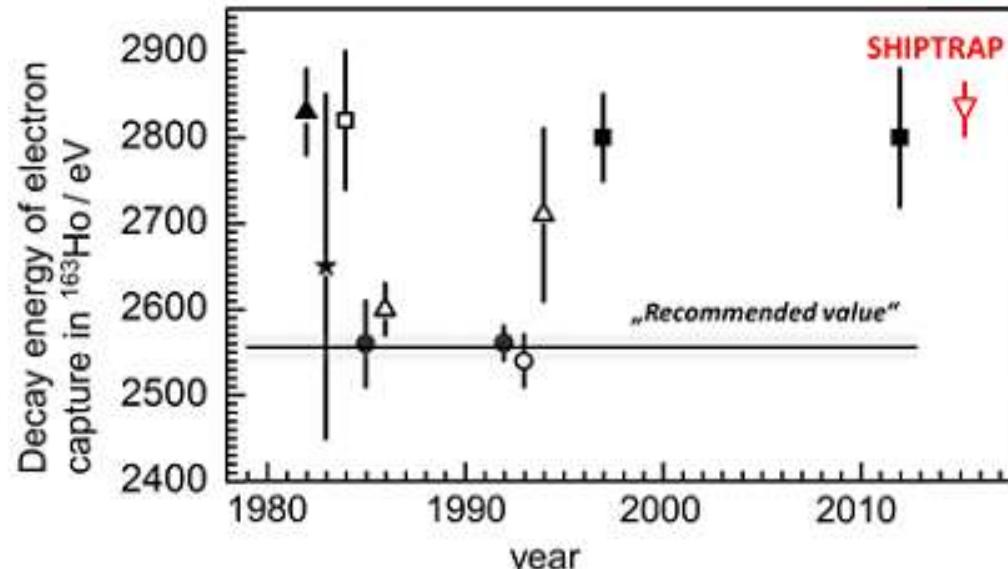
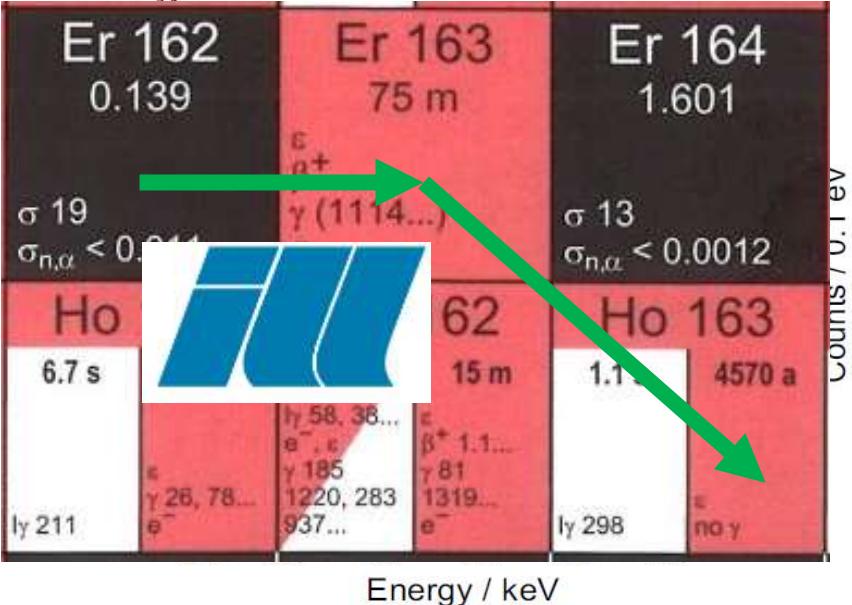


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u^b

UNIVERSITÄT
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S. Eliseev et al. Phys Rev Lett 2015;115:062501.

L. Gastaldo et al. Eur Phys J Spec Top 2017;226:1623.

HOLMES



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and Everything



The gap in Mendeleev's table



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- International Year
of the Periodic Table
of Chemical Elements

The figure is a periodic table where each element's color corresponds to its experimental value uncertainty. A legend on the left provides the key:

- Dark Green:** Uncertainty < 0.1 μeV
- Light Green:** Uncertainty 0.1 - 1.0 μeV
- Yellow:** Uncertainty 1 - 10 μeV
- Orange:** Uncertainty 10 - 100 μeV
- Red:** Uncertainty 0.1 - 1 meV
- White:** Uncertainty 10 - 200 meV
- Text in Red:** No experimental value

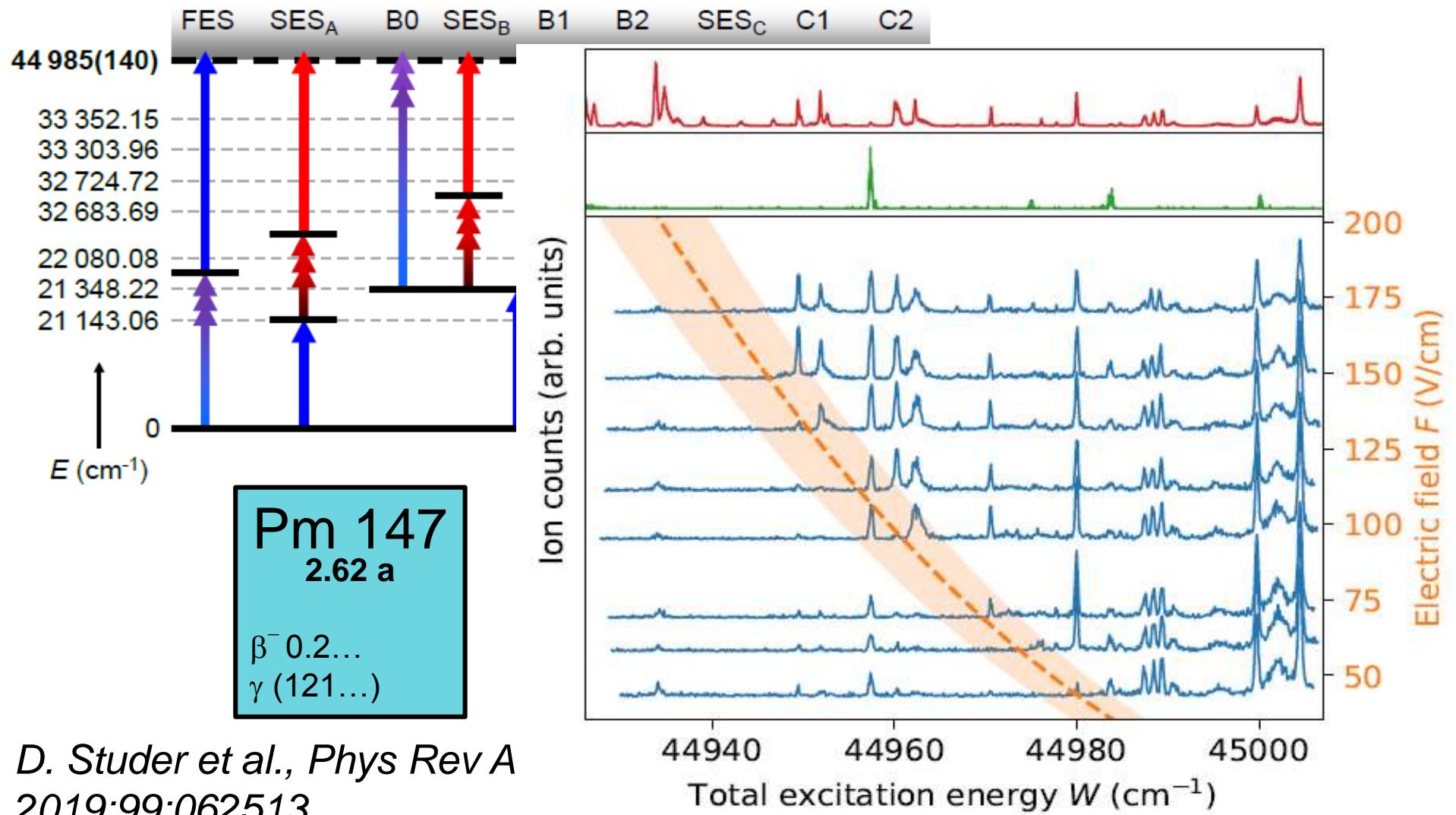
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of Chemical Elements

H		He															
Li	Be																
Na	Mg																
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cp	Nh	Fl	Mc	Lv	Ts	Og

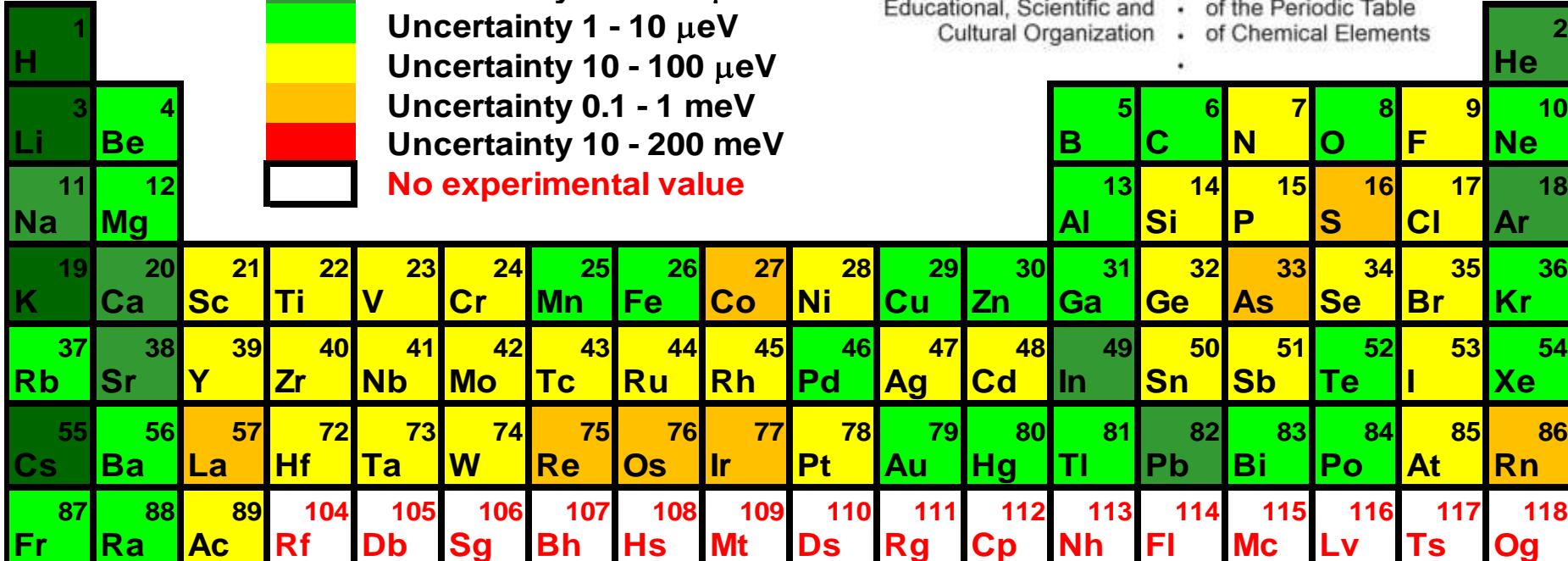
58	59	60	61	62	63	64	65	66	67	68	69	70	71
Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
90	91	92	93	94	95	96	97	98	99	100	101	102	103
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

Resonance ionisation spectroscopy of Pm I



D. Studer et al., Phys Rev A
2019;99:062513.

Filling the gap in Mendeleev's table



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of Chemical Elements

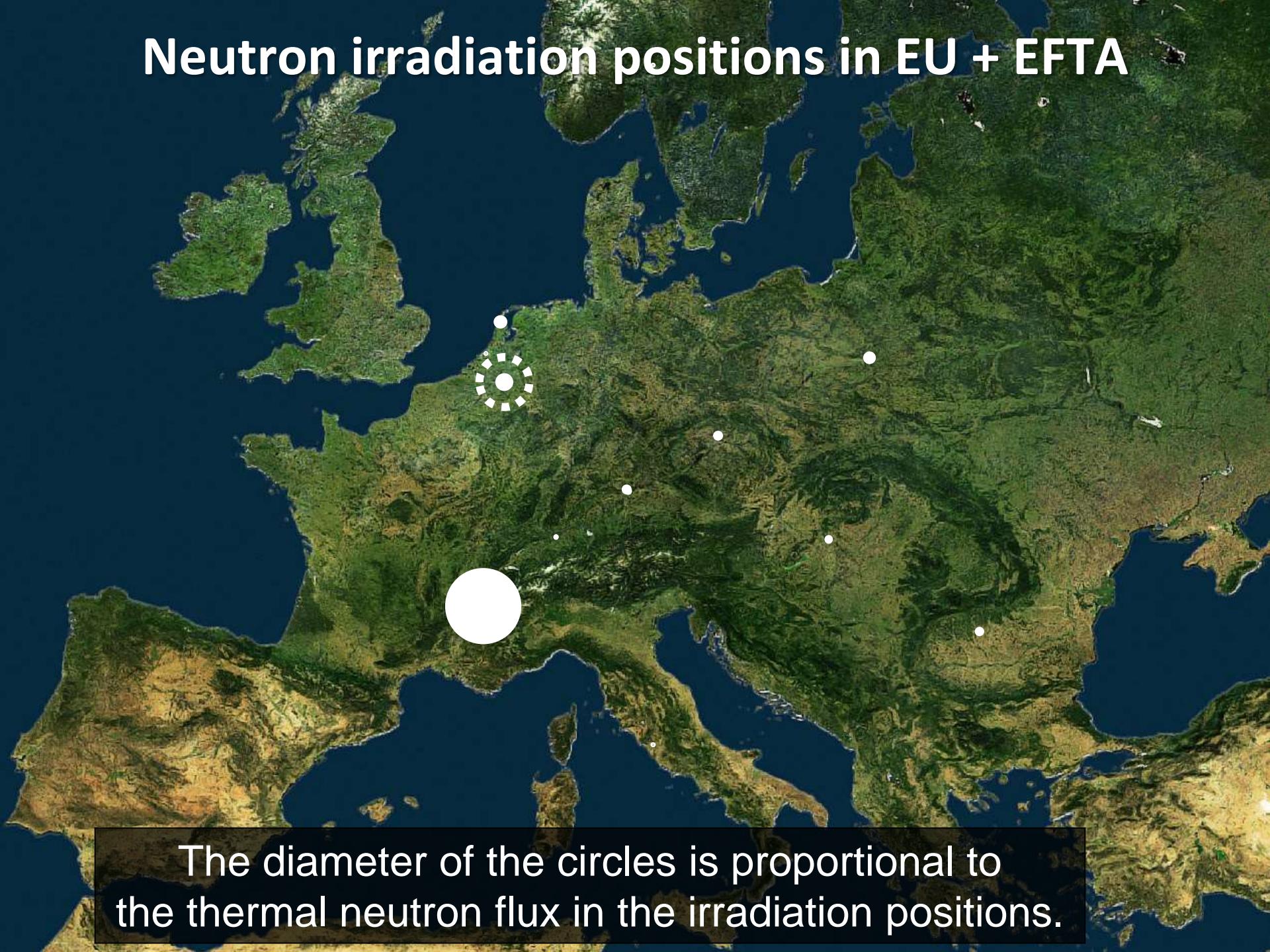
58	59	60	61	62	63	64	65	66	67	68	69	70	71
Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
90	91	92	93	94	95	96	97	98	99	100	101	102	103
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

The highest neutron flux in the European Union

$1.5 \cdot 10^{15} \text{ n.cm}^{-2}\text{s}^{-1}$

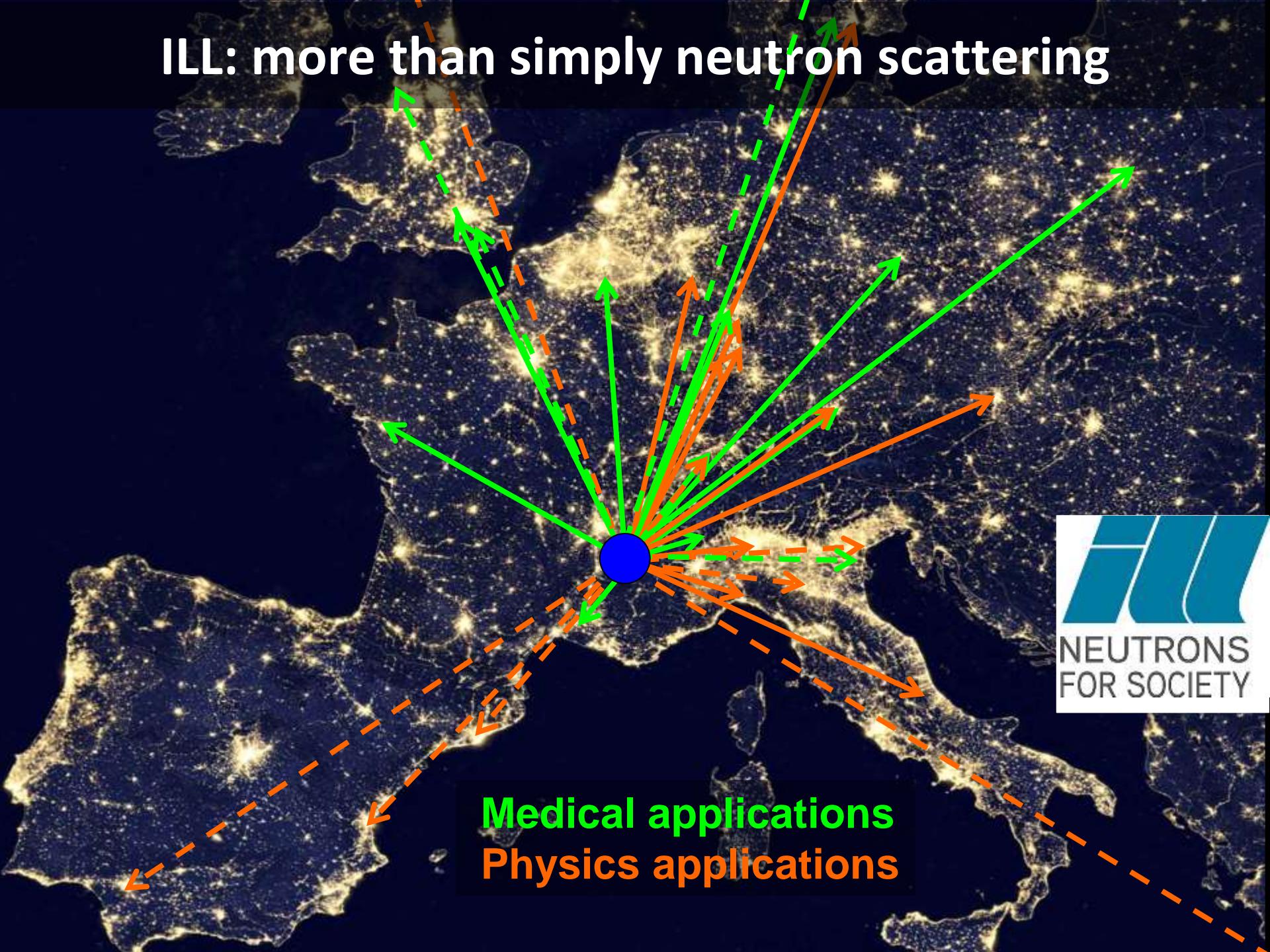


Neutron irradiation positions in EU + EFTA



The diameter of the circles is proportional to the thermal neutron flux in the irradiation positions.

ILL: more than simply neutron scattering



Medical applications
Physics applications

