Life, the Universe and Everything

Ulli Köster

12 November 2019

NEUTRONS FOR SOCIETY

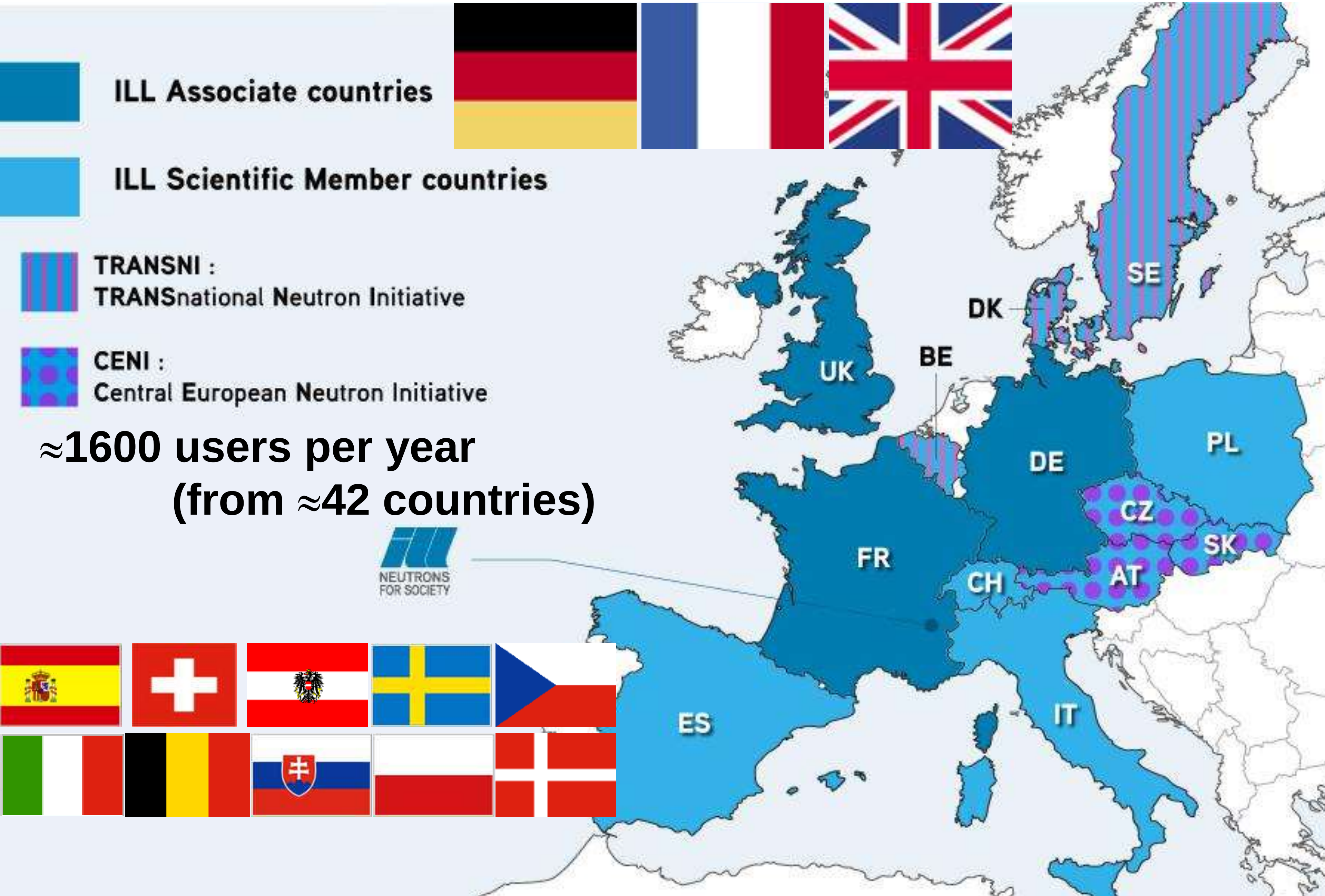
UNIVERSITÉ Grenoble Alpes

Institut Max von Laue – Paul Langevin

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

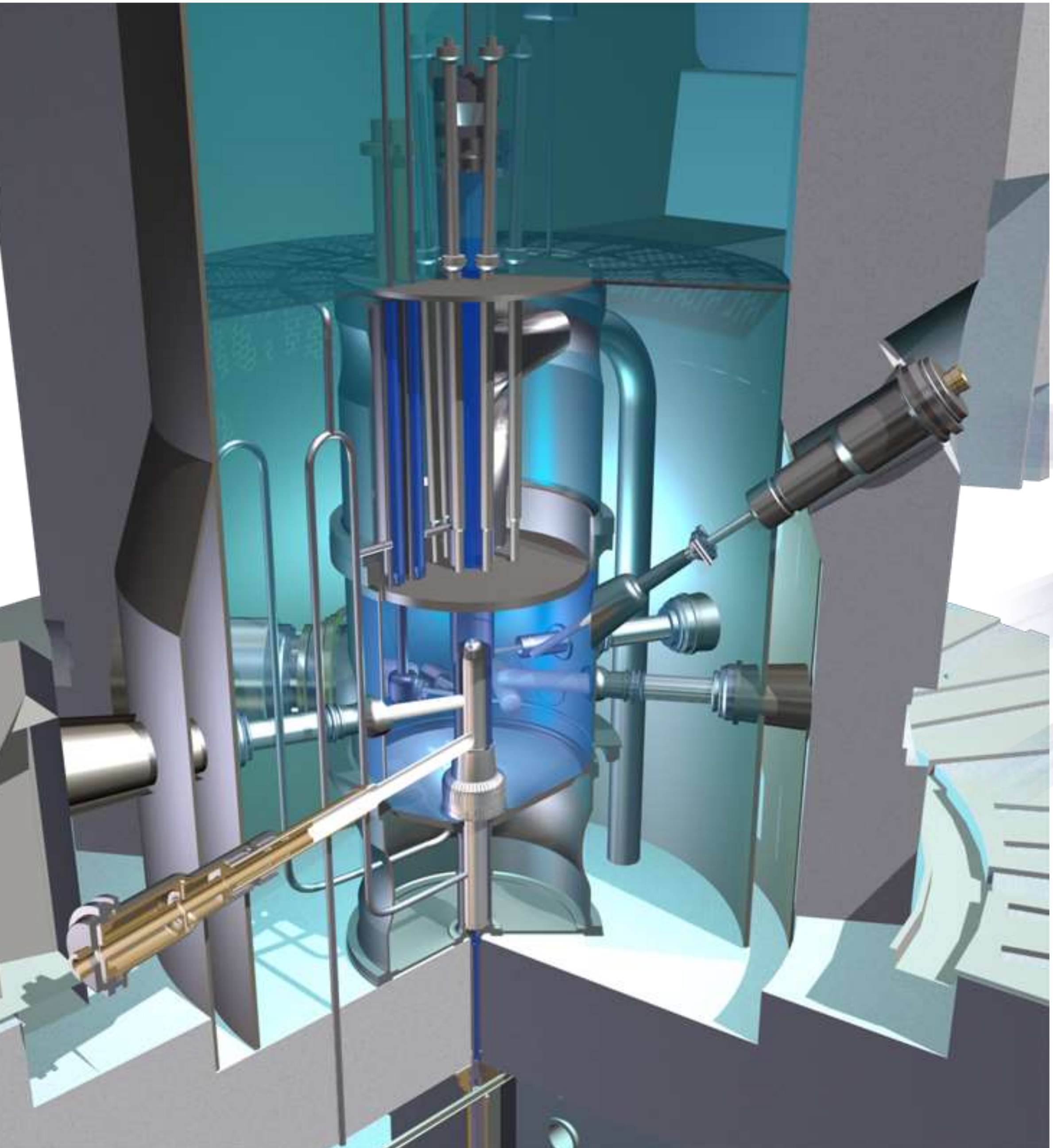
Paul Langevin
(1872-1946)
Langevin dynamics
Magnetism, etc.

An international user facility: ≈13 member states



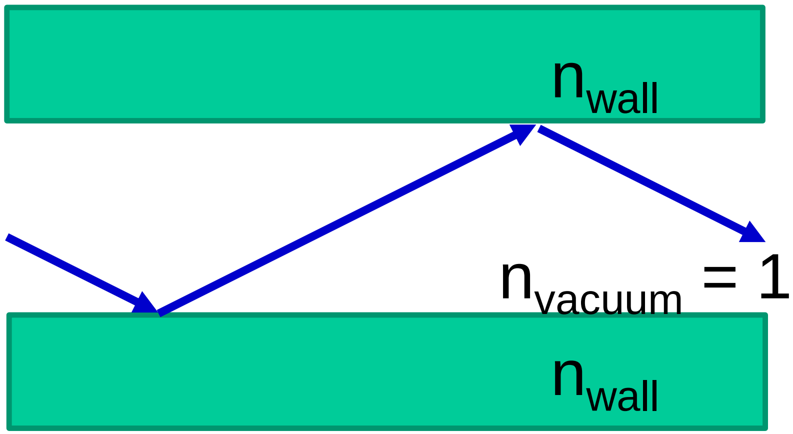
≈1600 users per year
(from ≈42 countries)

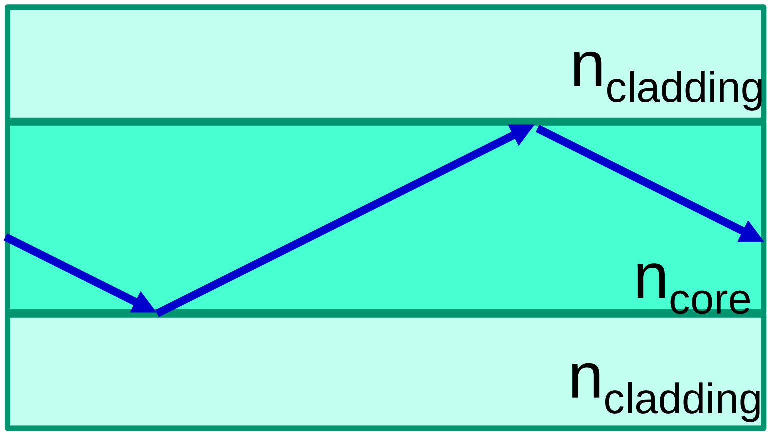
The ILL Reactor



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

Neutron guides vs. light guides

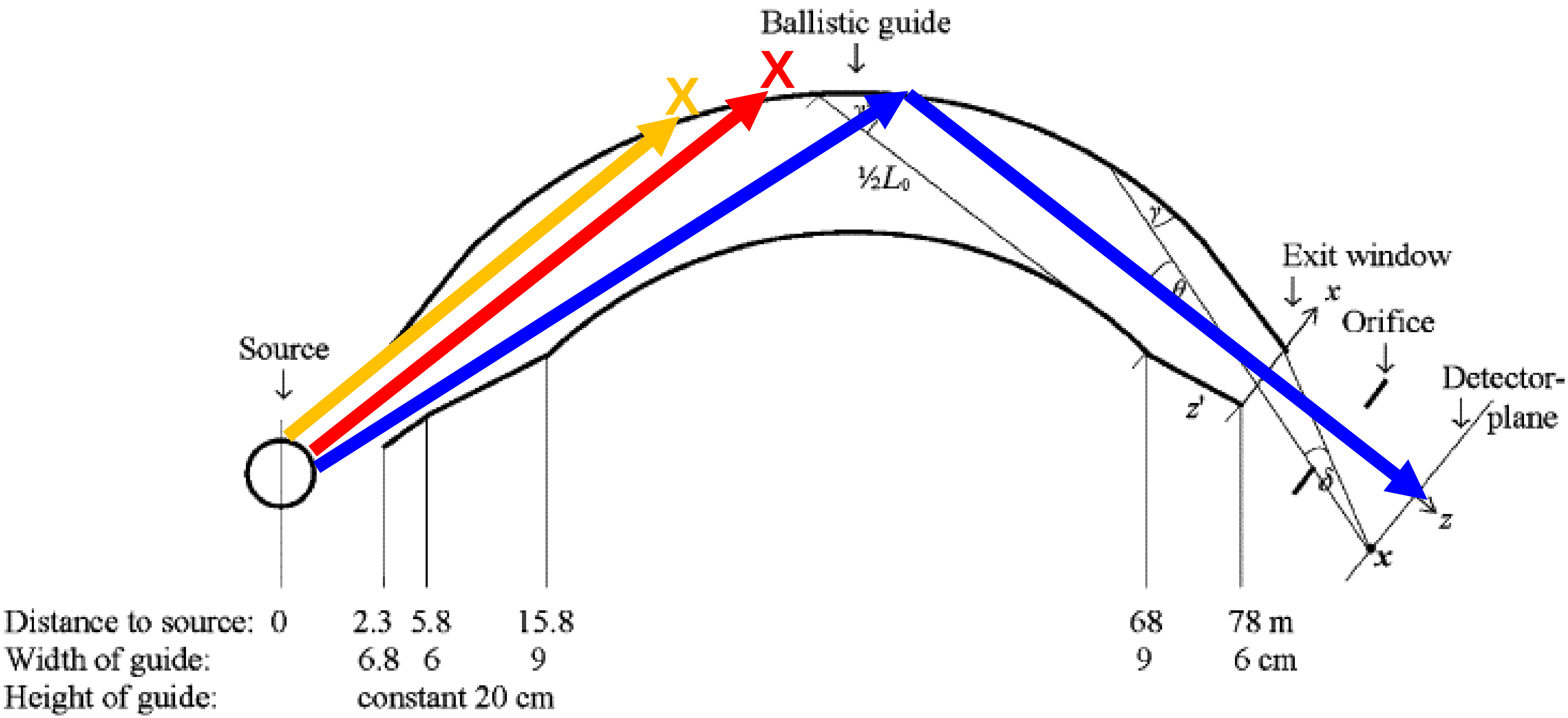




Neutron guide:
$n_{wall} < n_{vacuum} = 1$

Light guide:
$n_{core} > n_{cladding} > 1$

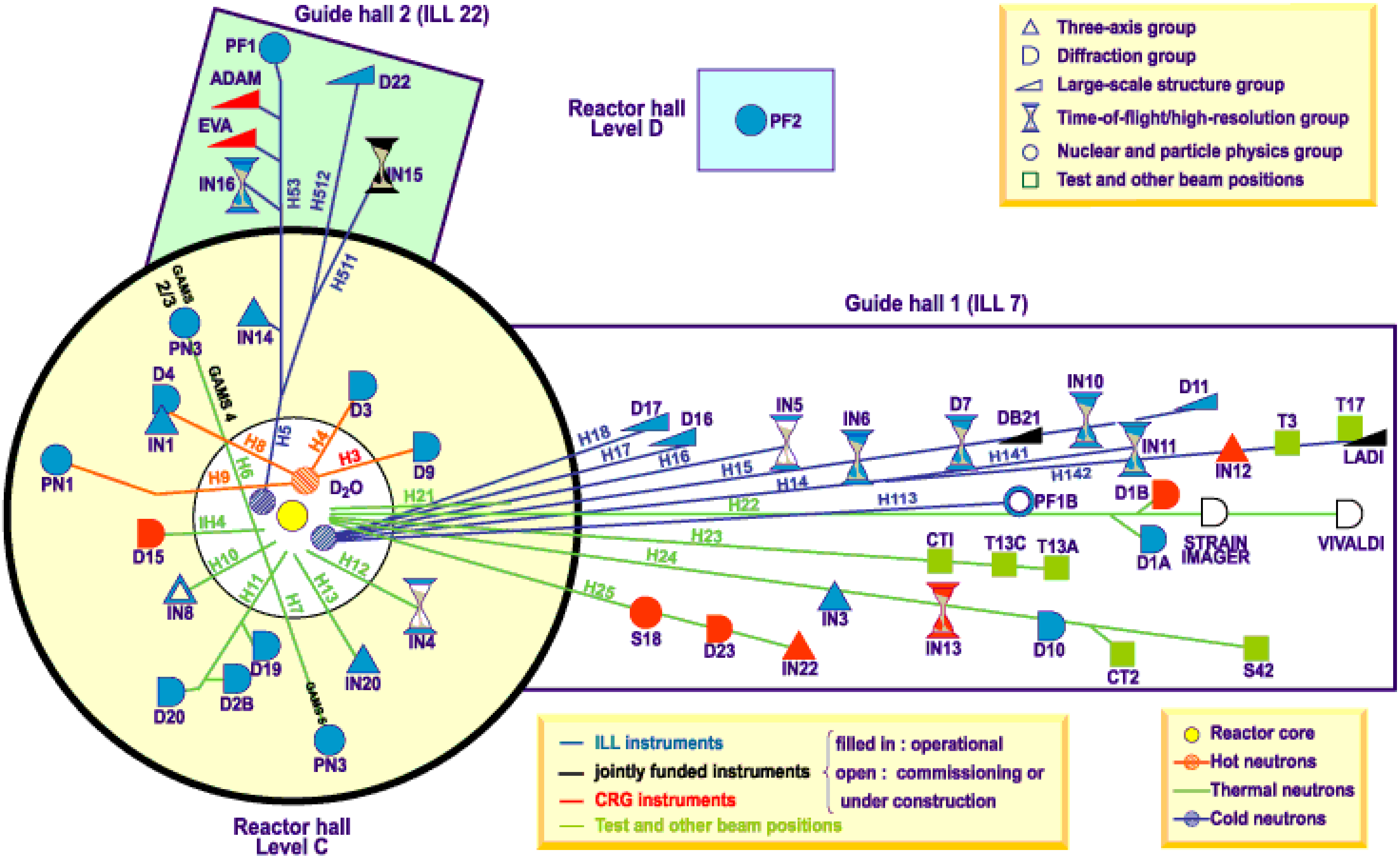
Guided neutron beams are "clean"



Fast neutrons and gamma rays are not transported.

H. Abele et al. Nucl. Instr. Meth. A562 (2006) 407.

ILL instruments



>40 instruments running simultaneously for 150-200 days per year

Neutron beams with up to $2{\cdot}10^{10}$ $n.cm^{-2}s^{-1}$ flux and up to 320 cm^2 area

Why neutrons ?

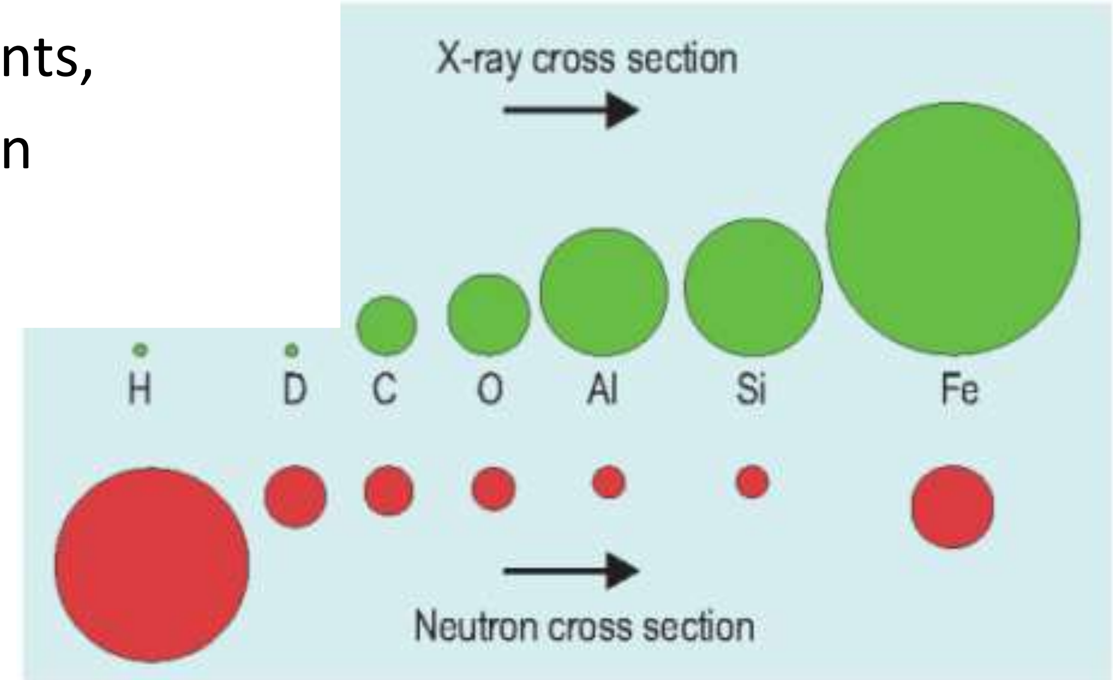
- wavelength of thermal neutrons ≈ interatomic distances (sol., liq.)
  ⇒ good for scattering

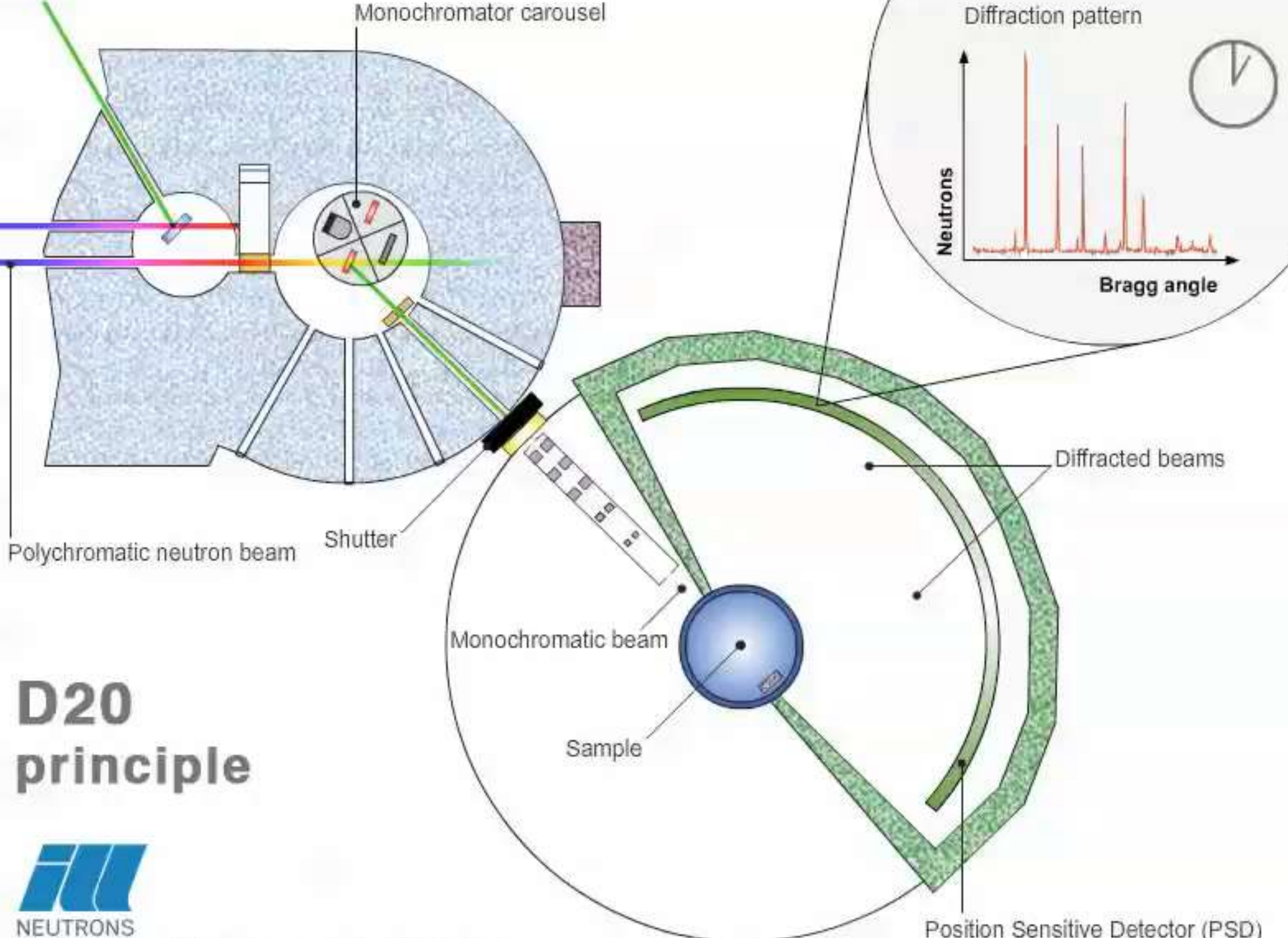
- neutron mass ≈ atom mass
  ⇒ large momentum transfer possible

- weakly interacting ⇒ good penetration (thicker samples...)

- good to "see" light elements,
  in particular hydrogen

- magnetic moment
  ⇒ magnetic scattering

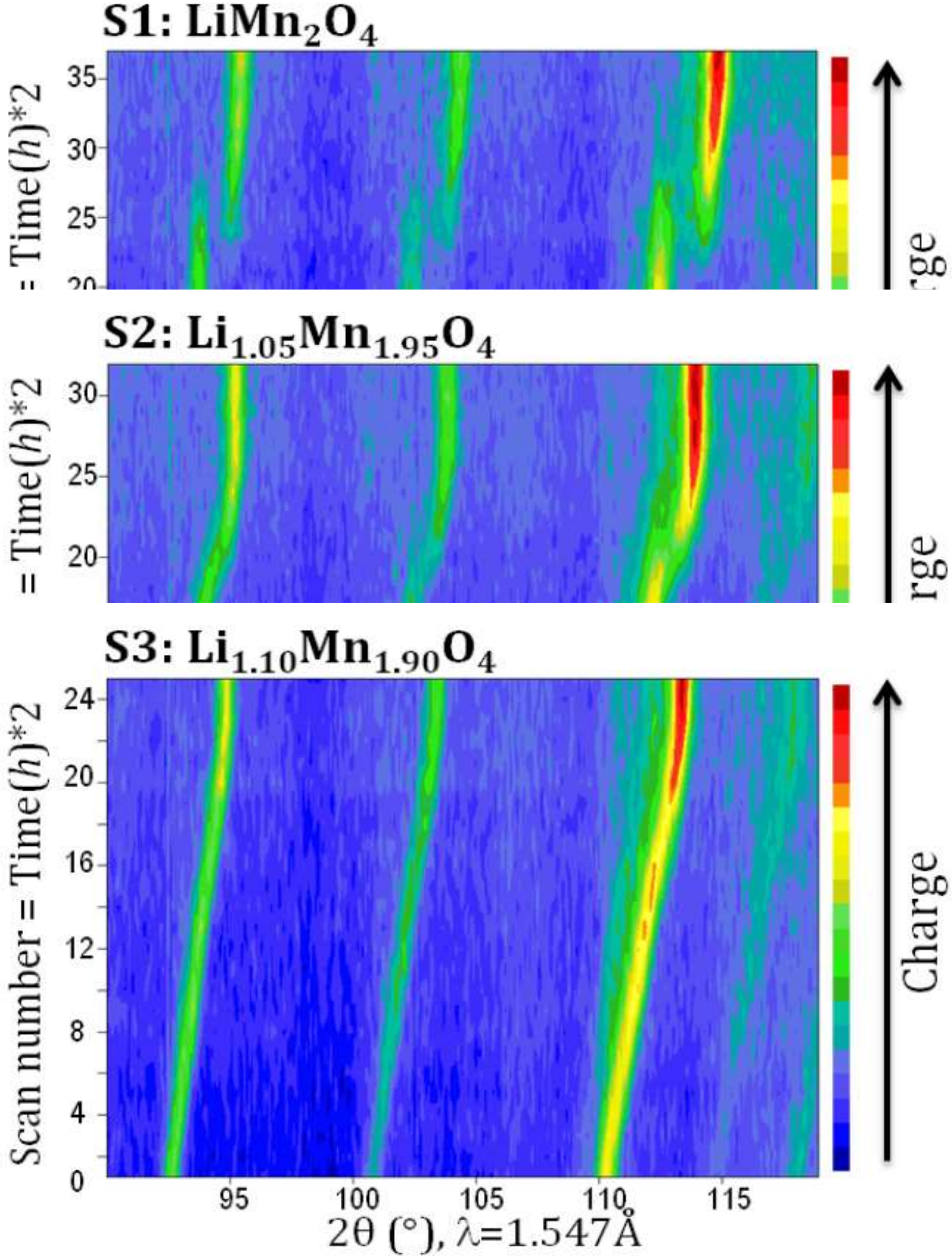




D20 principle

NEUTRONS FOR SOCIETY

In operando study of lithium batteries

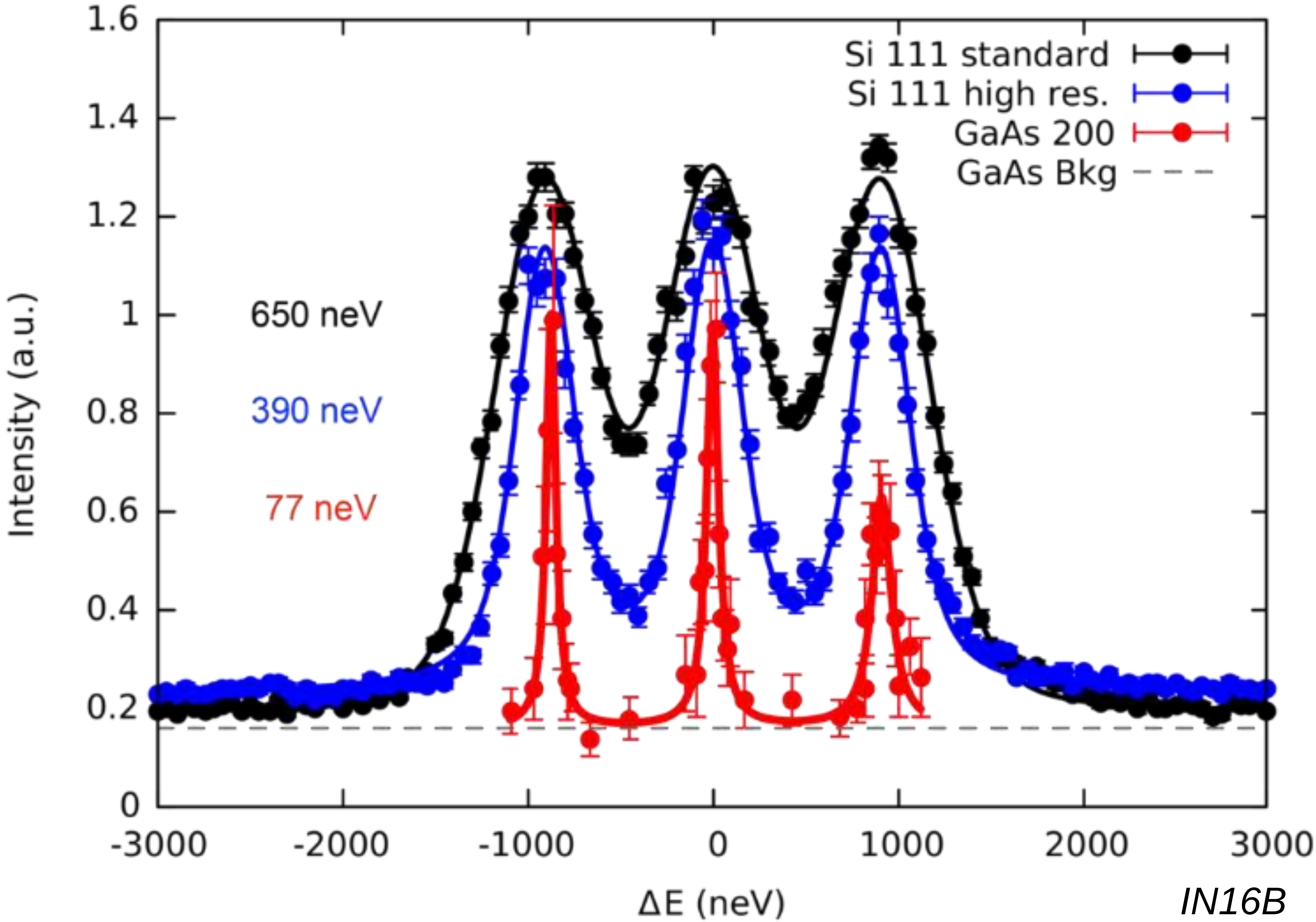


Also:

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

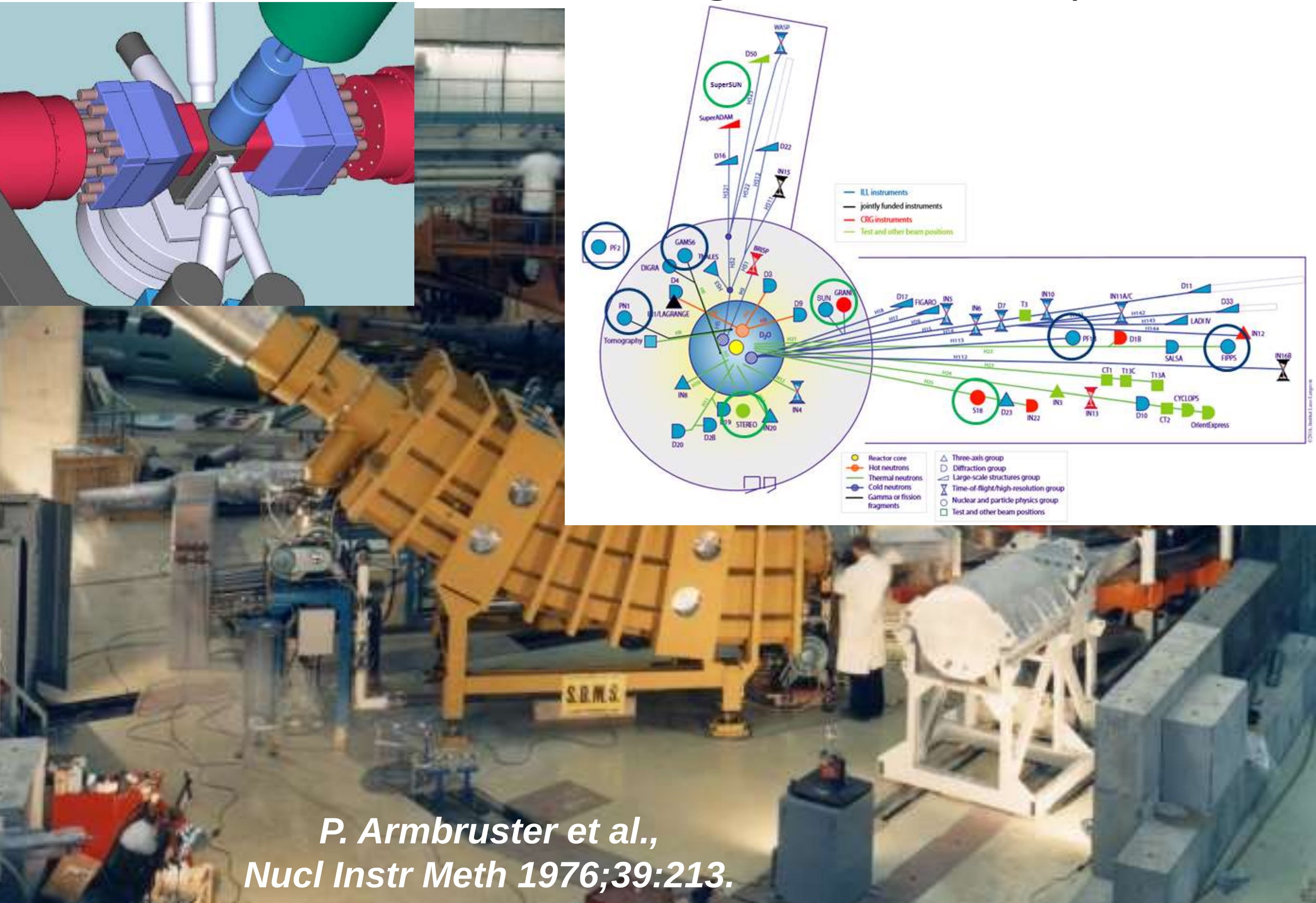
M. Bianchini et al.
JPC C 2014;118:25947.

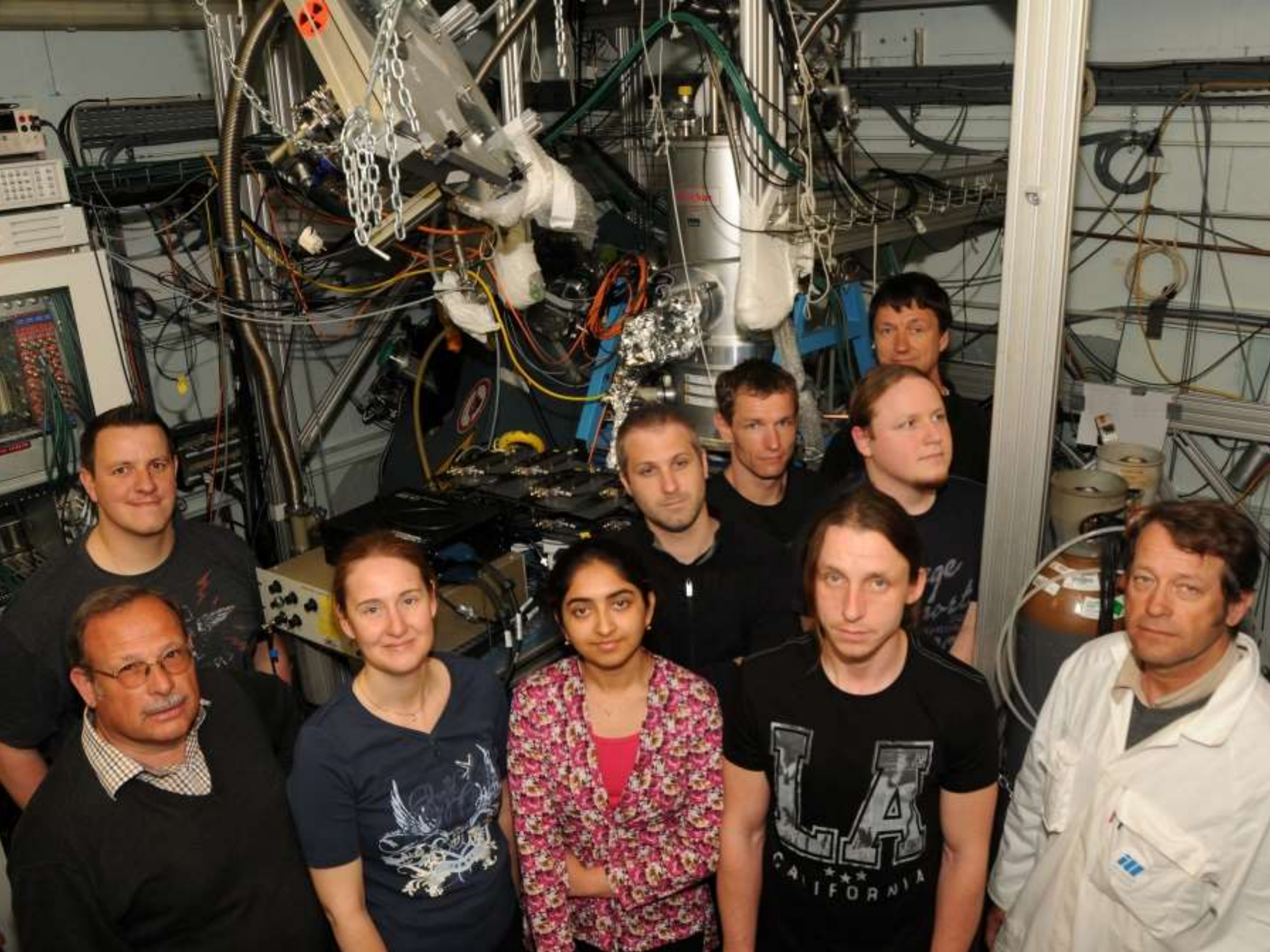
High resolution inelastic neutron spectroscopy



IN16B

The LOHENGRIN fission fragment recoil separator




LA
CALIFORNIA

Life, the Universe and Everything

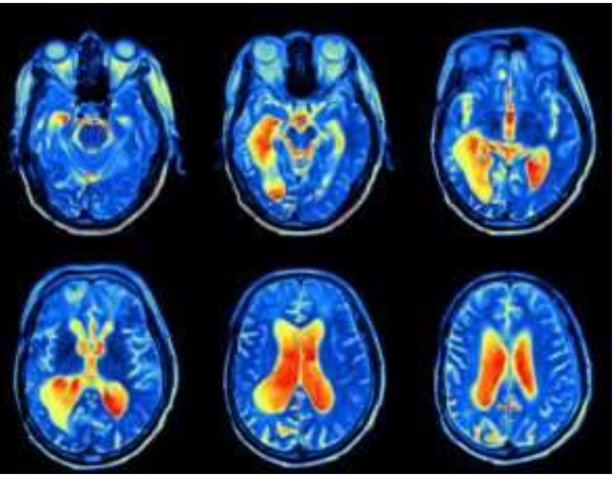
Structural imaging versus functional imaging

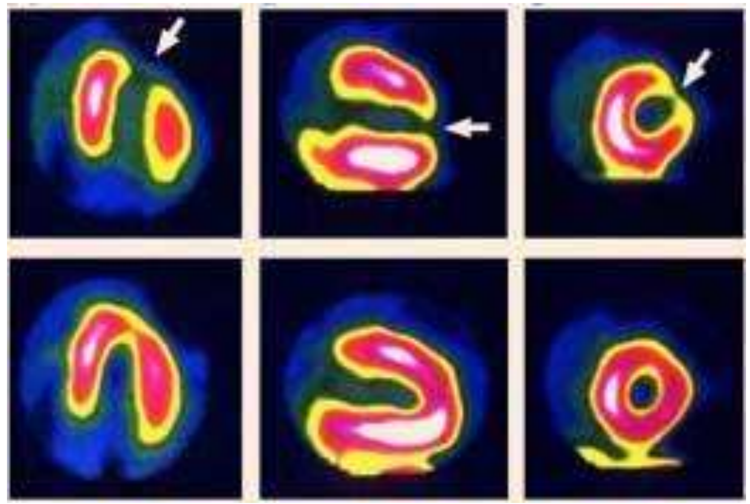
molecular imaging

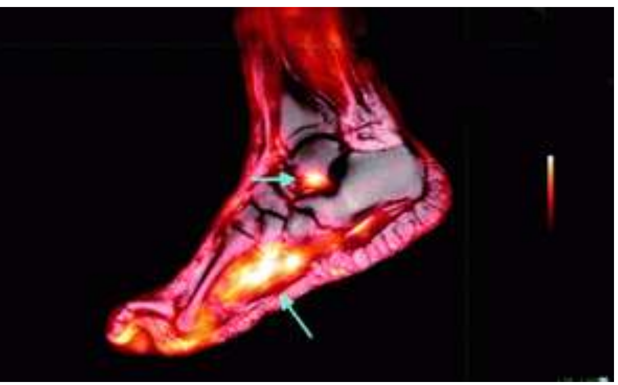
Radiology

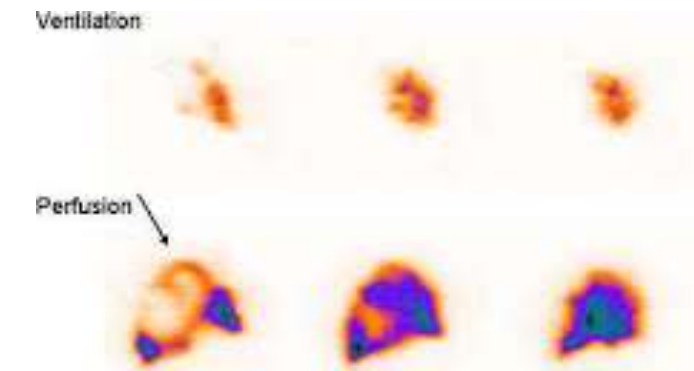
Nuclear Medicine

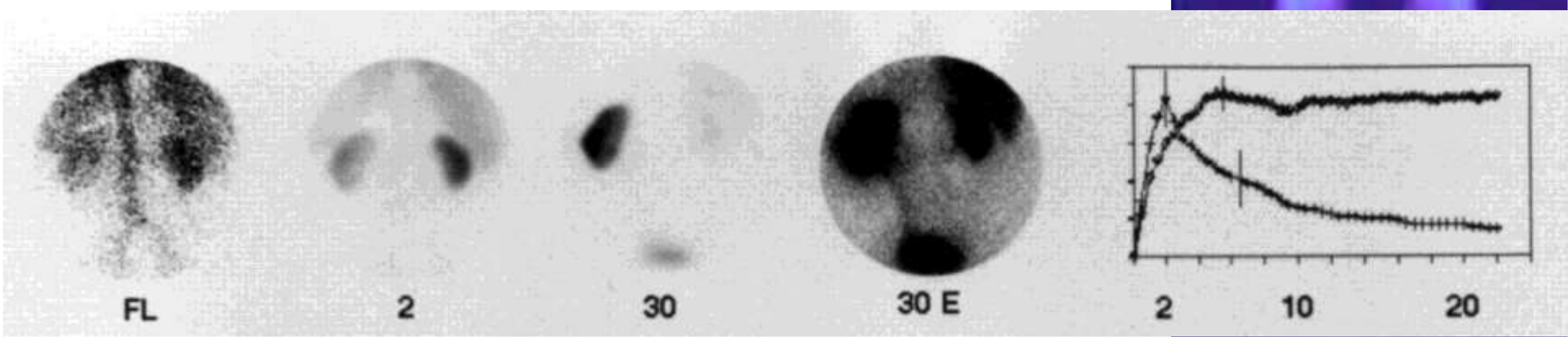
Molecular imaging











What is Theranostics ?

Therapy based on dia**gnostics**

personalized medicine, stratified medicine

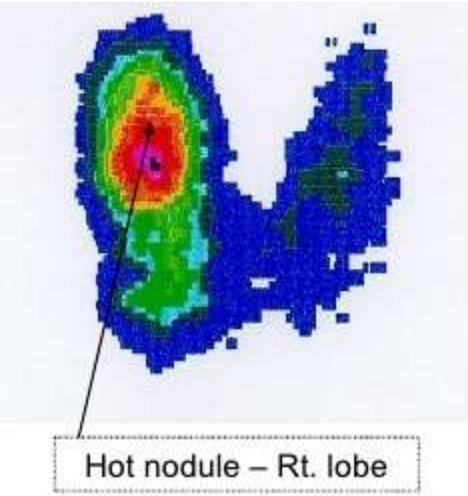
Saul Hertz (Massachusetts General Hospital):

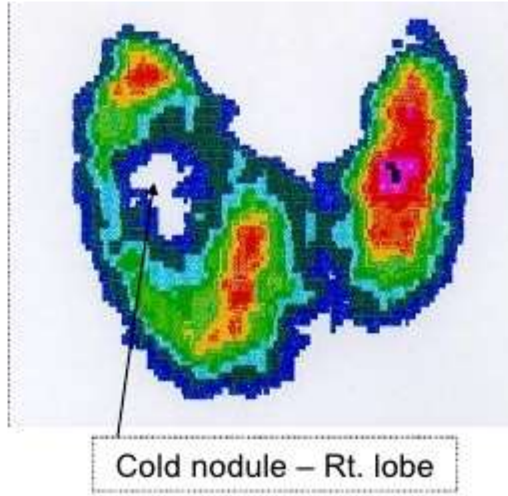
1936 proposes iodine radiotracer

1937 rabbit studies with ^{128}I

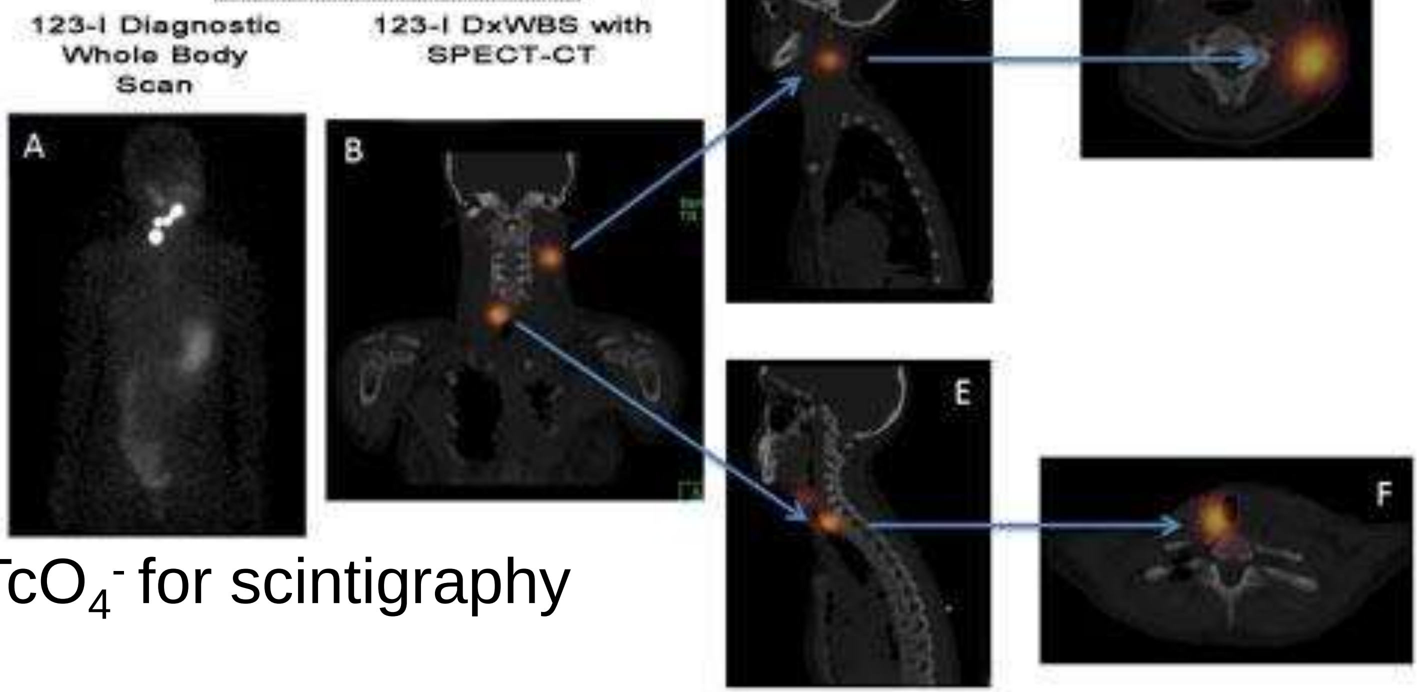
1941 clinical therapy studies with ^{130}I

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…

$^{123}I^-$, $^{131}I^-$ or $^{99m}TcO_4^-$ for scintigraphy
$^{131}I^-$ for therapy

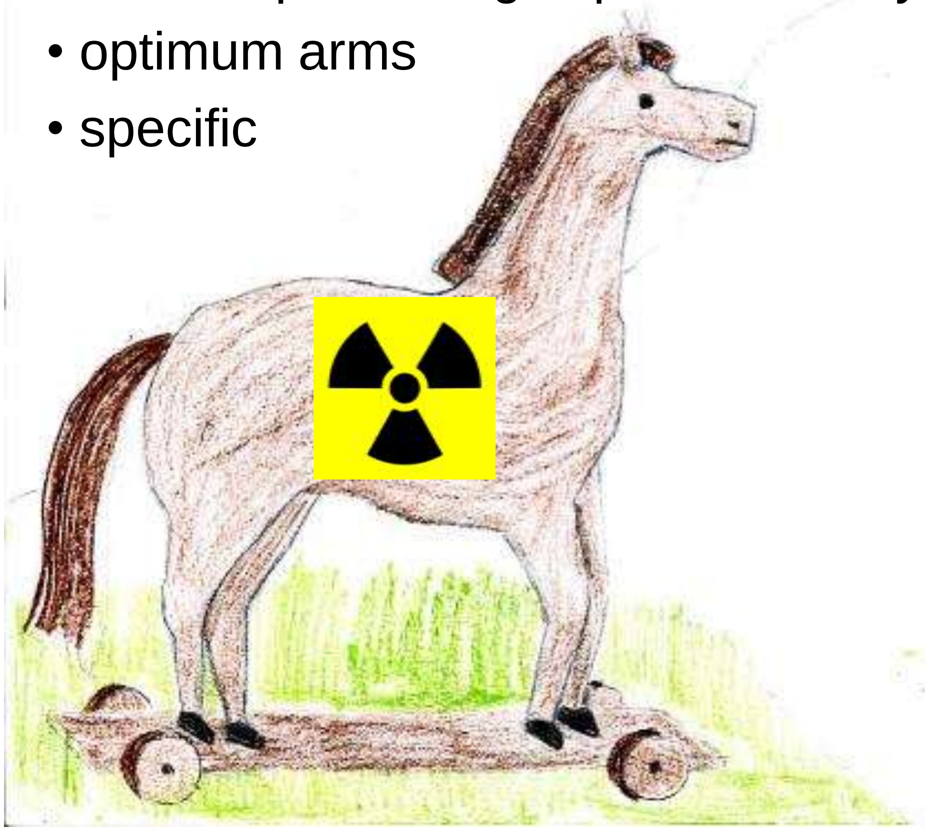
(Papillary) thyroid cancer has the **highest survival** of all malignant cancers!

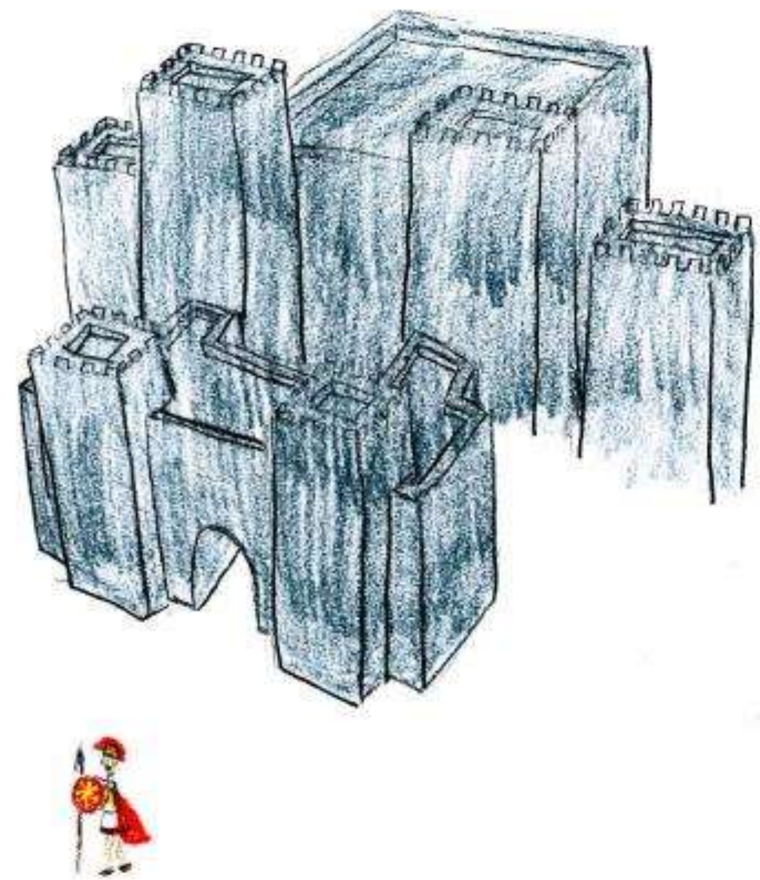
How can one treat such patients?

Learning from history

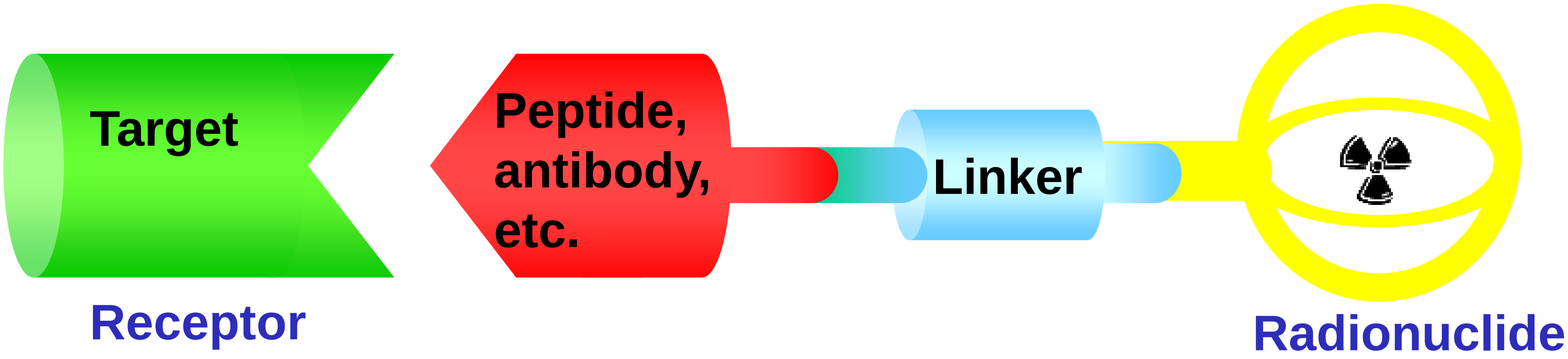
The principle of targeted therapies

- “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



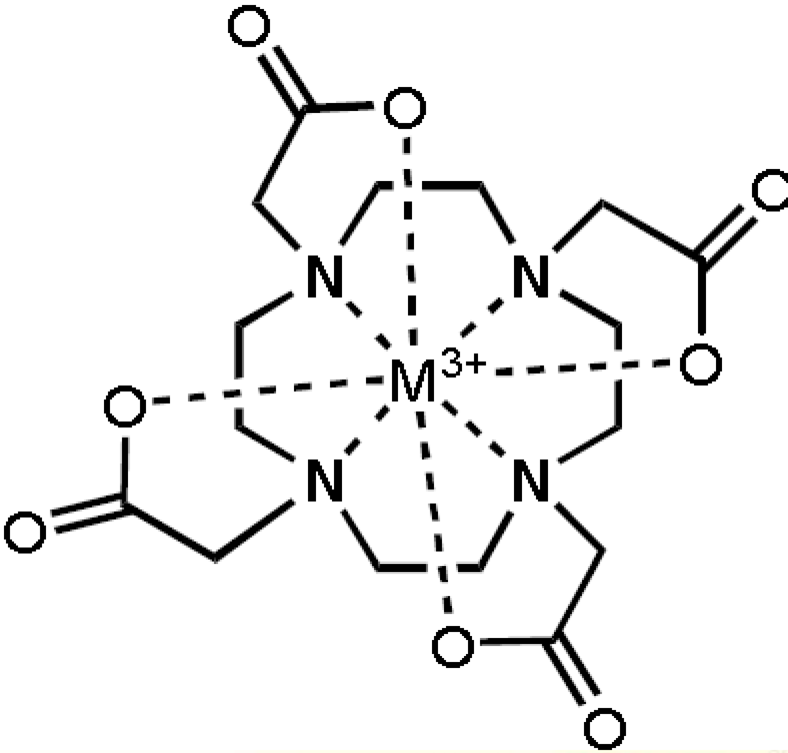
Immunology
Structural biology

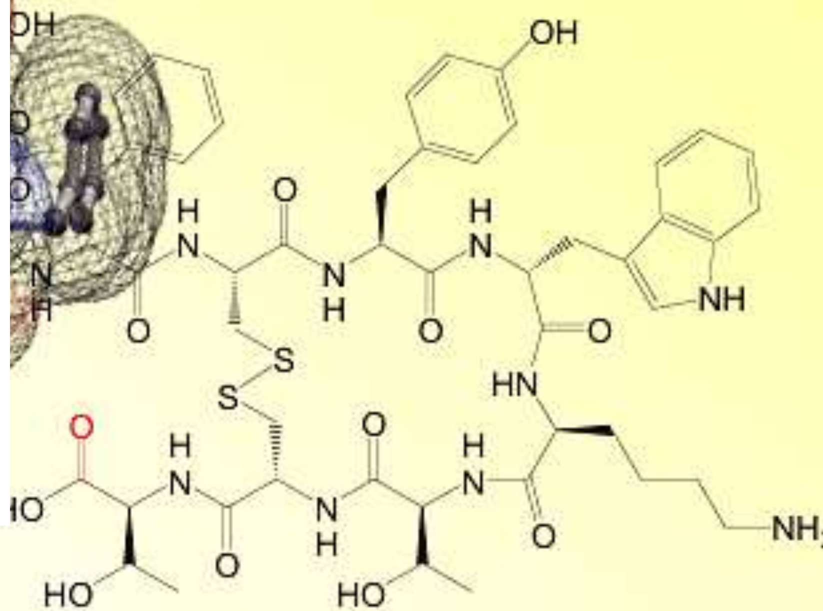
Coordination chemistry

Nuclear physics and radiochemistry

Nuclear medicine and medical physics

Structural Formula of DOTA-TOC/TATE





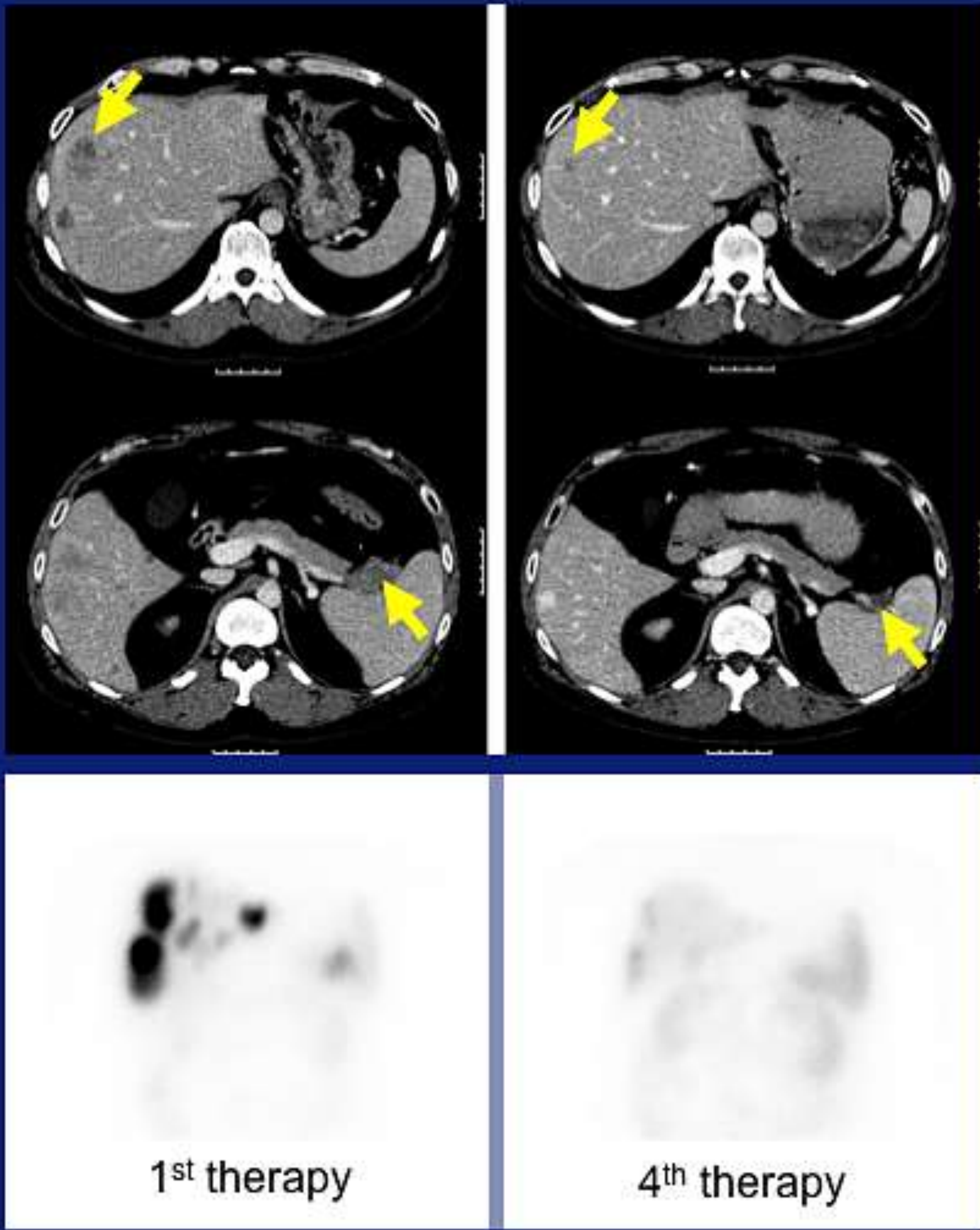
DOTA-TATE

1,4,7,10-tetraazacyclododecantetraacetate

^{111}In ^{90}Y
^{67}Ga ^{177}Lu
^{68}Ga ^{213}Bi

IC_{50} (Y^{III}) = 1.6 ± 0.4 nM

Helmut Maecke, EANM-2007.



Male

36 years of age

Small cell pancreatic neuroendocrine tumour

Liver metastases

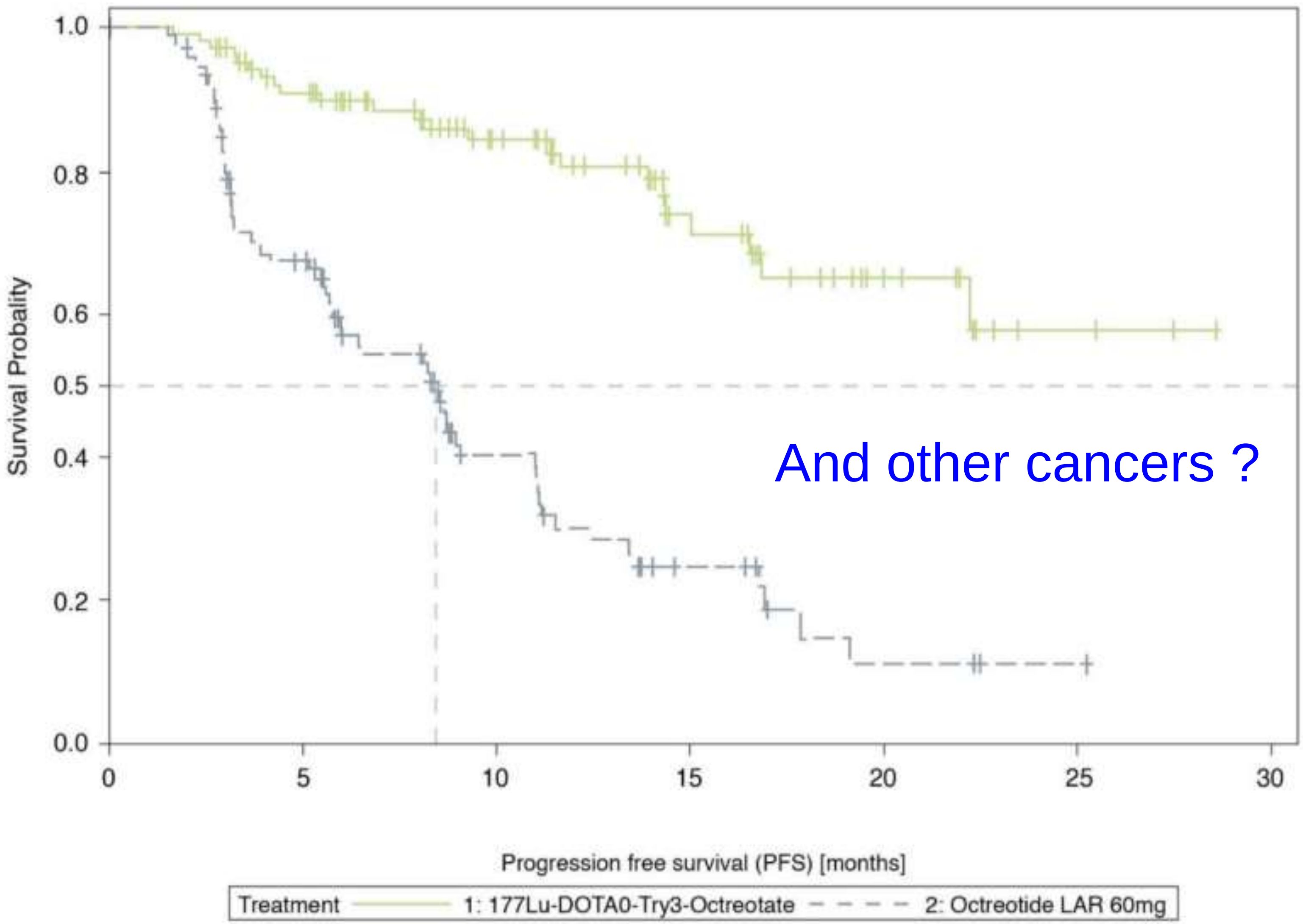
Ki-67 index 10-15% (liver biopsy)

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

Partial remission

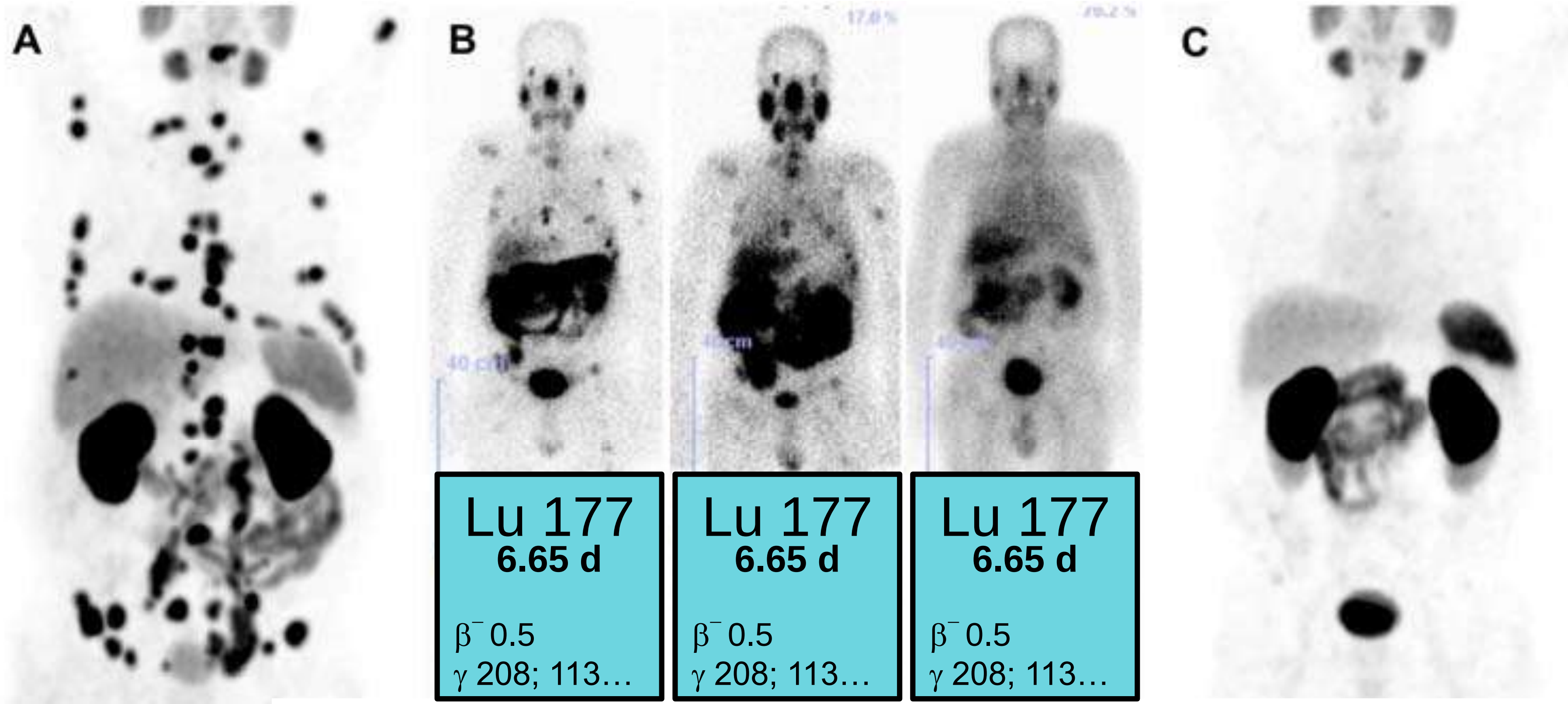
Roelf Valkema, EANM-2008.

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



J. Strosberg et al., N Engl J Med 2017;376:125.

^{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

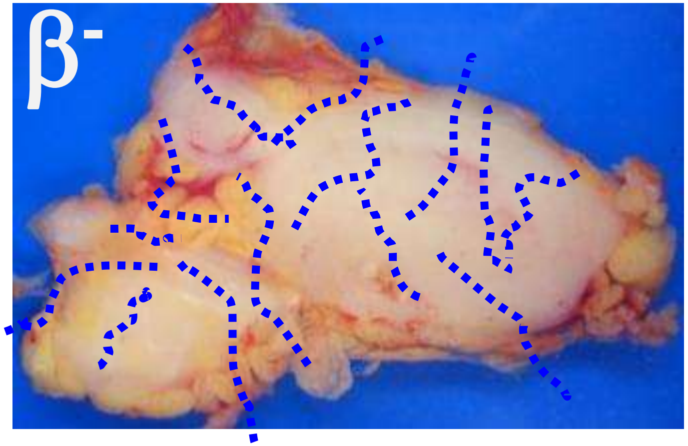
Institut Laue-Langevin 2018:

≈ **1600** scientific users came to ILL

≈ **4000** patients got ^{177}Lu from ILL

Radionuclides for Radioligand Therapy

Radio-nuclide	Half-life	E mean (keV)	Eγ (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



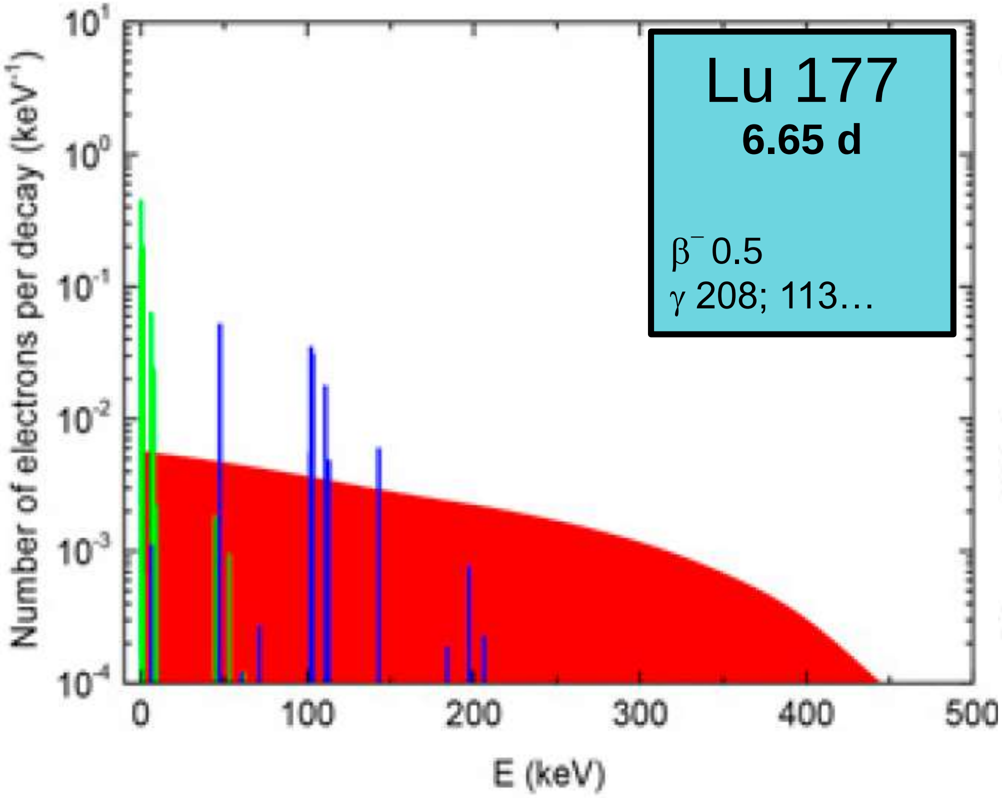
cross-fire

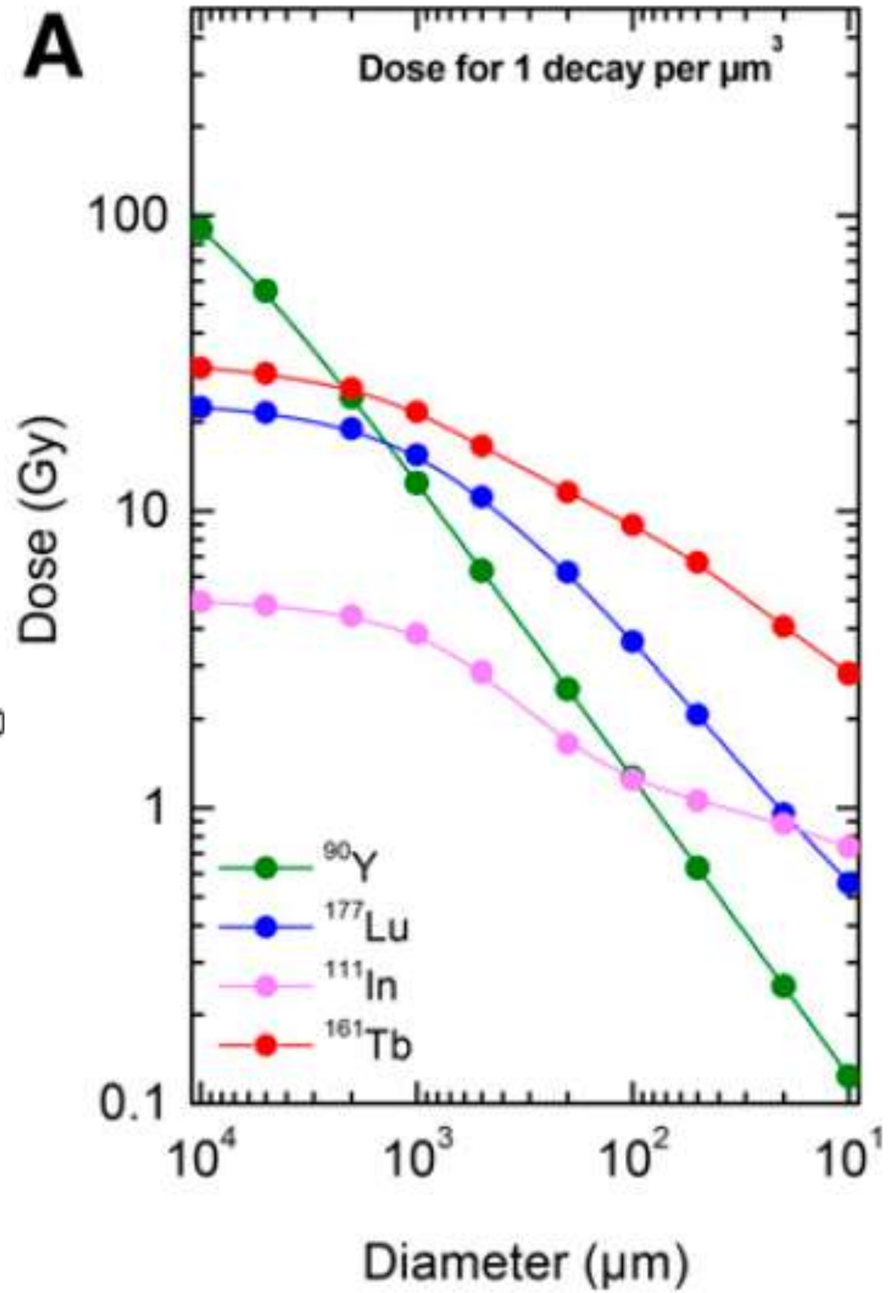
Estab-lished isotopes

Emerging isotopes

localized

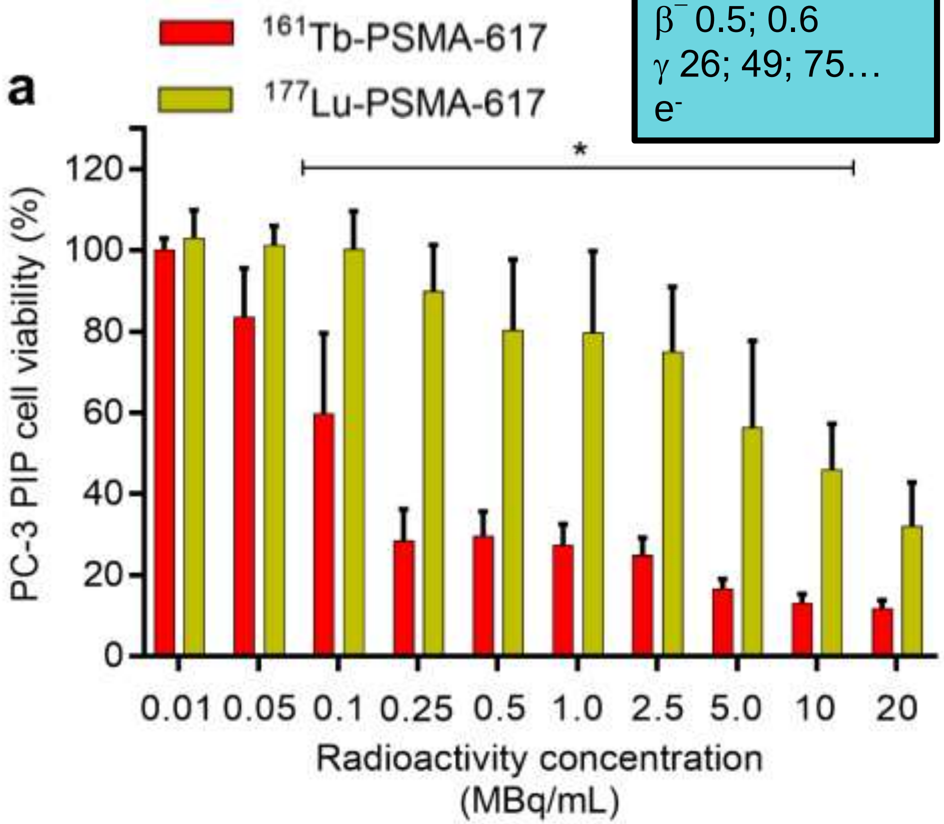
^{161}Tb versus ^{177}Lu





E. Hindié et al., J Nucl Med 2016;57:759.

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



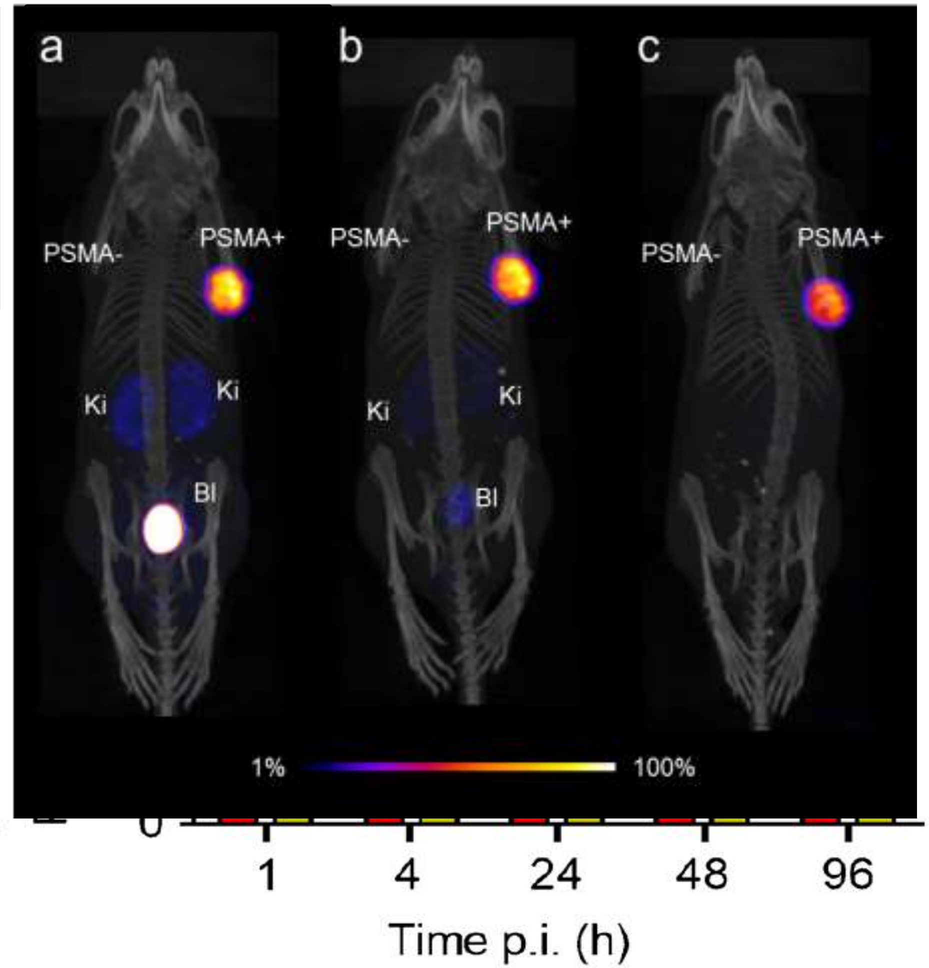
Tb 161

6.9 d

β^- 0.5; 0.6

γ 26; 49; 75…

e^-



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

PAUL SCHERRER INSTITUT PSI

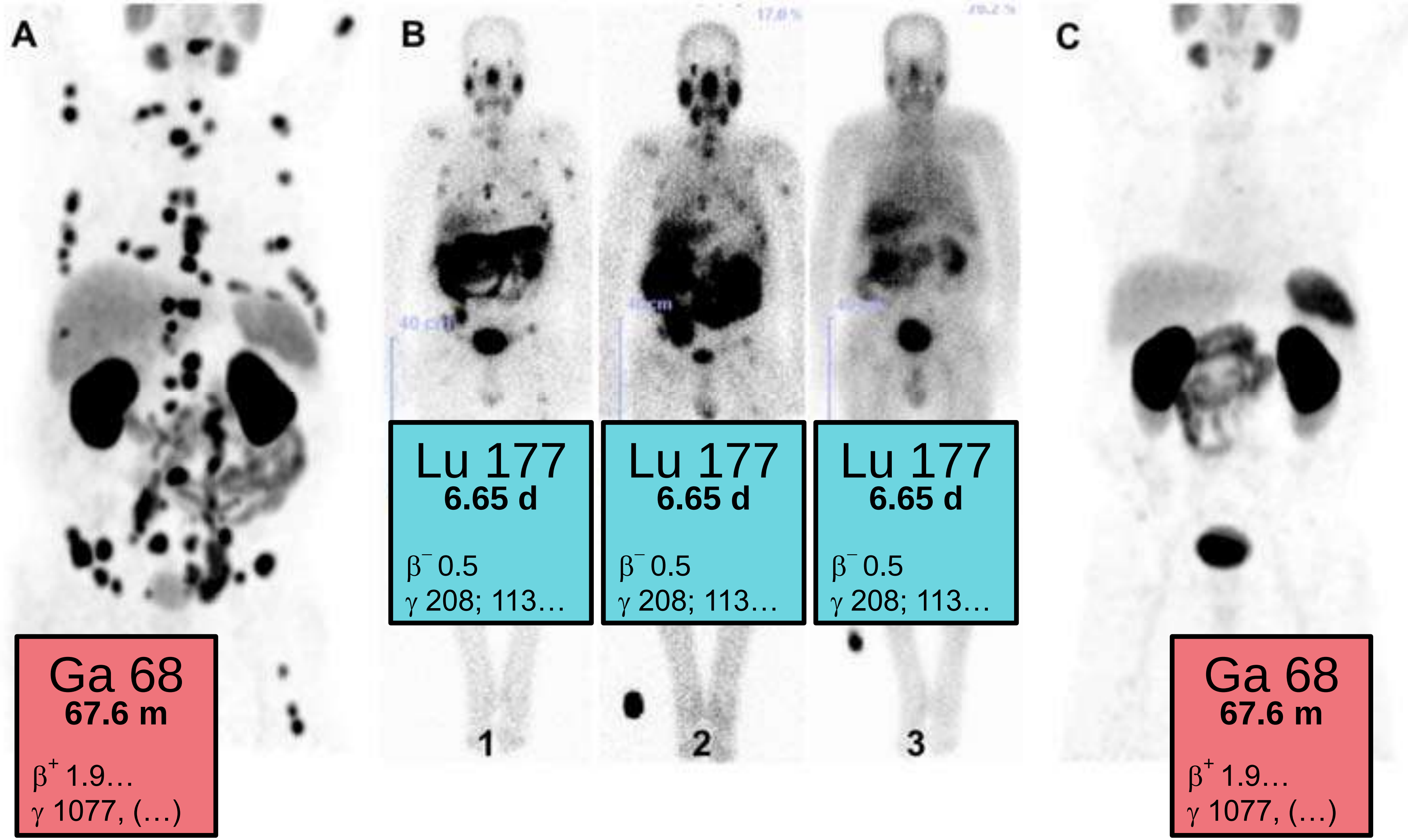
University of Zurich UZH

UNIVERSITY OF GOTHENBURG

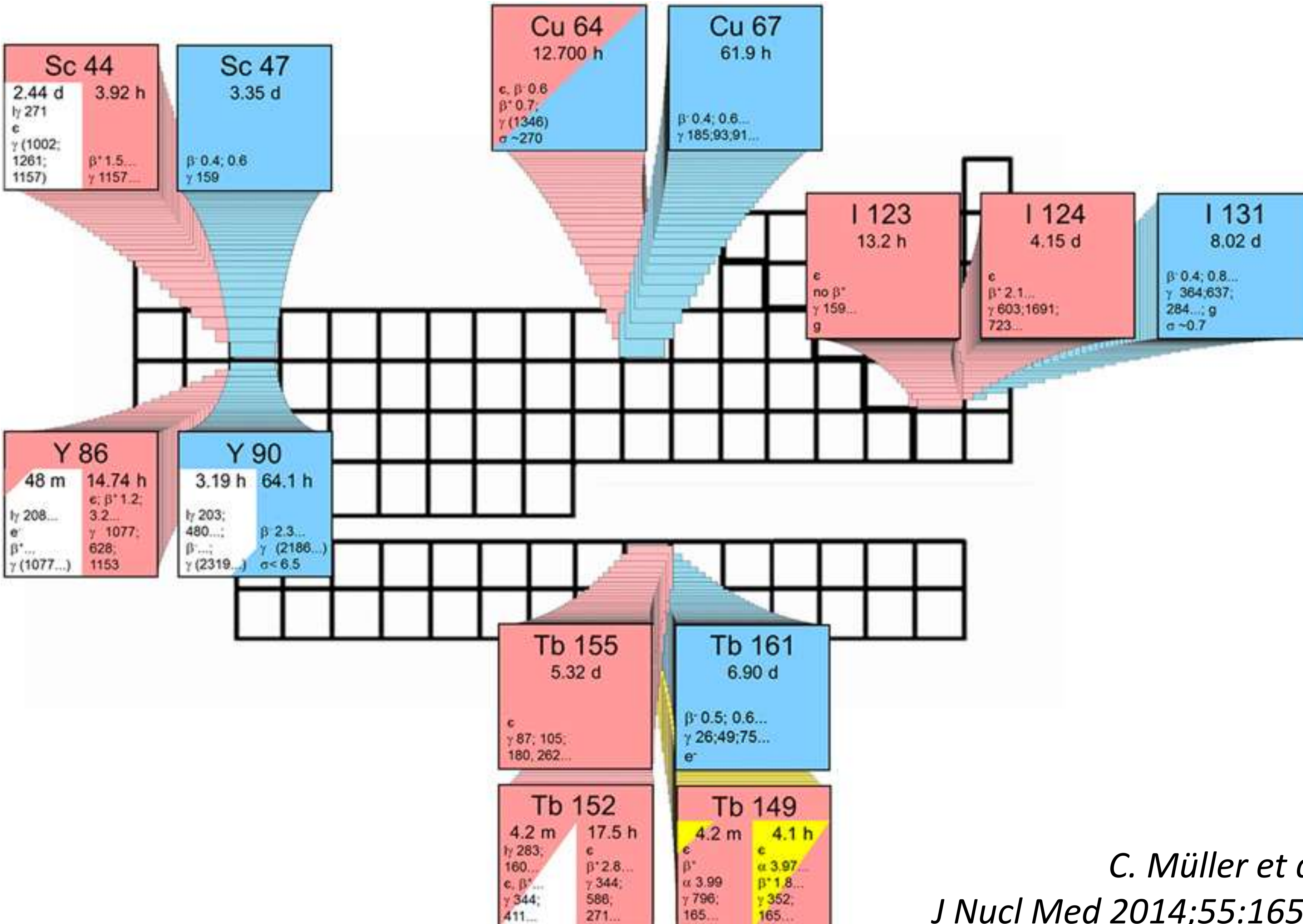
necsa We're in your world

NEUTRONS FOR SOCIETY

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



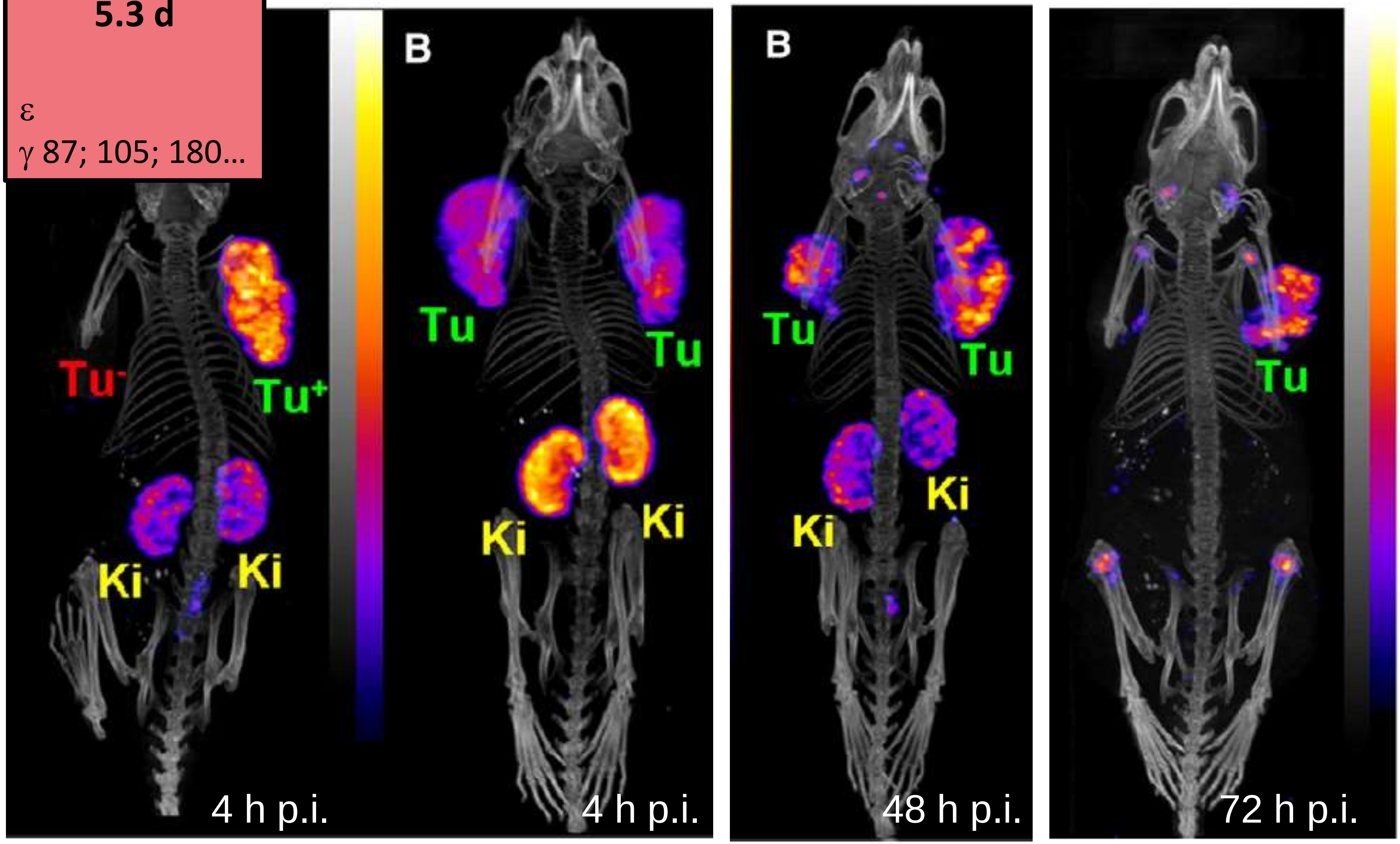
Matched pairs for theranostics



C. Müller et al.
J Nucl Med 2014;55:1658.

^{155}Tb for SPECT

Tb 155
5.3 d
ε
γ 87; 105; 180…



minigastrin
A431 tumor

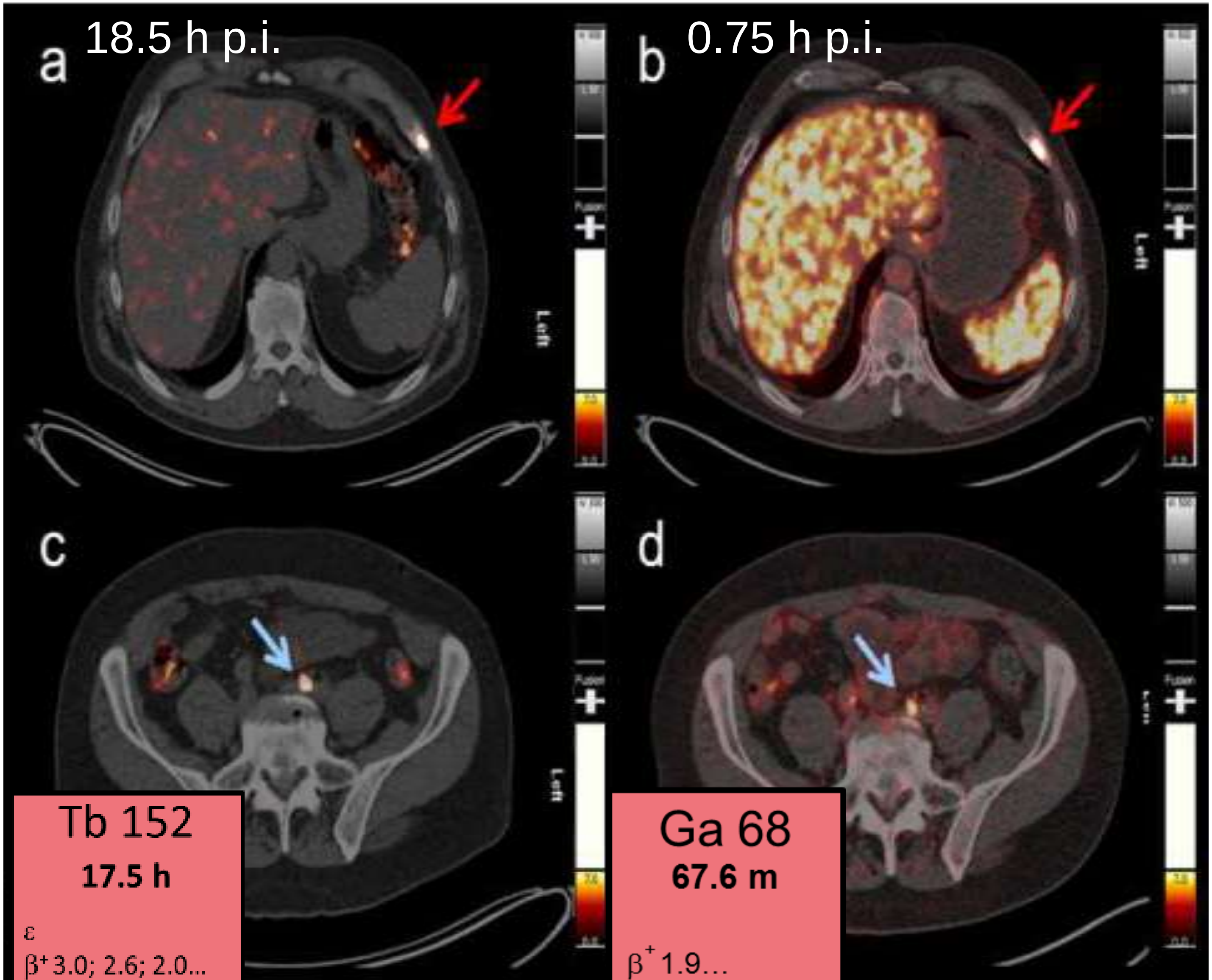
DOTATATE
A431 tumor

cm09
IGROV-1 tumor

chCE7
SKOV-3ip tumor

C. Müller et al. Nucl Med Biol 2014;41:e58.

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



Zentralklinik Bad Berka

PAUL SCHERRER INSTITUT PSI

ETH zürich

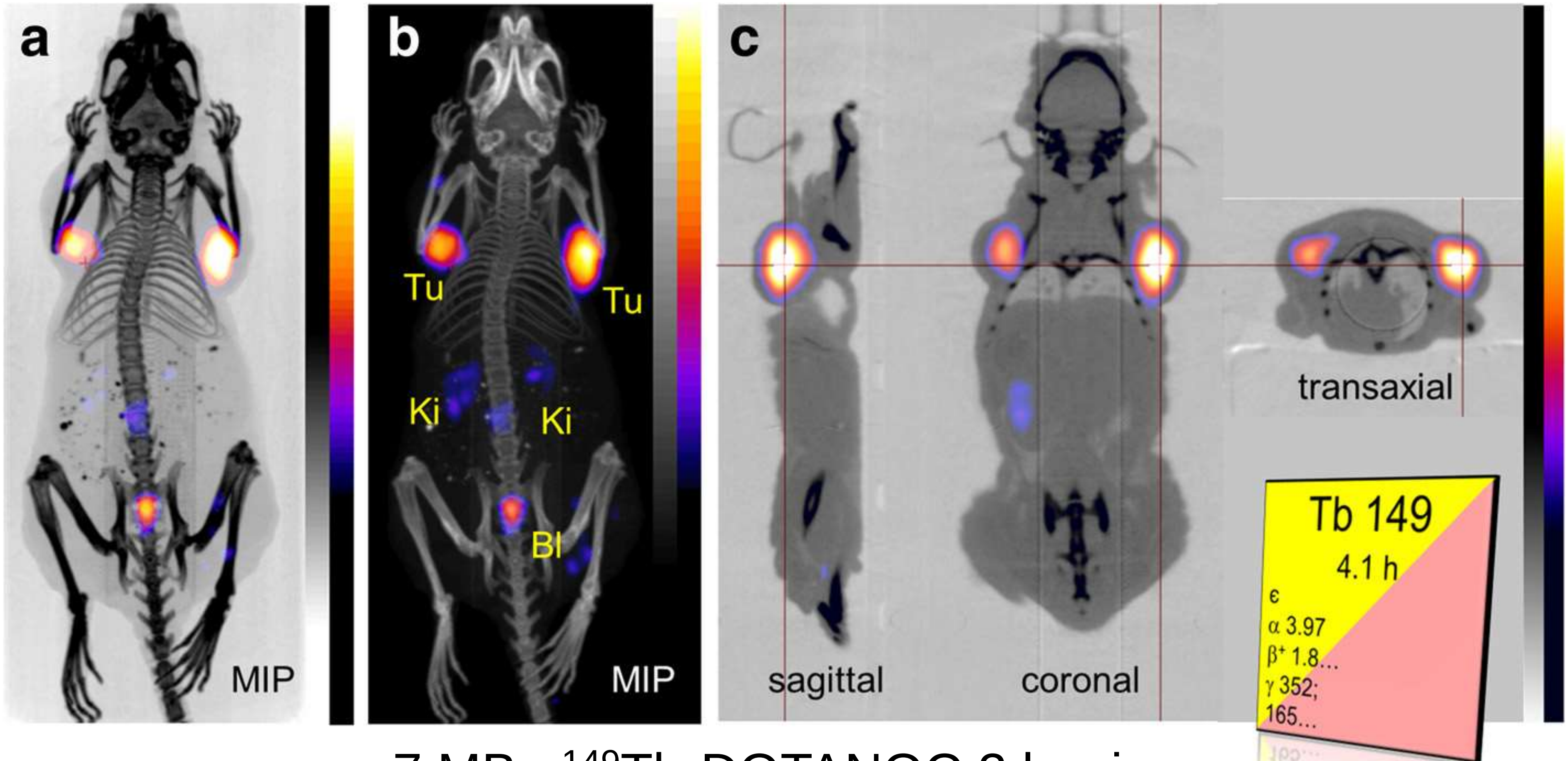
ISOLDE

NEUTRONS FOR SOCIETY

ENSAR2

C. Müller et al. EJNMMI Research 2019;9:68.

Alpha-PET with ^{149}Tb

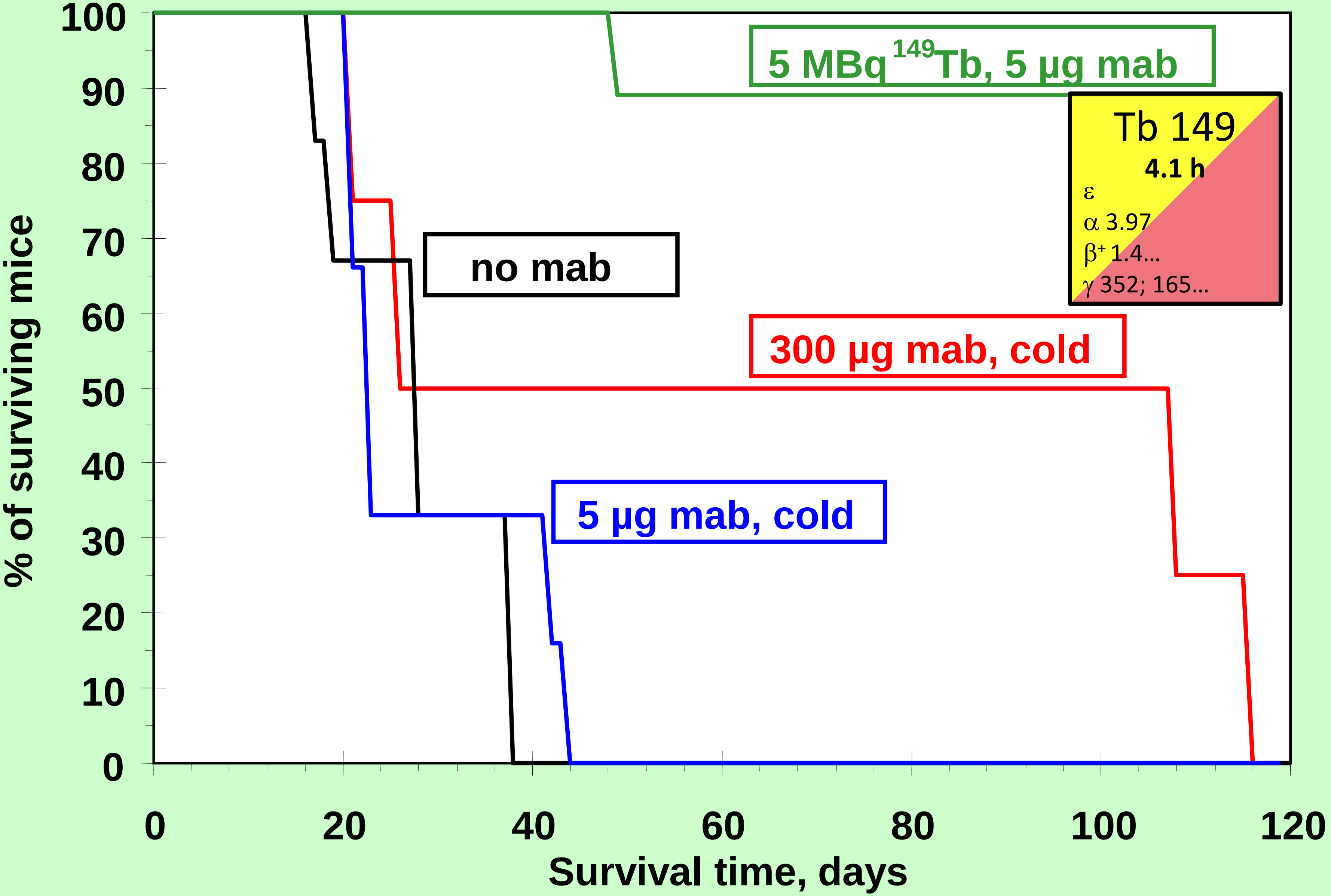


7 MBq ^{149}Tb-DOTANOC 2 h p.i.

ISOLDE PAUL SCHERRER INSTITUT PSI ETH zürich ILL NEUTRONS FOR SOCIETY UNIVERSITÄT BERN ENSAR

C. Müller et al. EJNMMI Radiopharm Chem 2016;1:5.

^{149}Tb-rituximab in leukemia mouse model



G.J. Beyer et al., Eur J Nucl Med Mol Imaging 2004;31:547.

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…

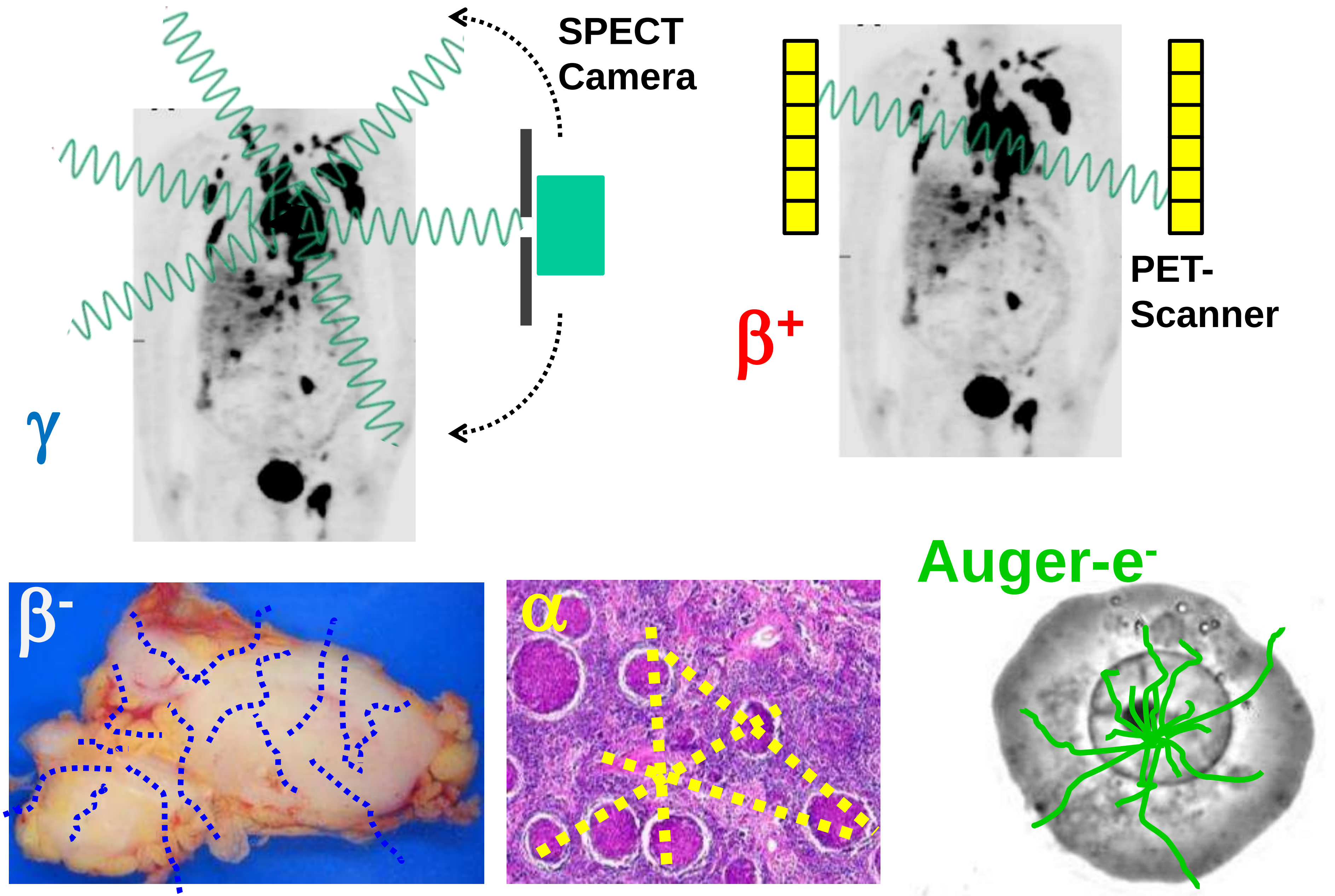
Tb 161
6.9 d

β^- 0.5; 0.6
γ 26; 49; 75…
e^-

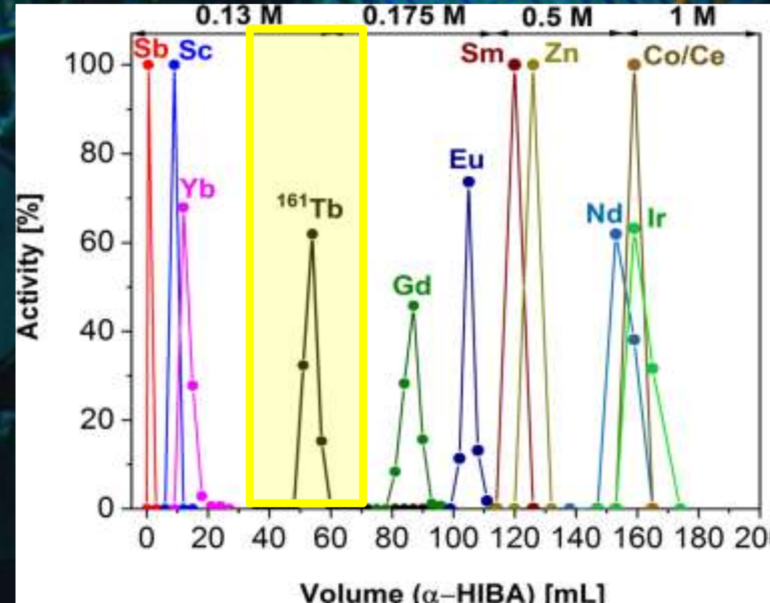
Tb 149
4.1 h

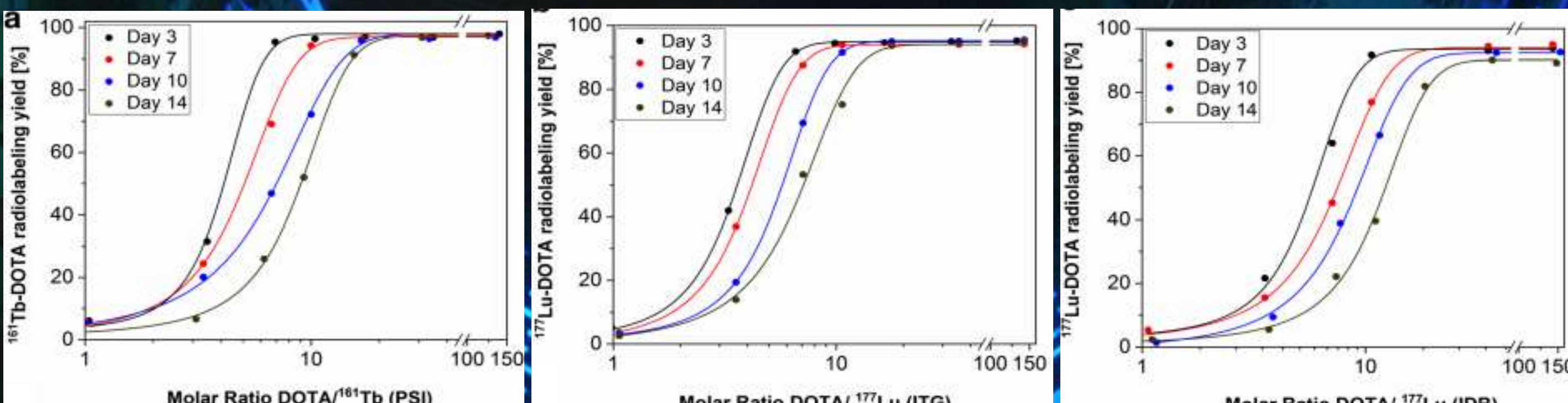
ε
α 3.97
β^+ 1.4…
γ 352; 165…

The Nuclear Medicine Alphabet



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

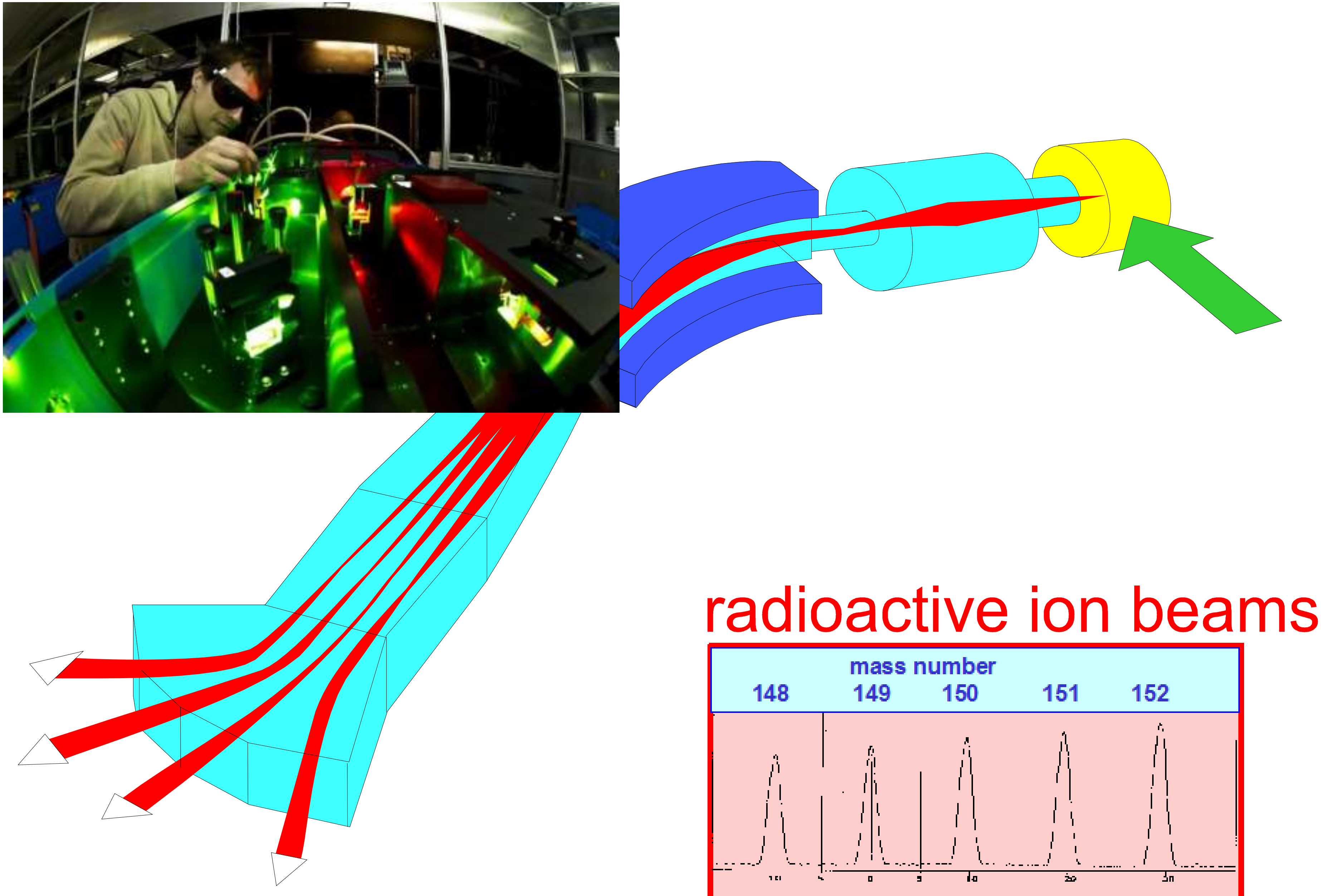




Irradiation at ILL & Necsa, chemical separation at PSI

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

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



Efficient parallel operation

ISOLTRAP

^{152}Tb

^{149}Tb

^{155}Tb

HRS setup

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 20 GBq ^{161}Tb	1×10^{1}
Alpha emitting nuclides but no neutron emitters are known to be present	0.2	9×10^{-5} 90 MBq ^{149}Tb	1×10^{-1}

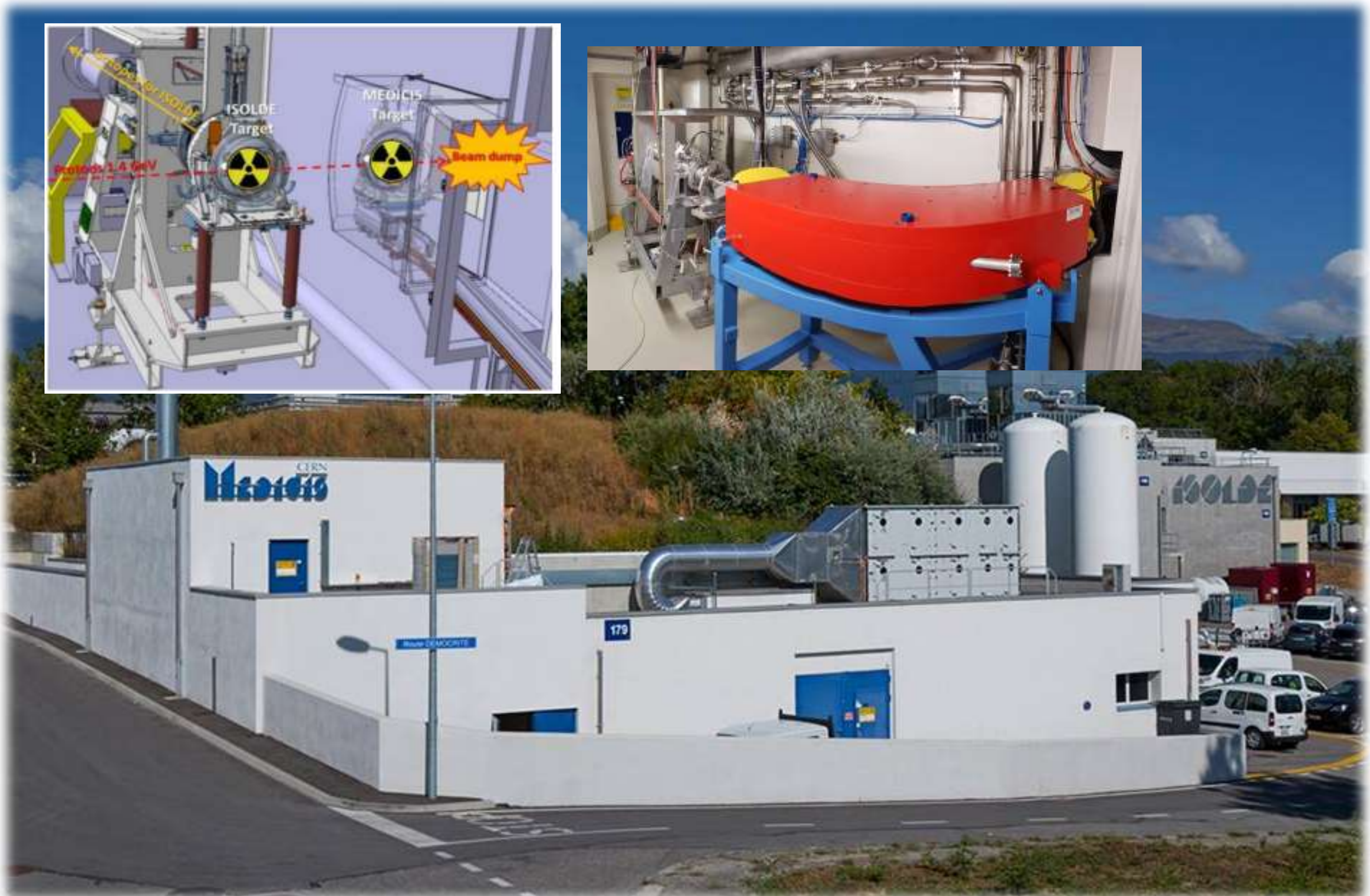
T. Frosio et al., Health Phys 2019;116:607.

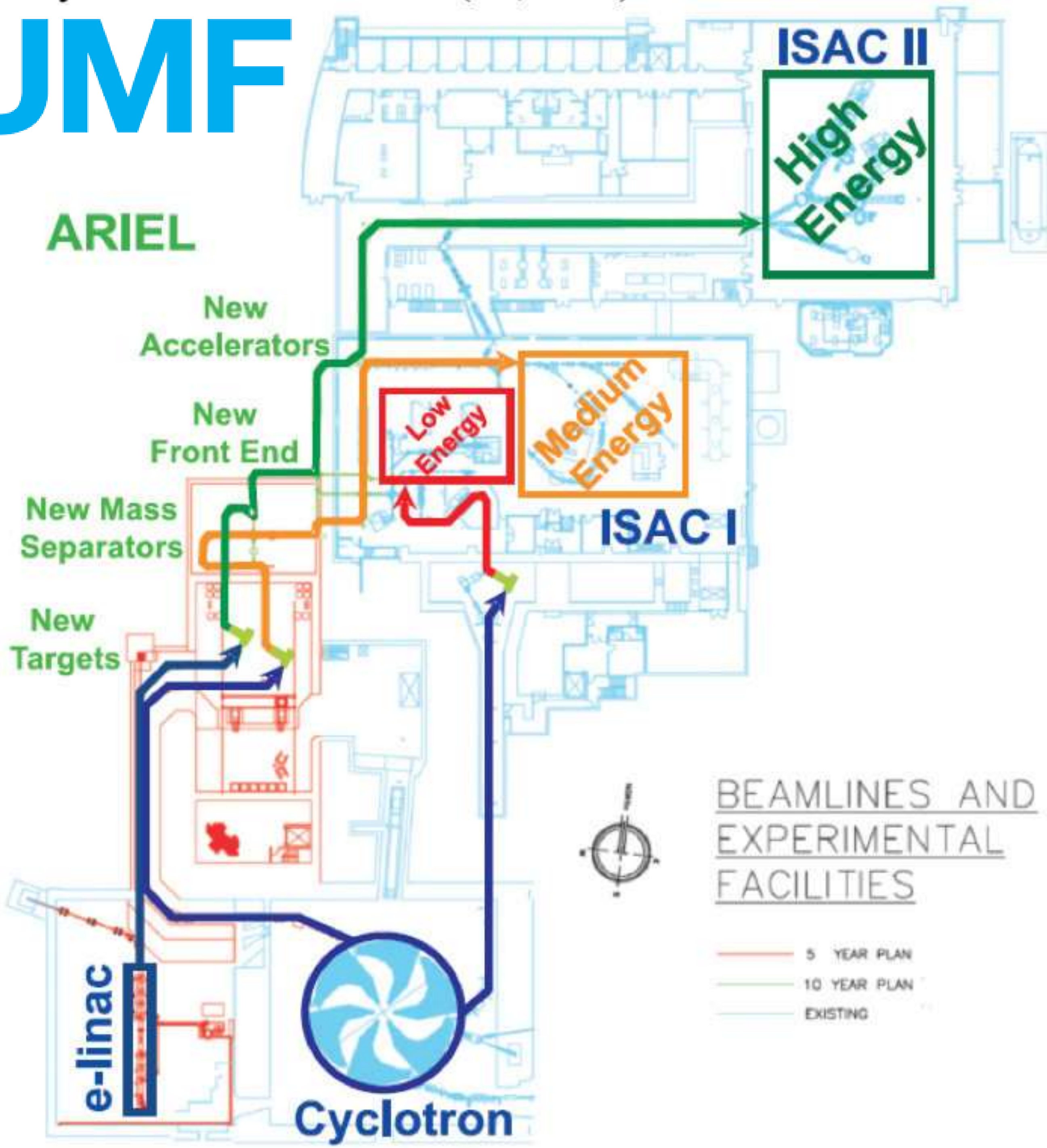
IAEA

Terbium (65)		A_2 (TBq)
Tb-149	8×10^{-1}	8×10^{-1}
Tb-157	4×10^{1}	4×10^{1}
Tb-158	1×10^{0}	1×10^{0}
Tb-160	1×10^{0}	6×10^{-1}
Tb-161	3×10^{1}	7×10^{-1}

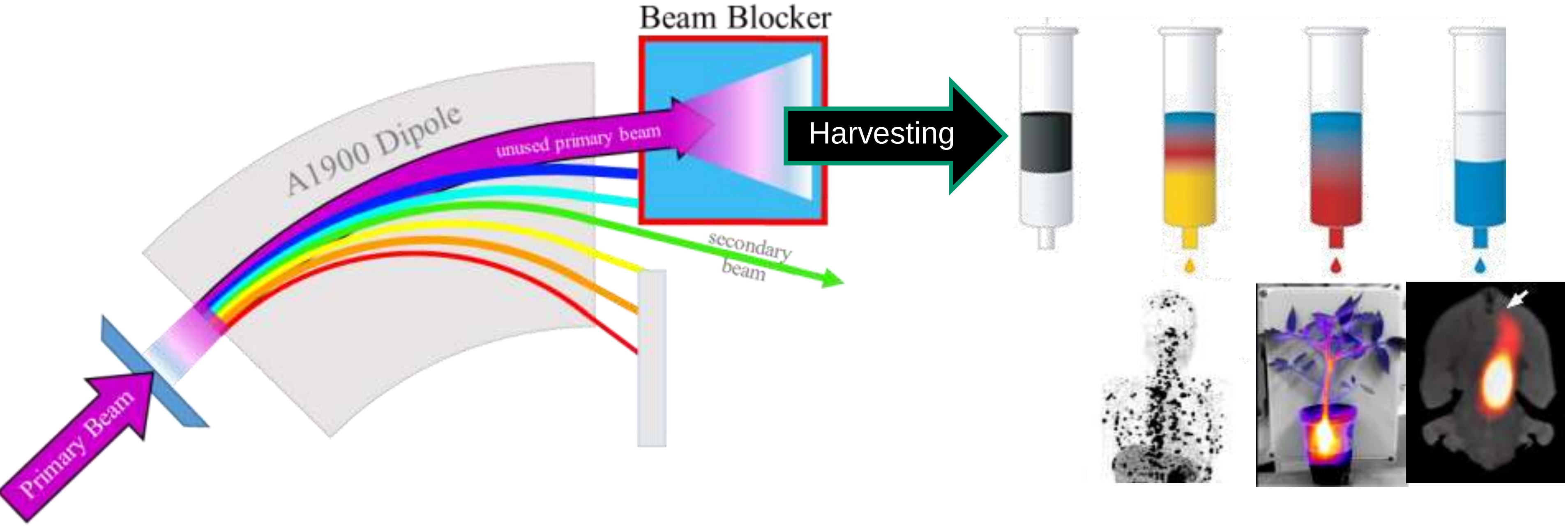
2018 Edition
Specific Safety Requirements
No. SSR-6 (Rev. 1)
IAEA
International Atomic Energy Agency

a very useful beam dump !




ISAC II
High Energy
ARIEL
New Accelerators
New Front End
New Mass Separators
New Targets
Low Energy
Medium Energy
ISAC I
BEAMLINES AND EXPERIMENTAL FACILITIES
5 YEAR PLAN
10 YEAR PLAN
EXISTING
e-linac
Cyclotron

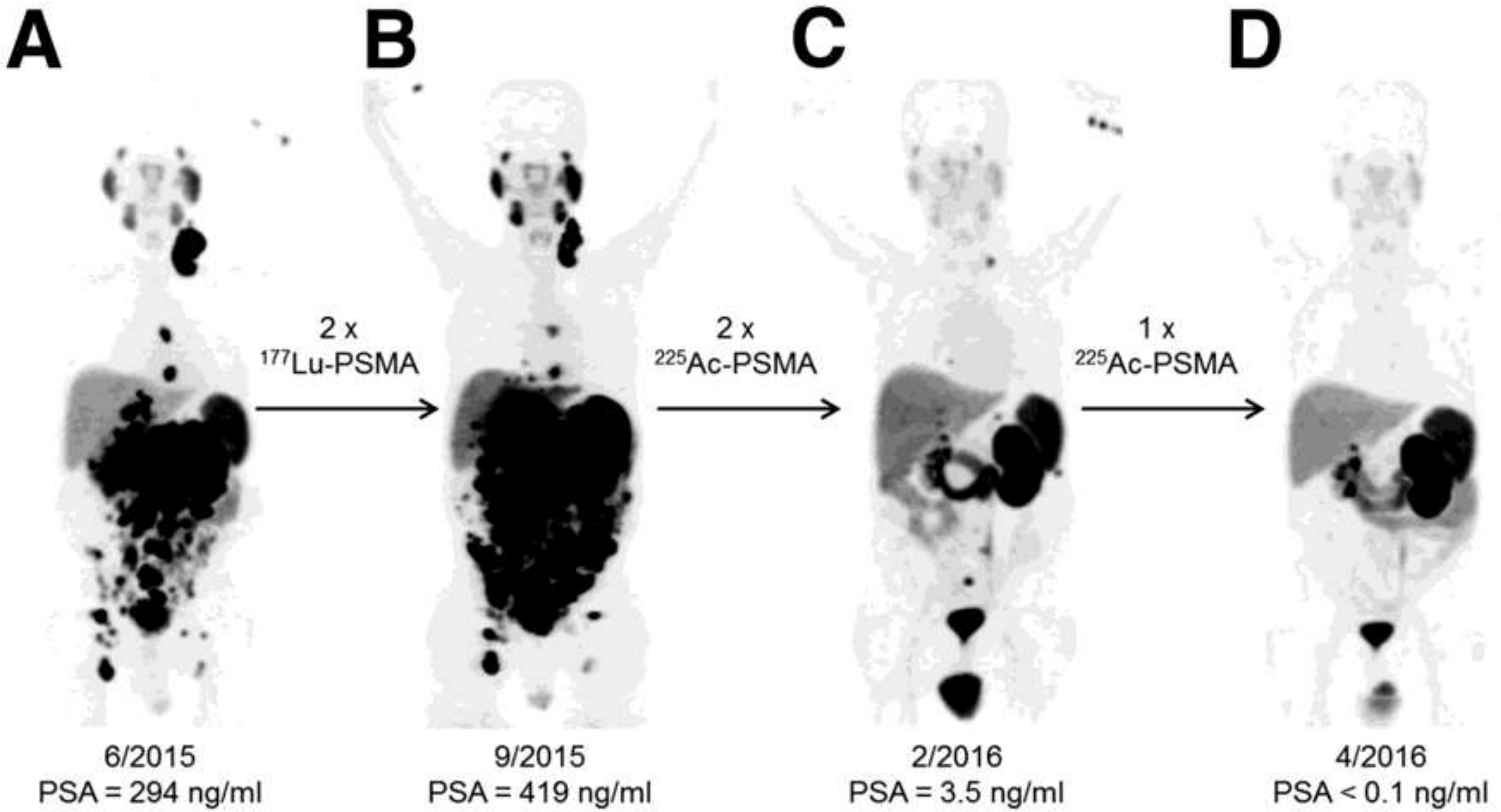
Harvesting isotopes at FRIB



courtesy: Greg Severin (MSU)

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

Targeted therapy with ^{225}Ac

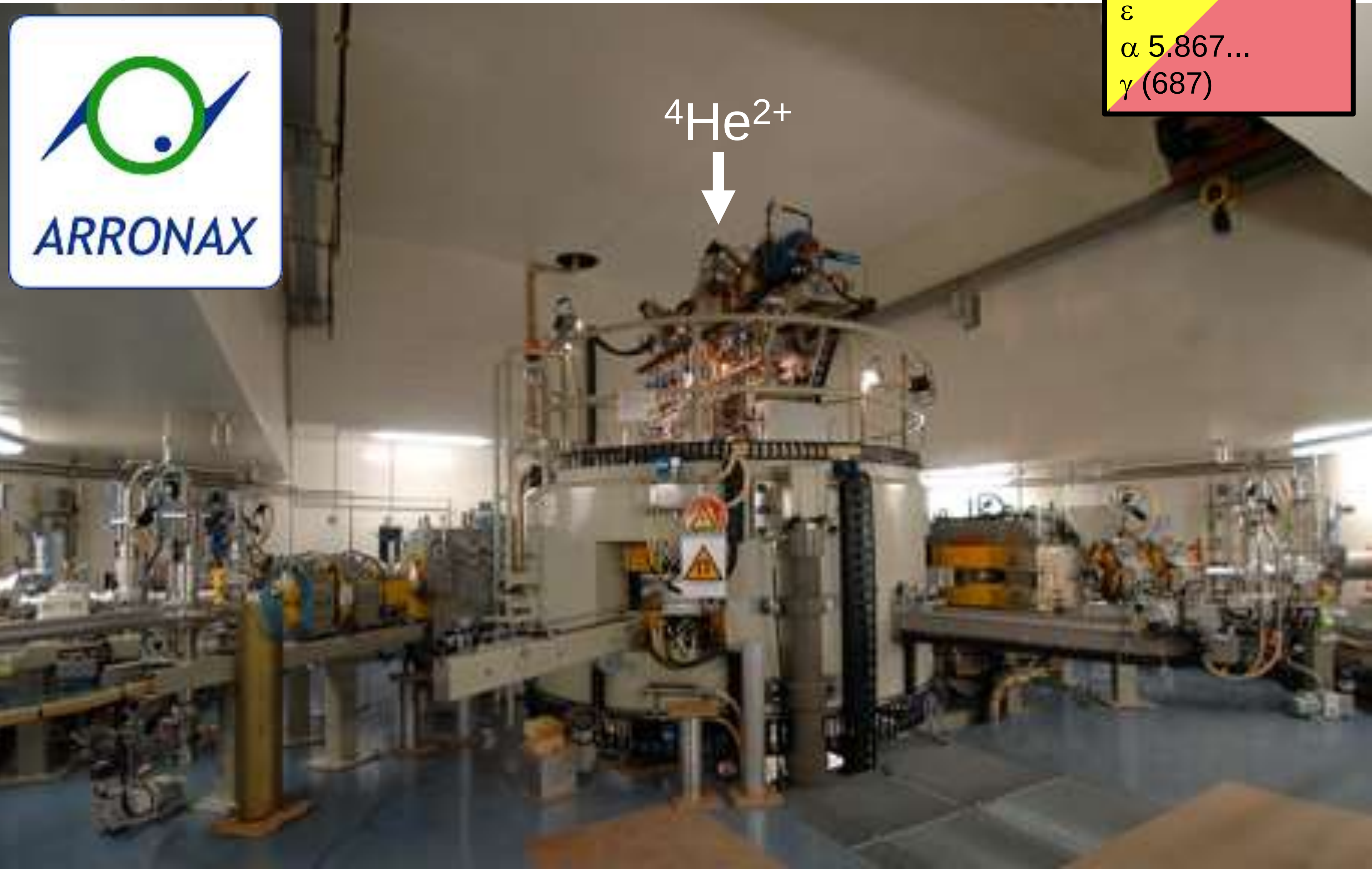


Clemens Kratochwil et al. J Nucl Med 2016;57:1941.

Isotopes for targeted alpha therapy

^{211}At production at ARRONAX

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

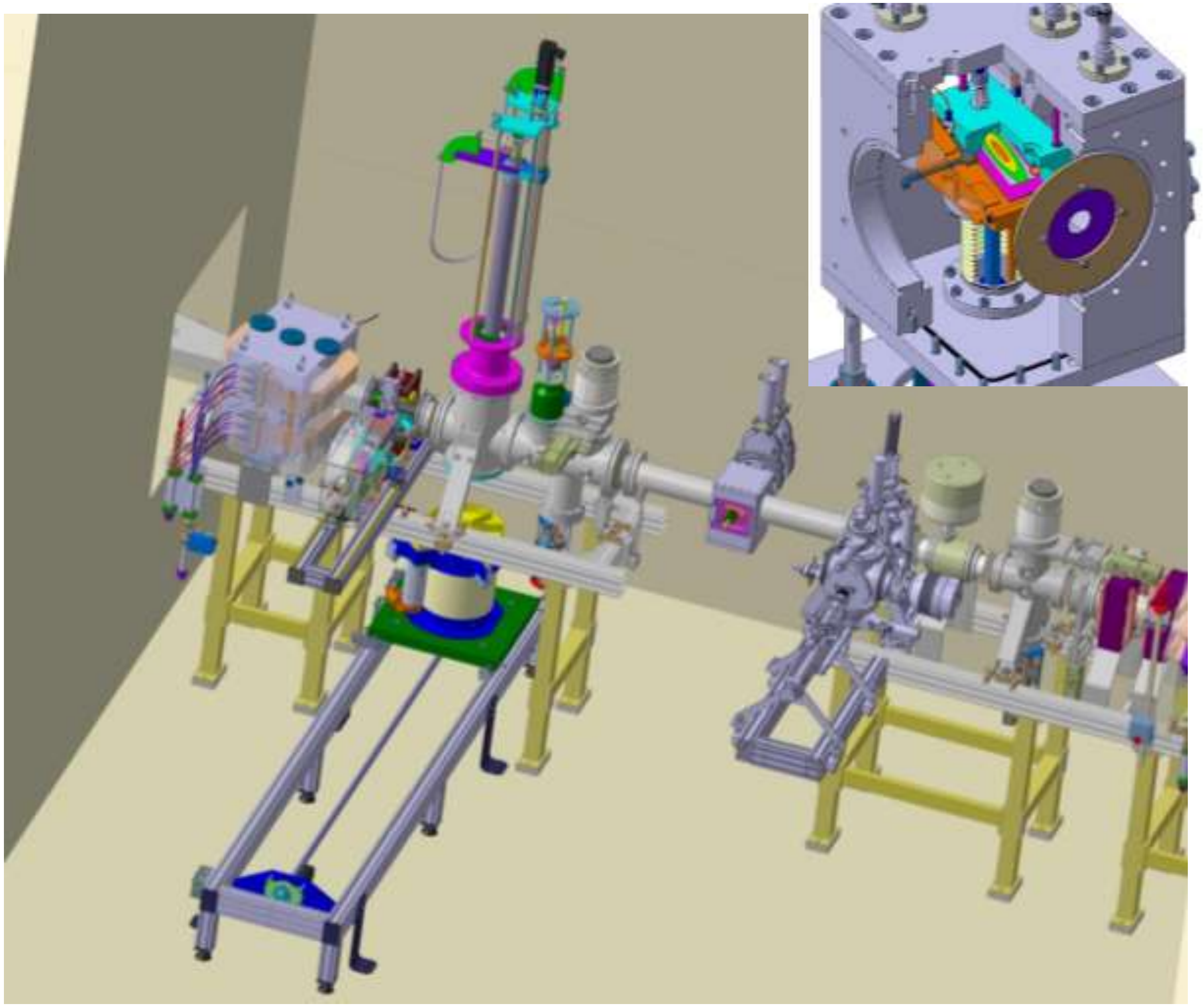


At 211
7.2 h
ε
α 5.867...
γ (687)

^{211}At production at SPIRAL2

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

At 211
7.2 h
ε
α 5.867...
γ (687)



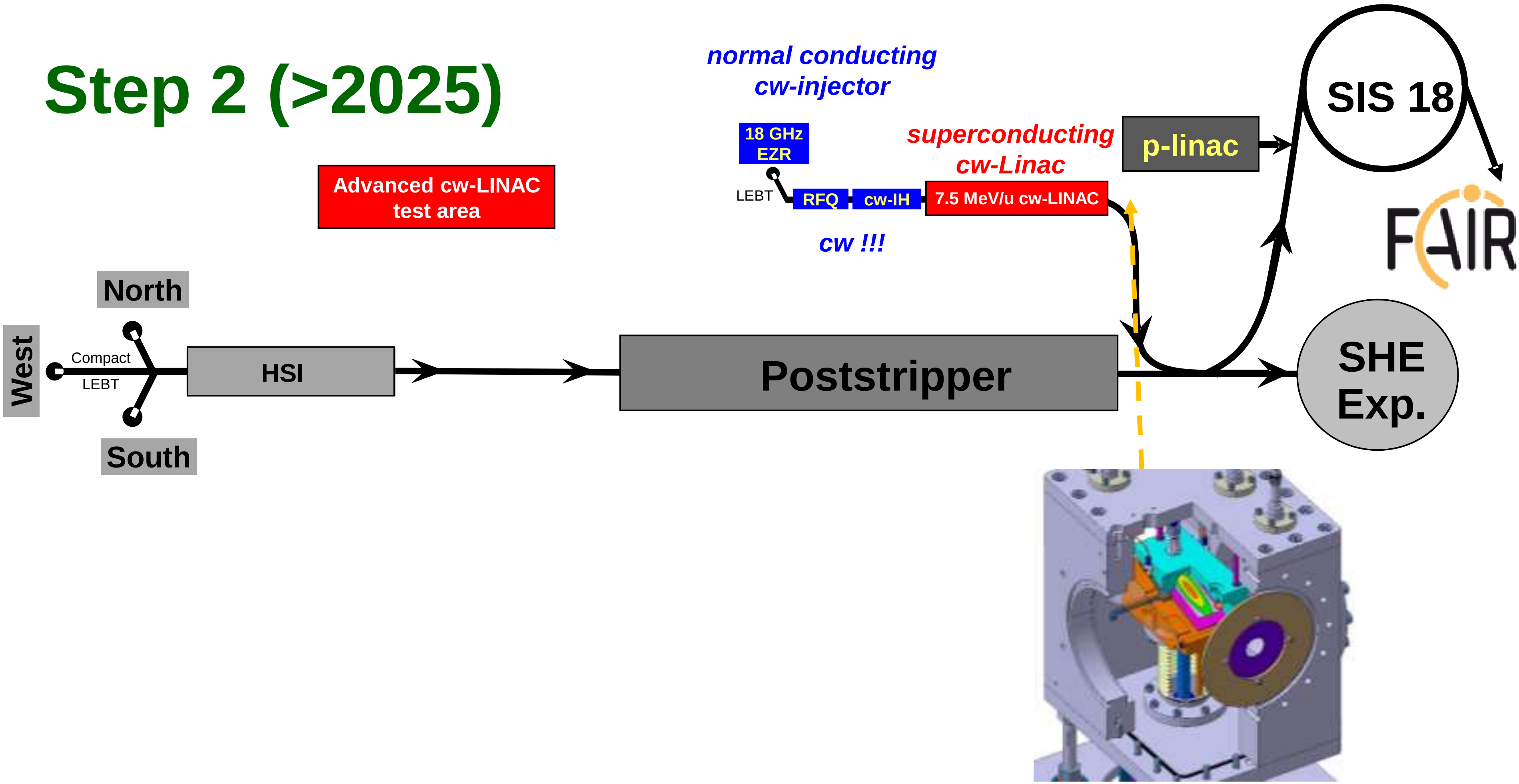
1. Use of 1 kW station (≈10 doses in 4 h) in 2020 once alpha beams are available at SPIRAL2.

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.

ENSAR2 · GANIL spiral2 laboratoire commun CEA/DRF CNRS/IN2P3 · ARRONAX · Subatech · IJF

Future superconducting cw-Linac at GSI



W. Barth, "Acceleration of Heavy Ion Beams with a Superconducting cw-Linac at GSI", GSI-Acc. Seminar, 11 April 2019

Radionuclides for Radioligand Therapy

Radio-nuclide	Half-life	E mean (keV)	Eγ (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

Estab-lished 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
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."

...

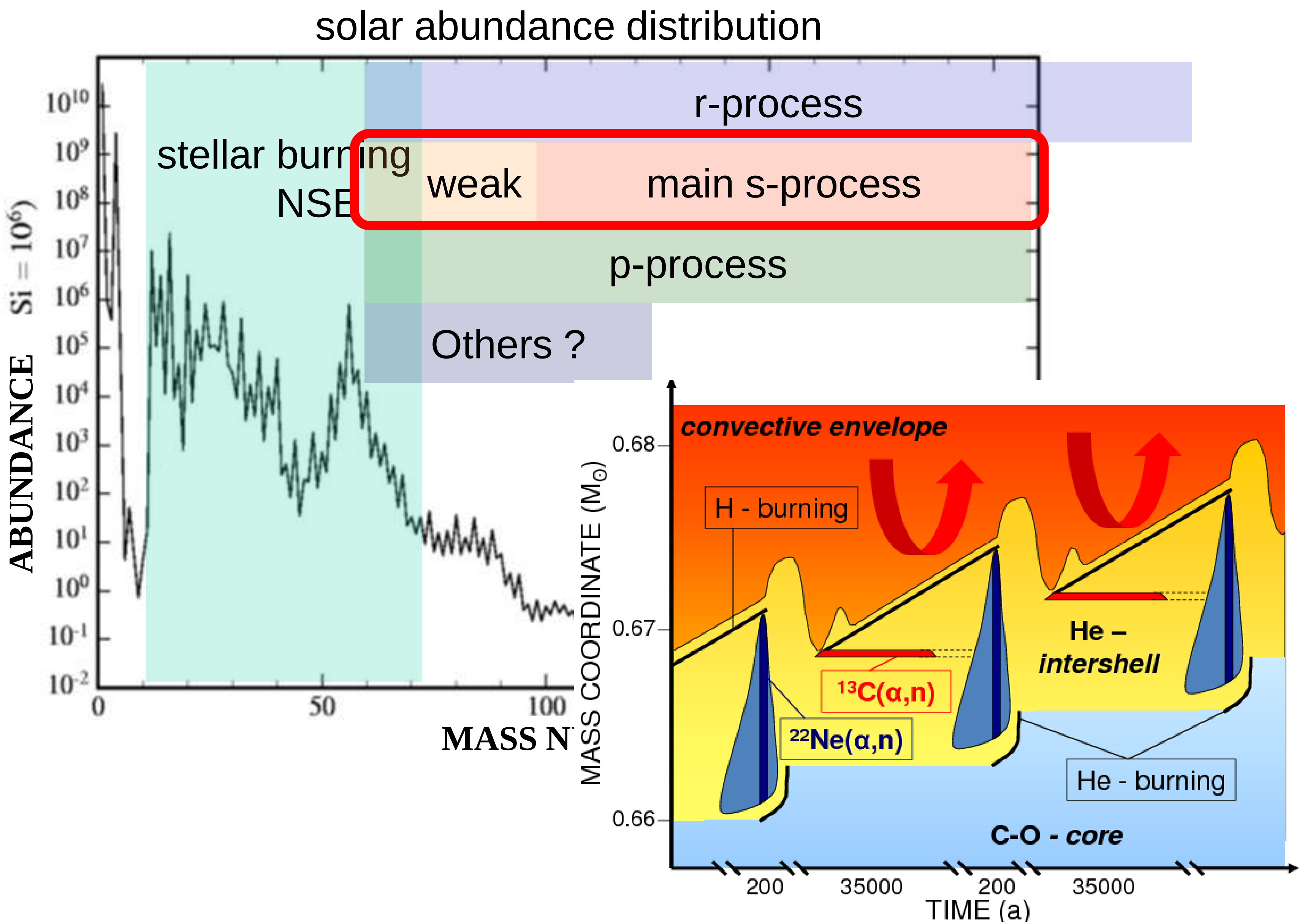
believe that this attitude is significant. We are not aware of a potential market for technetium-99 great enough to encourage one to undertake the risk of patenting in hopes of successful and rewarding licensing. We would recommend against filing on the Tucker, Greene and Murrenhoff separation process."

A great model: the US DOE Isotope Program

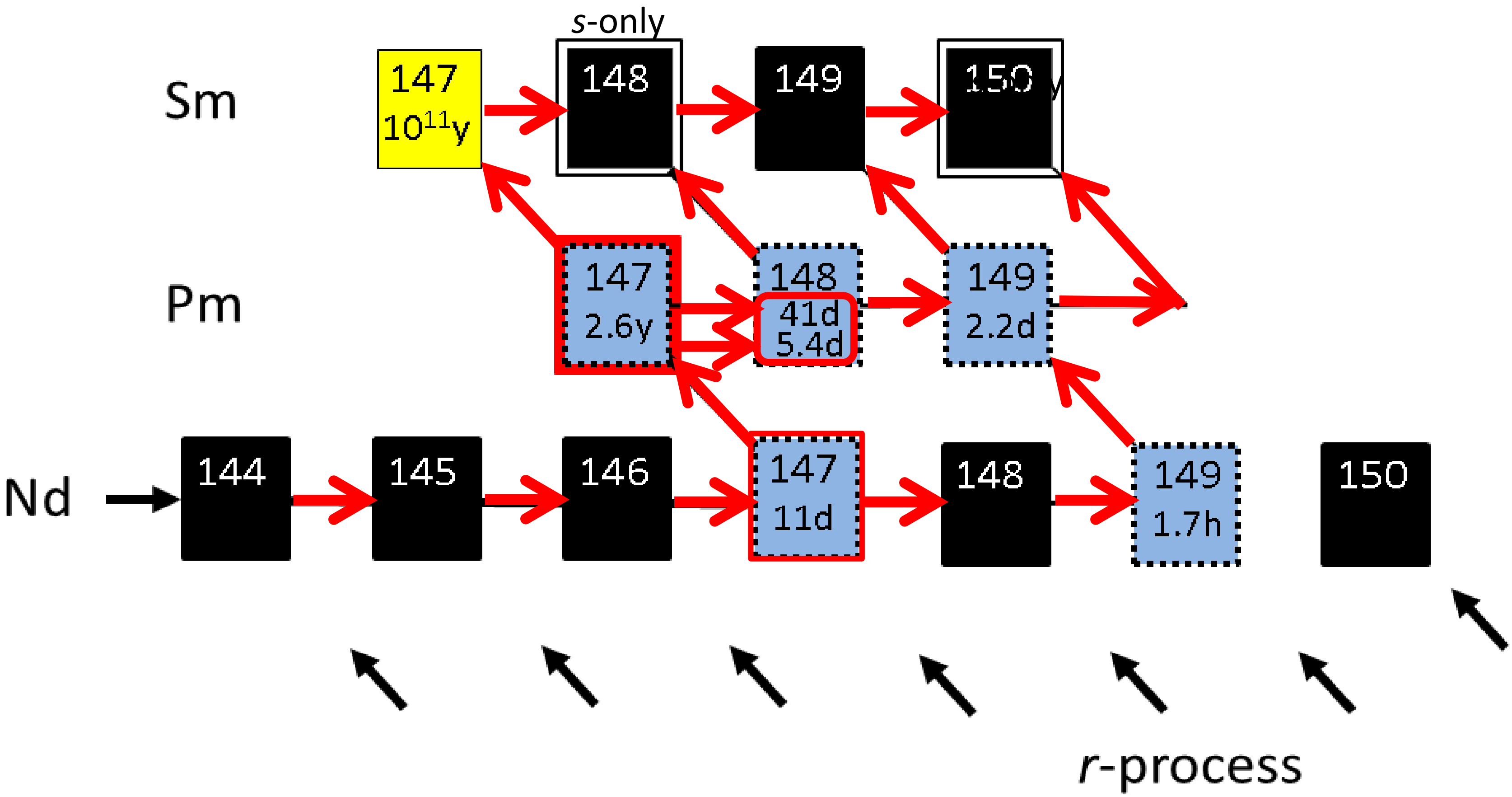
PRISMAS-MAP: improved access to emerging medical radioisotopes

Life, the Universe and Everything

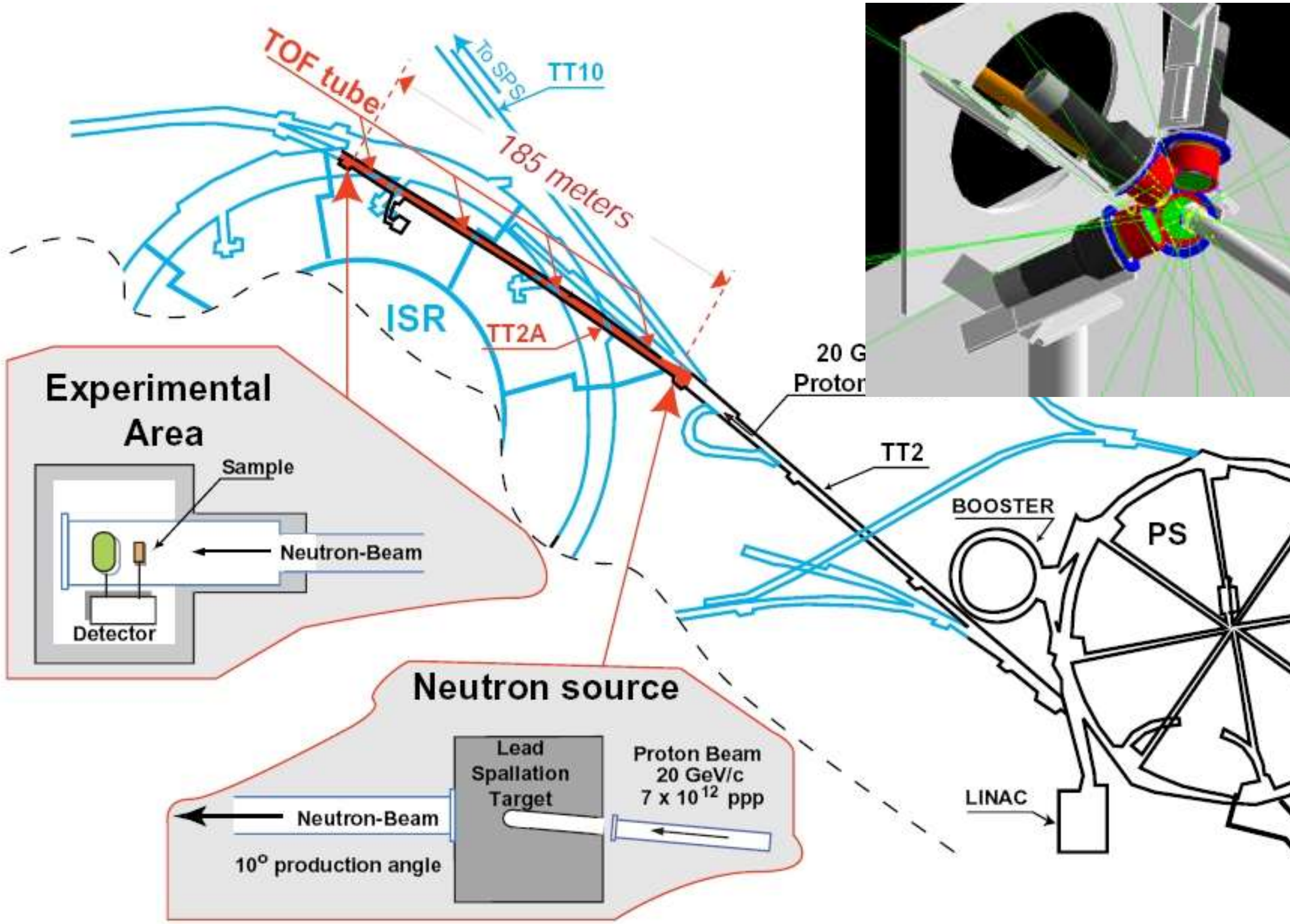
the Universe: nucleosynthesis



Branching points: example at A=147/148

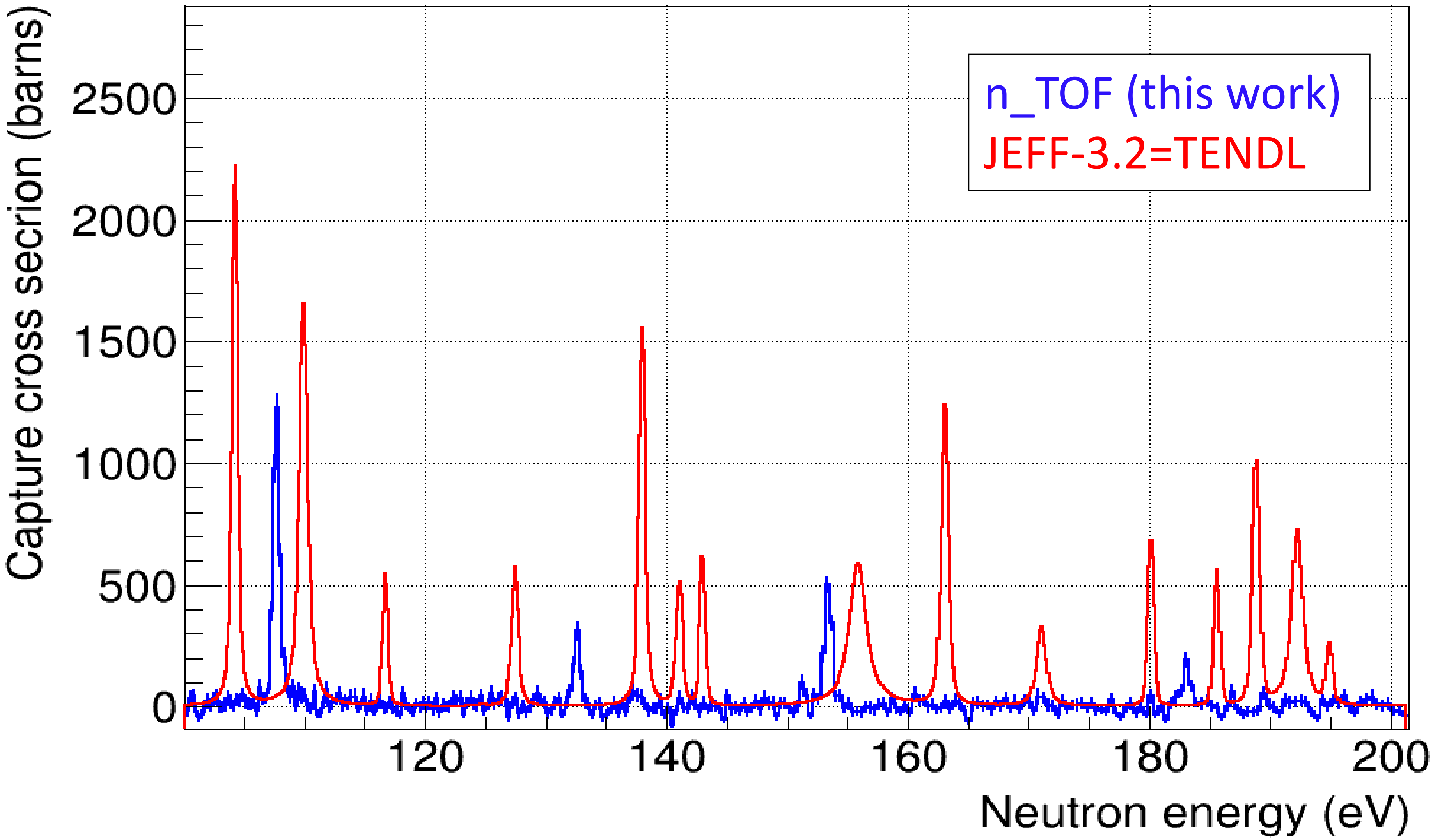


Neutron capture at s-process branching points



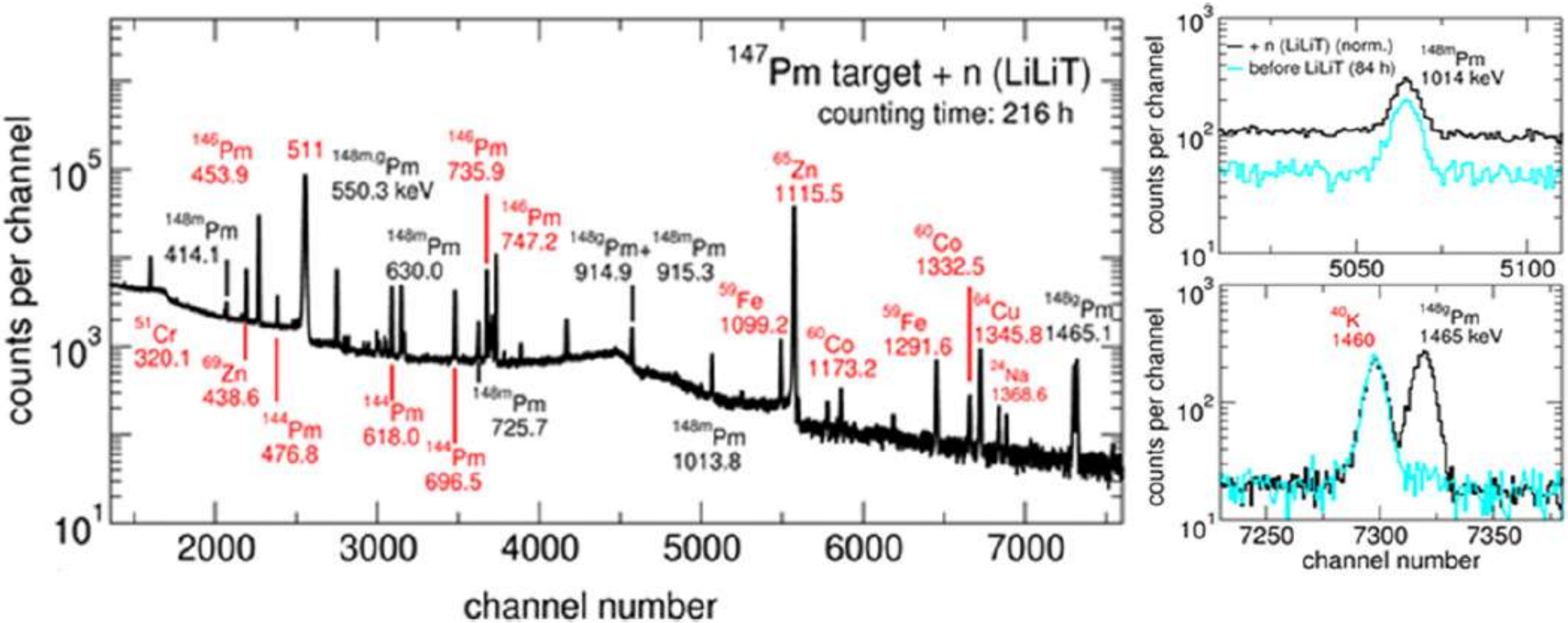
J. Lerendegui et al. EPJ WoC 193 (2018) 04007.

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



C. Guerrero et al. ND-2016.

^{147}Pm(n,γ)^{148g,m}Pm MACS at SARAF-LiLiT

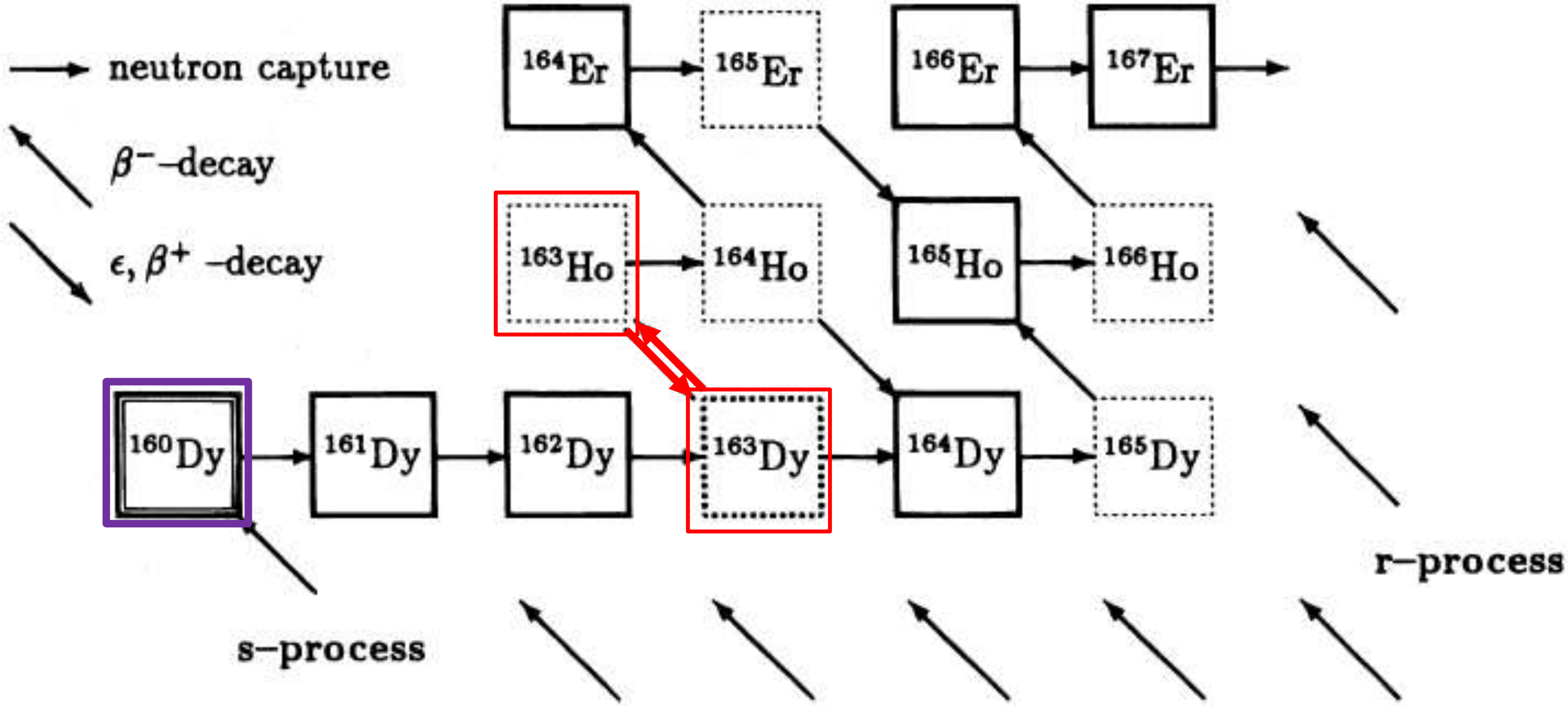


^{147}Pm(n,γ)^{148g}Pm	469(50) mb MACS at 30 keV
^{147}Pm(n,γ)^{148m}Pm	357(27) mb MACS at 30 keV
^{147}Pm(n,γ)^{148g,m}Pm	826(57) mb MACS at 30 keV

C. Guerrero et al. Phys Lett B 2019;797:134809.

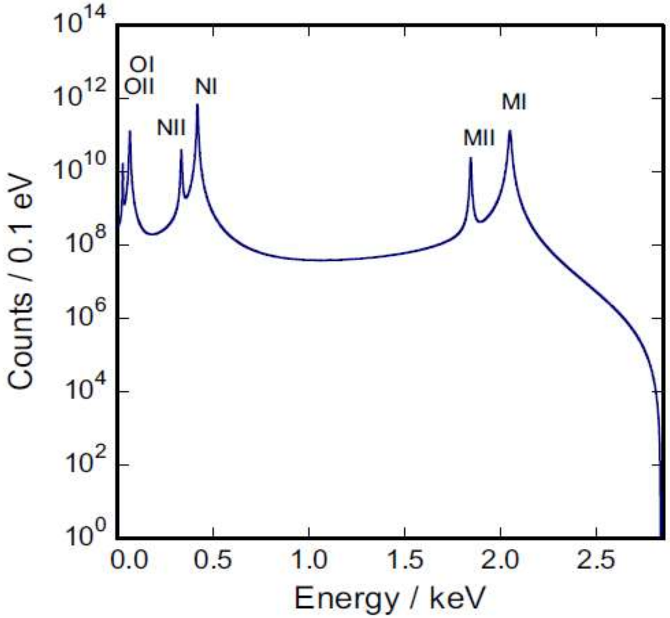
^{163}Ho as part of branching at A=163

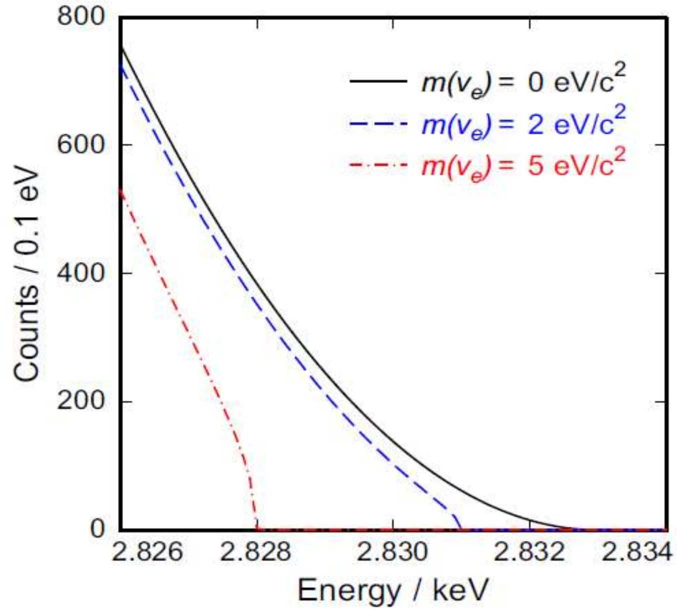
^{163}Dy stable, but β^- (47 d) to ^{163}Ho when fully ionized (stellar plasma)
Equilibrium abundance of ^{163}Ho (from ^{163}Dy) produces ^{164}Ho via (n,γ).
The equilibrium abundance of ^{163}Ho is determined by the temperature and electron density in the star.

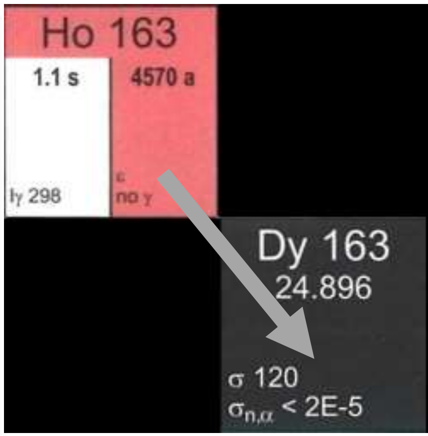


M. Jung et al., Phys Rev Lett 1992;69:2164.

^{163}Ho for Neutrino Mass Measurements

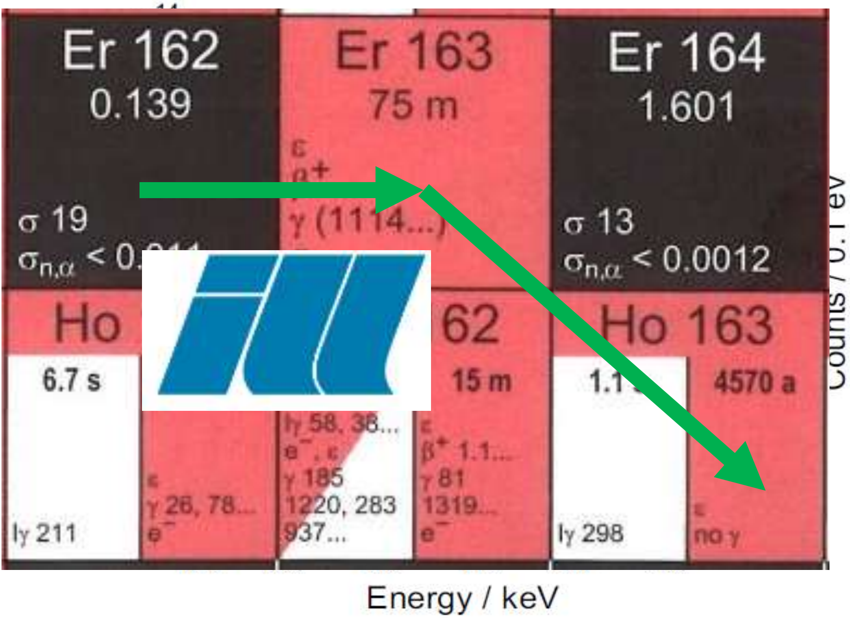


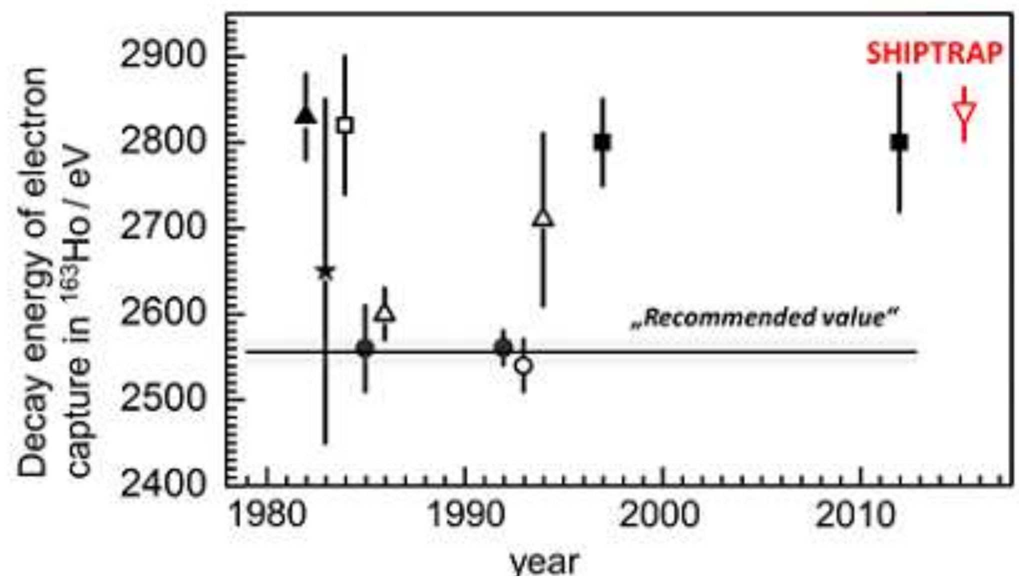




L. Gastaldo et al. Eur Phys J Spec Top 2017;226:1623.

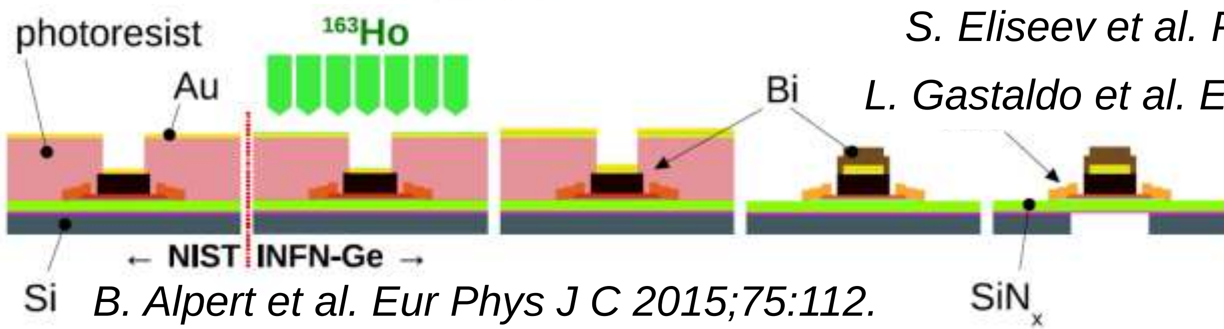
^{163}Ho for Neutrino Mass Measurements





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

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



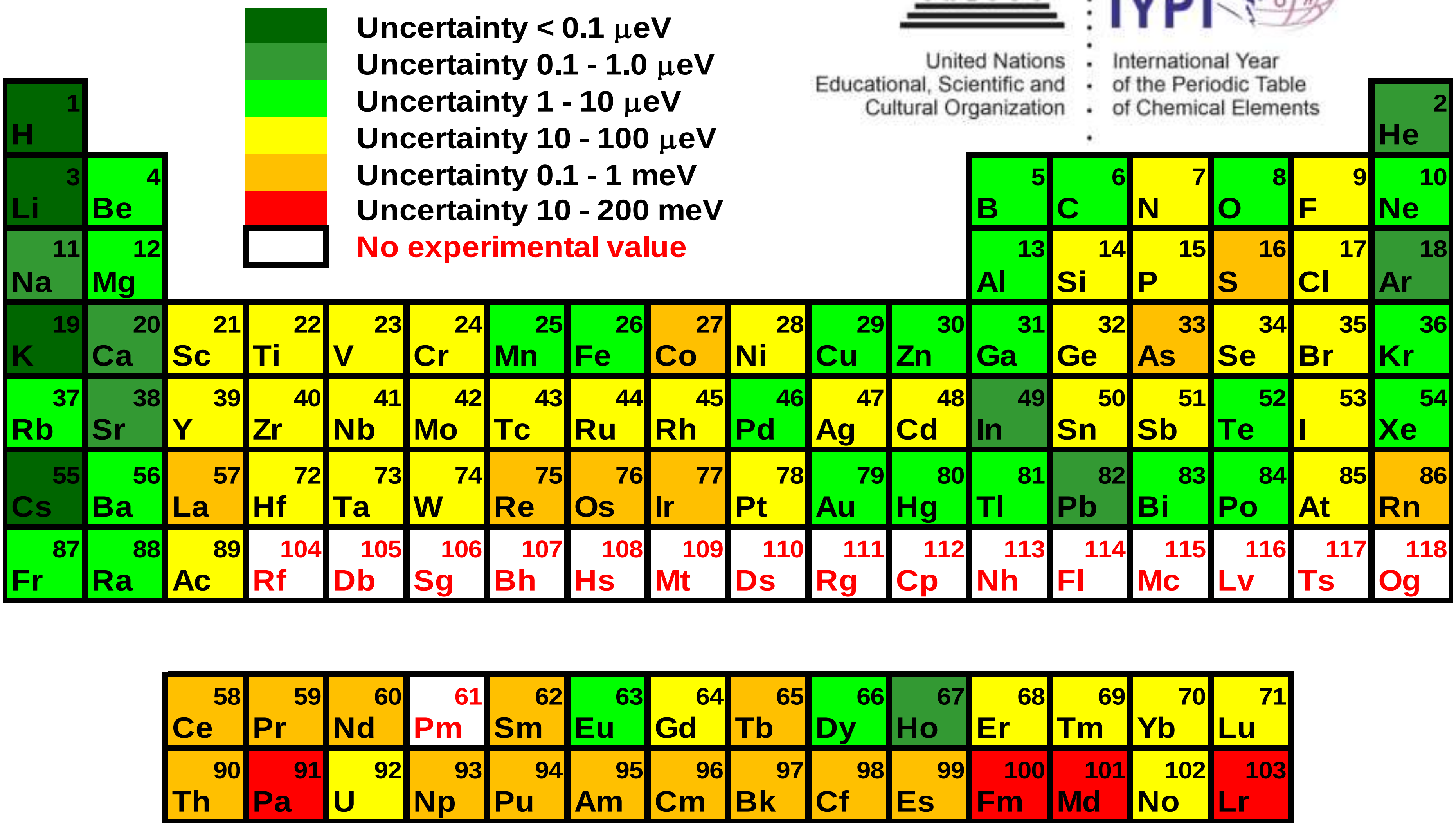
B. Alpert et al. Eur Phys J C 2015;75:112.

and Everything

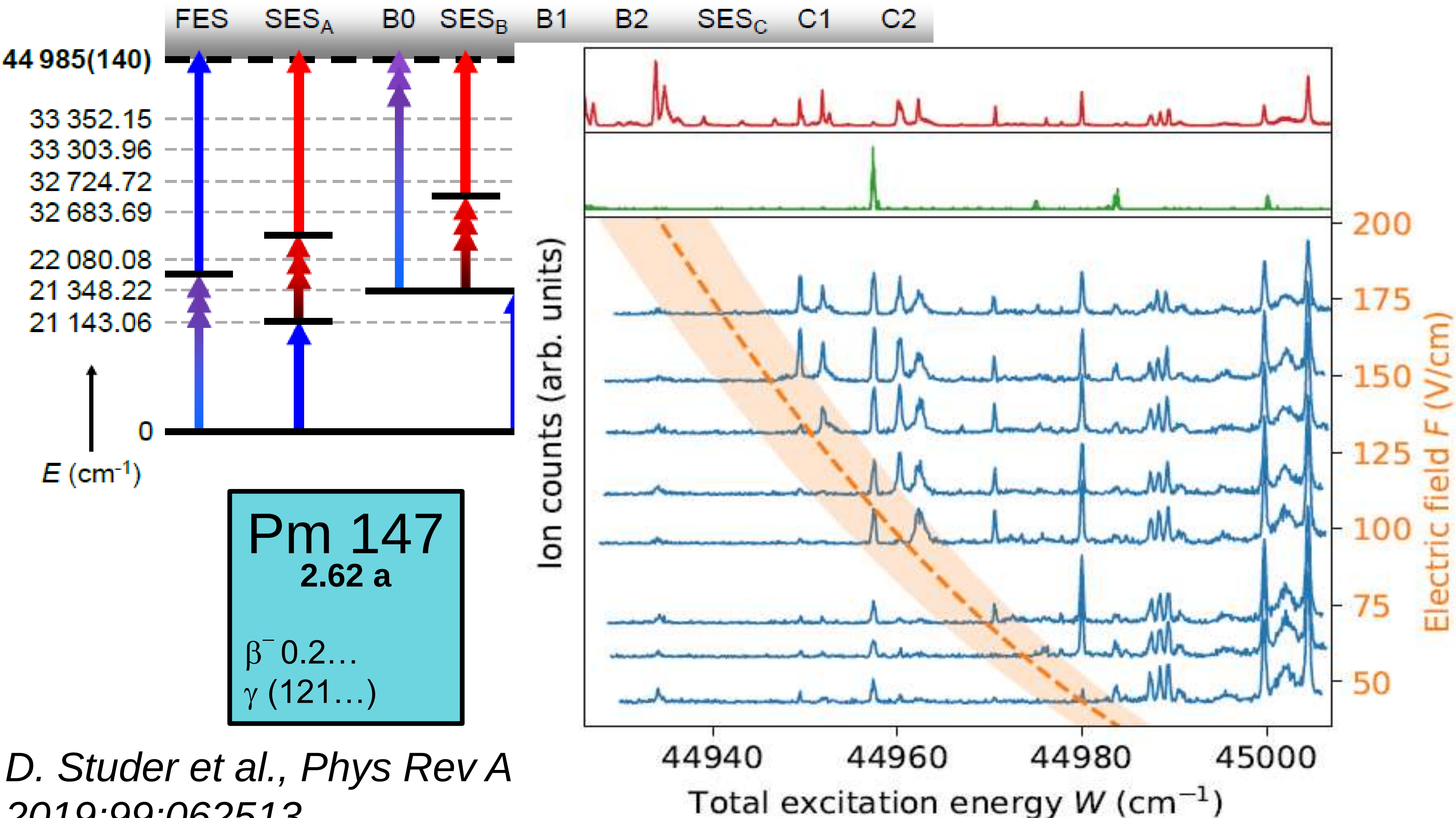
The gap in Mendeleev's table

United Nations
Educational, Scientific and
Cultural Organization

2019 IYPT
International Year
of the Periodic Table
of Chemical Elements



Resonance ionisation spectroscopy of Pm I

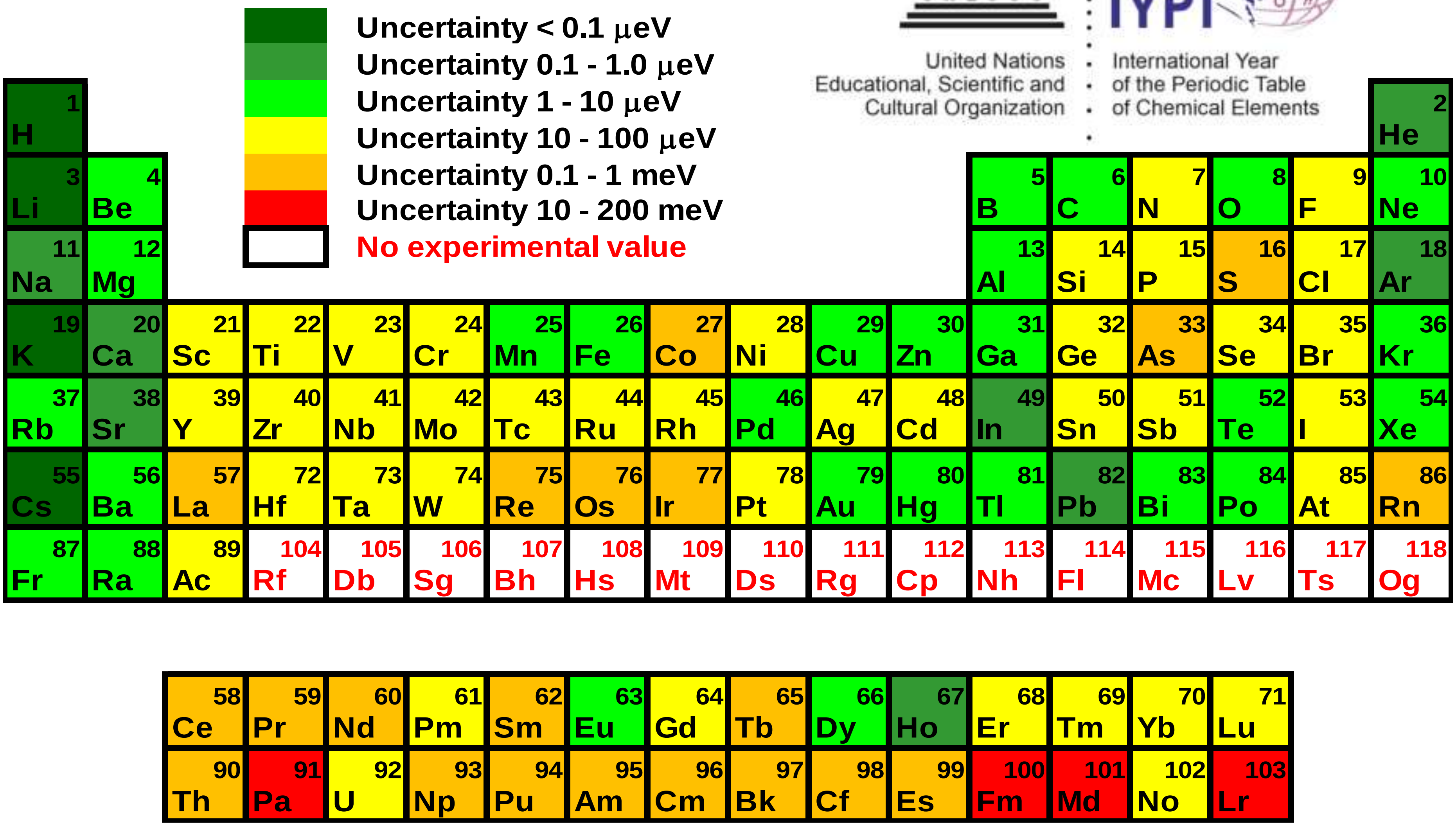


D. Studer et al., Phys Rev A 2019;99:062513.

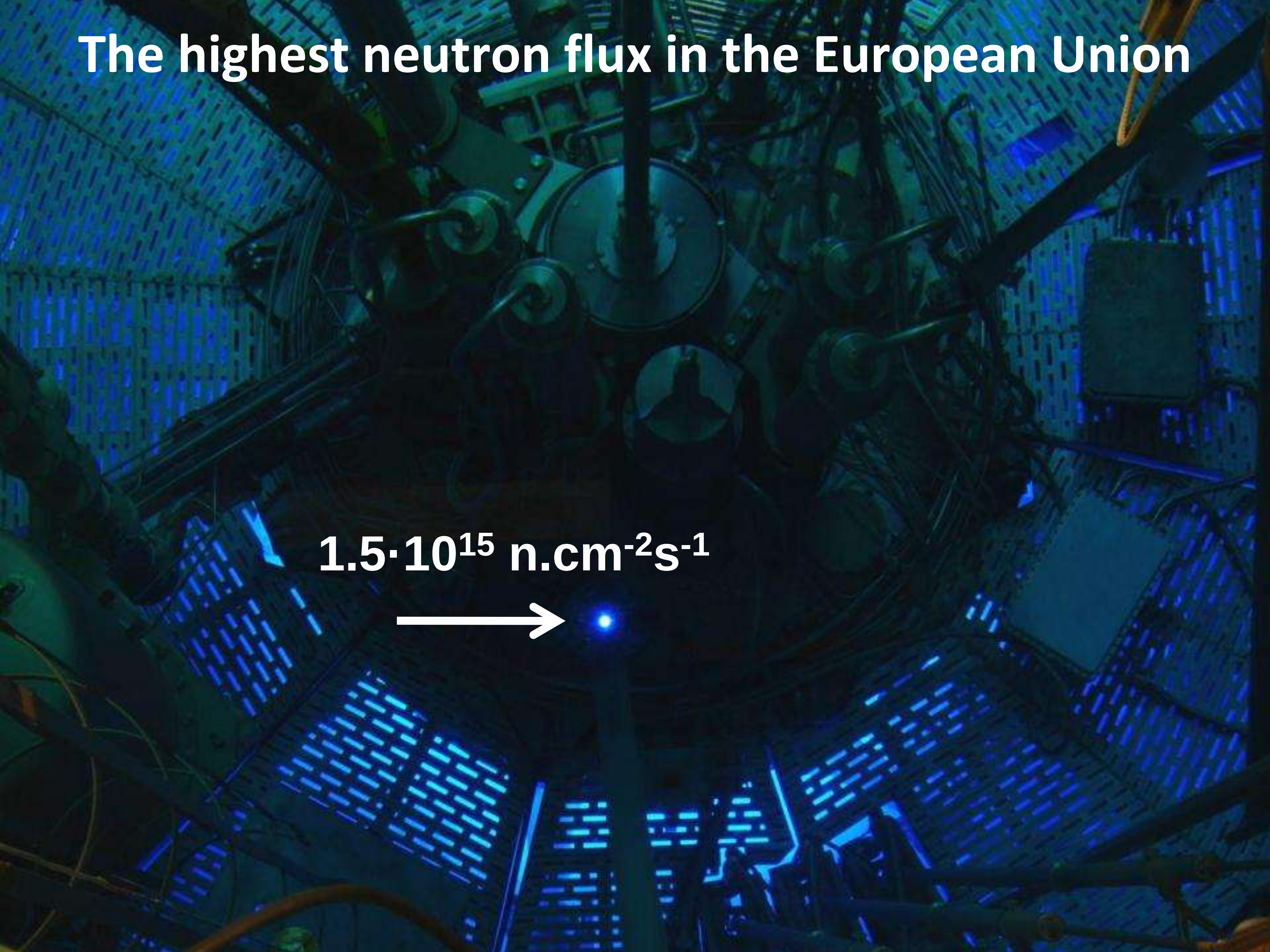
Filling the gap in Mendeleev's table

United Nations
Educational, Scientific and
Cultural Organization

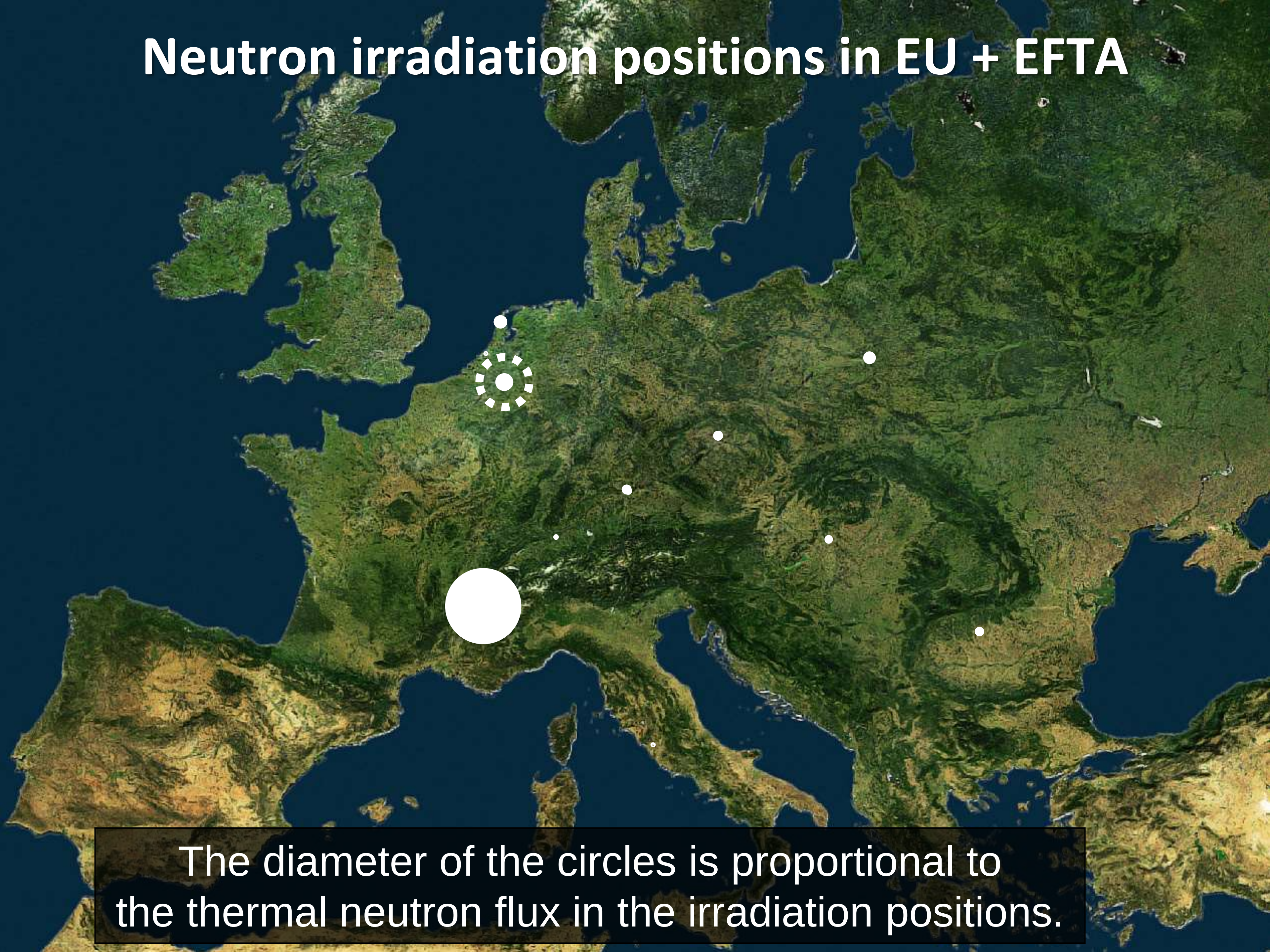
2019 IYPT
International Year
of the Periodic Table
of Chemical Elements



The highest neutron flux in the European Union



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