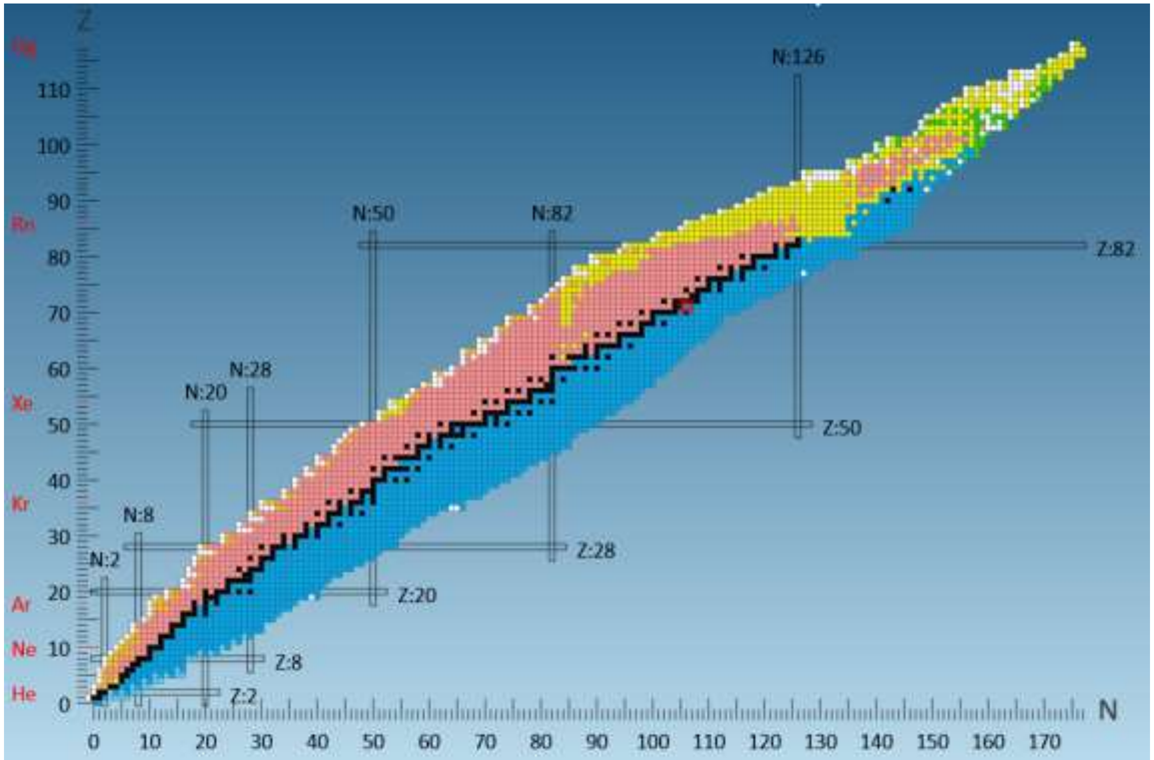
(Cyclotron-produced)

Radionuclides for medicine



NEUTRONS FOR SOCIETY

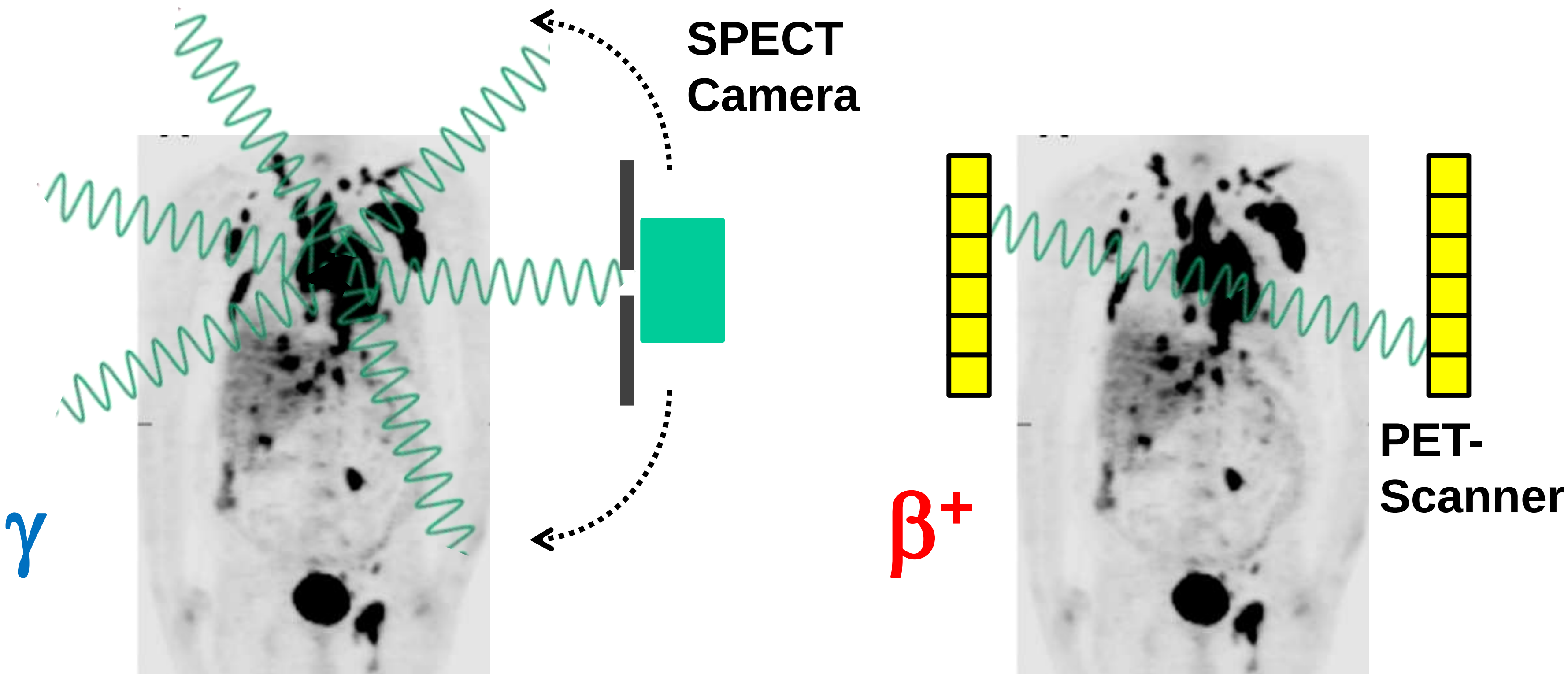
Ulli Köster

ILL Grenoble, France

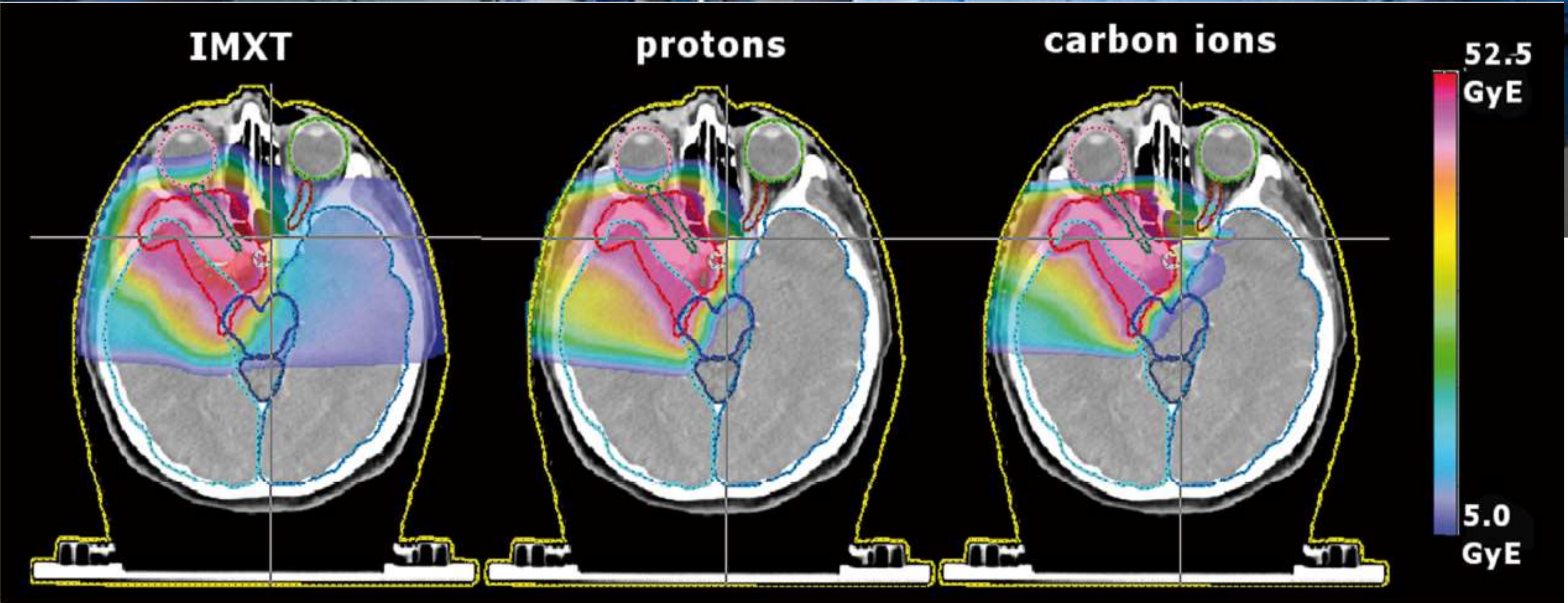
SECURE

PRISMAP Medical Radionuclides

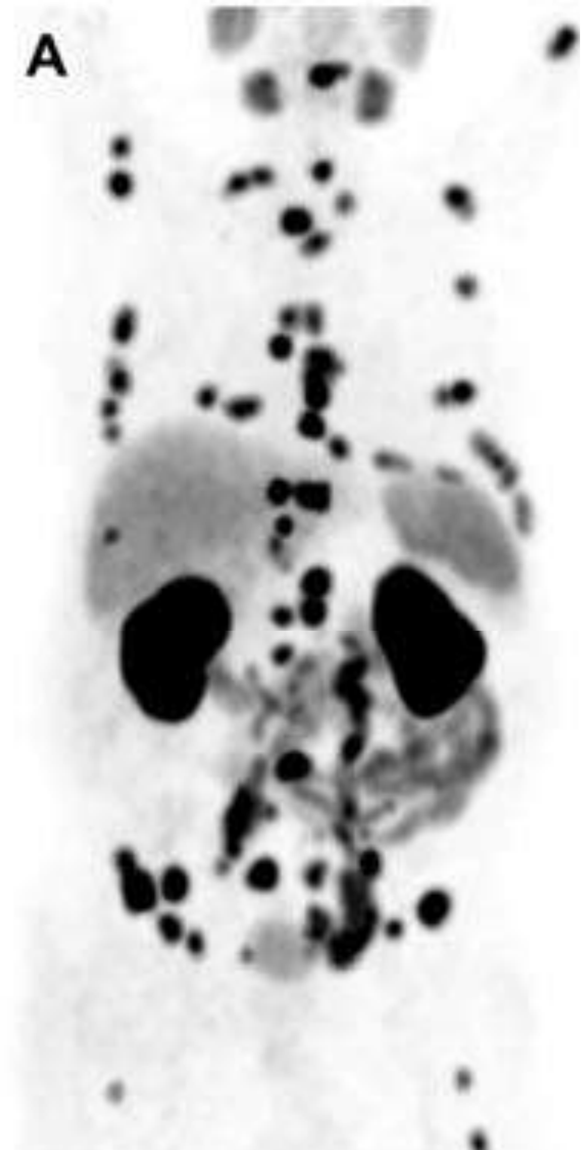
The alphabet of nuclear medicine



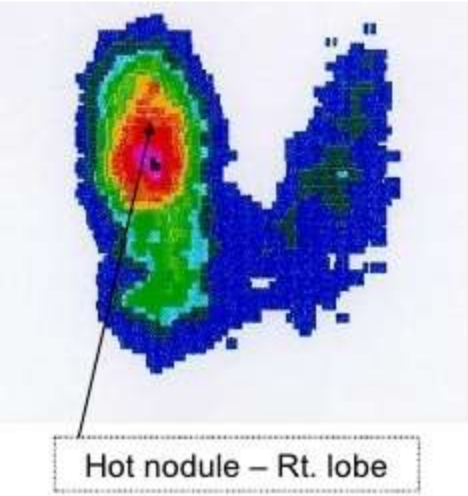
Progress in cancer treatment

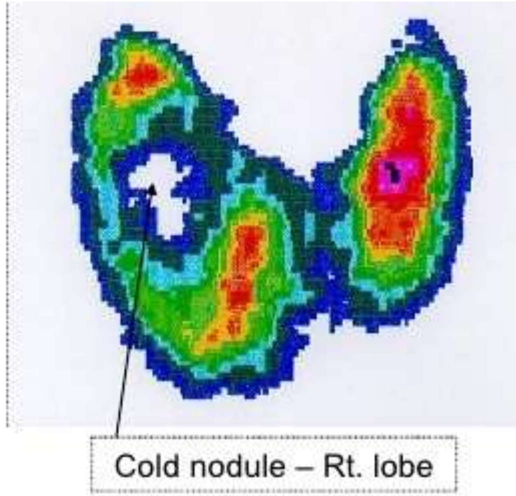


How can one treat such patients?



Thyroid scintigraphy and therapy





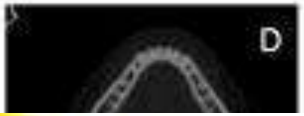
I 123

13.2 h

ε

no β^+

γ 159

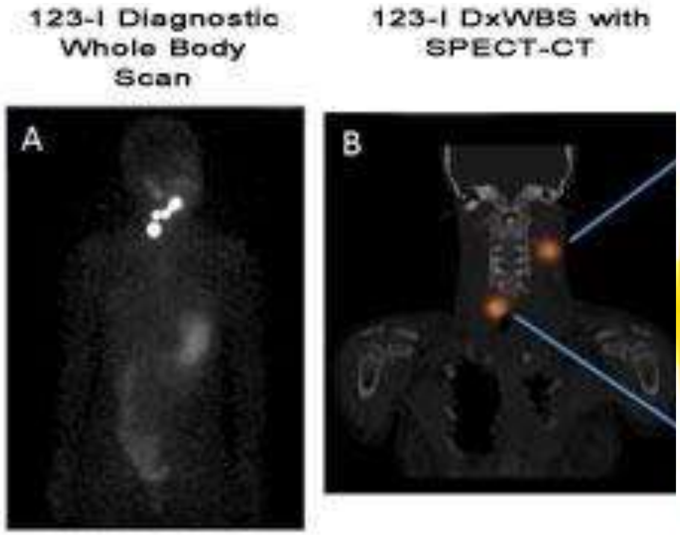


I 131

8.0 d

β^- 1.0, 1.8,…

γ 364, 637…

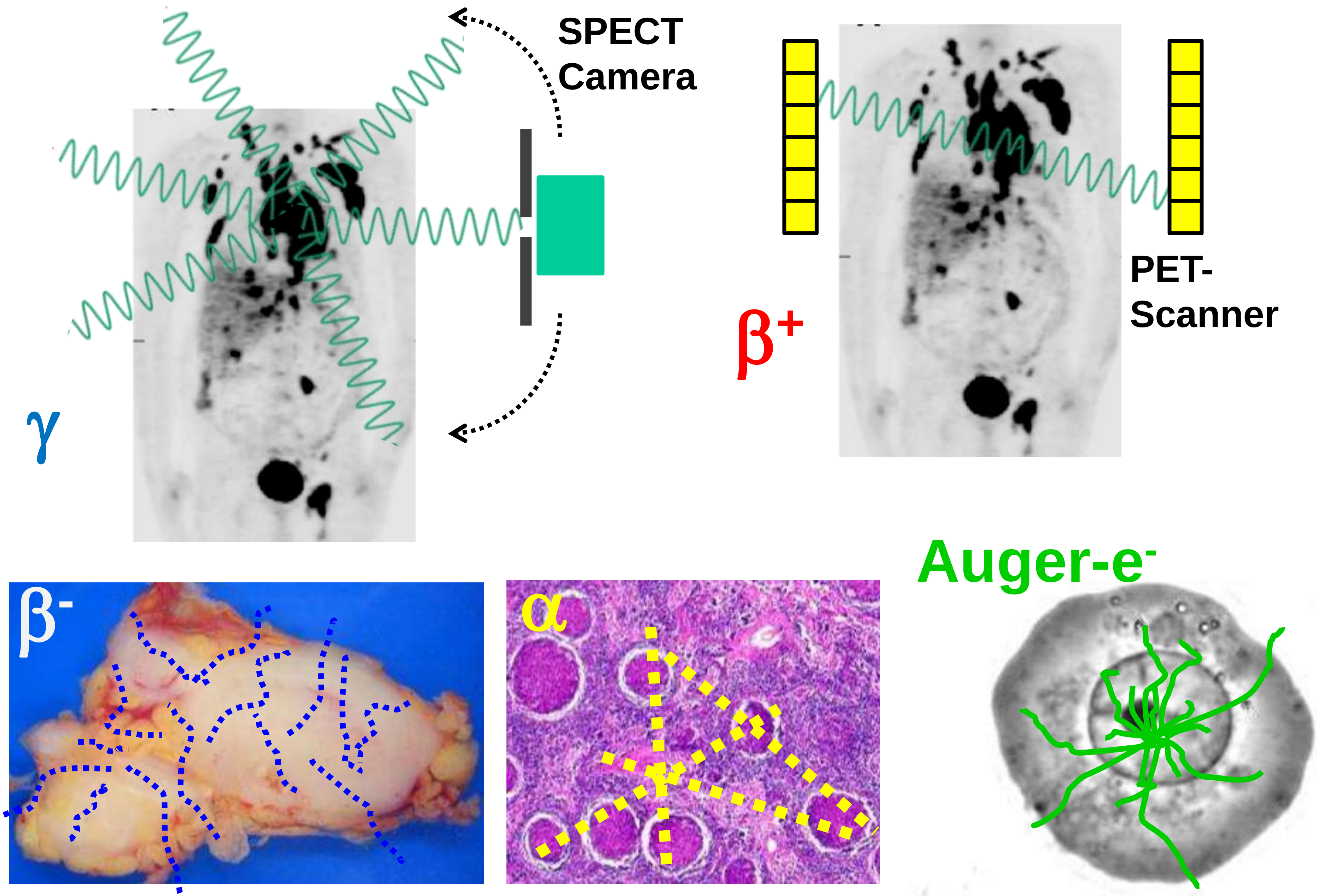


$^{123}I^-$, $^{131}I^-$ or $^{99m}TcO_4^-$ for scintigraphy

$^{131}I^-$ for therapy

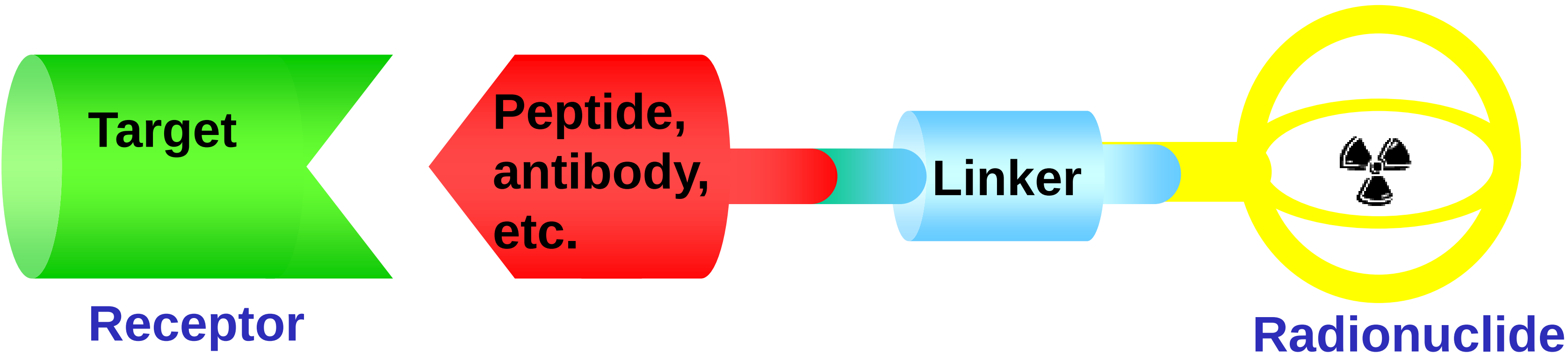
(Papillary) thyroid cancer has the **highest survival** of all malignant cancers!

The Nuclear Medicine Alphabet



Multidisciplinary collaboration to fight cancer

Targeted Radionuclide Therapy (TRT)
Radioligand Therapy (RLT)



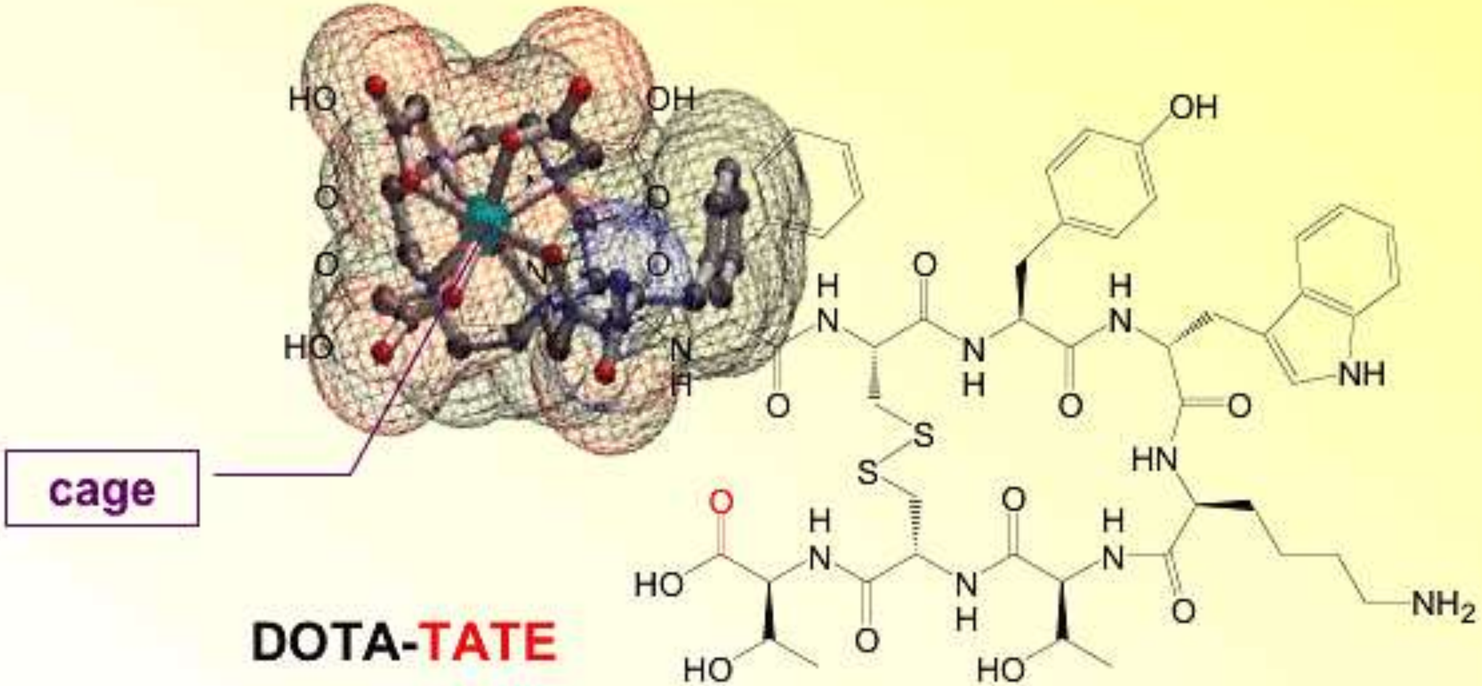
Immunology
Structural biology

Coordination chemistry

Nuclear physics and radiochemistry

Nuclear medicine and medical physics

Structural Formula of DOTA-TOC/TATE



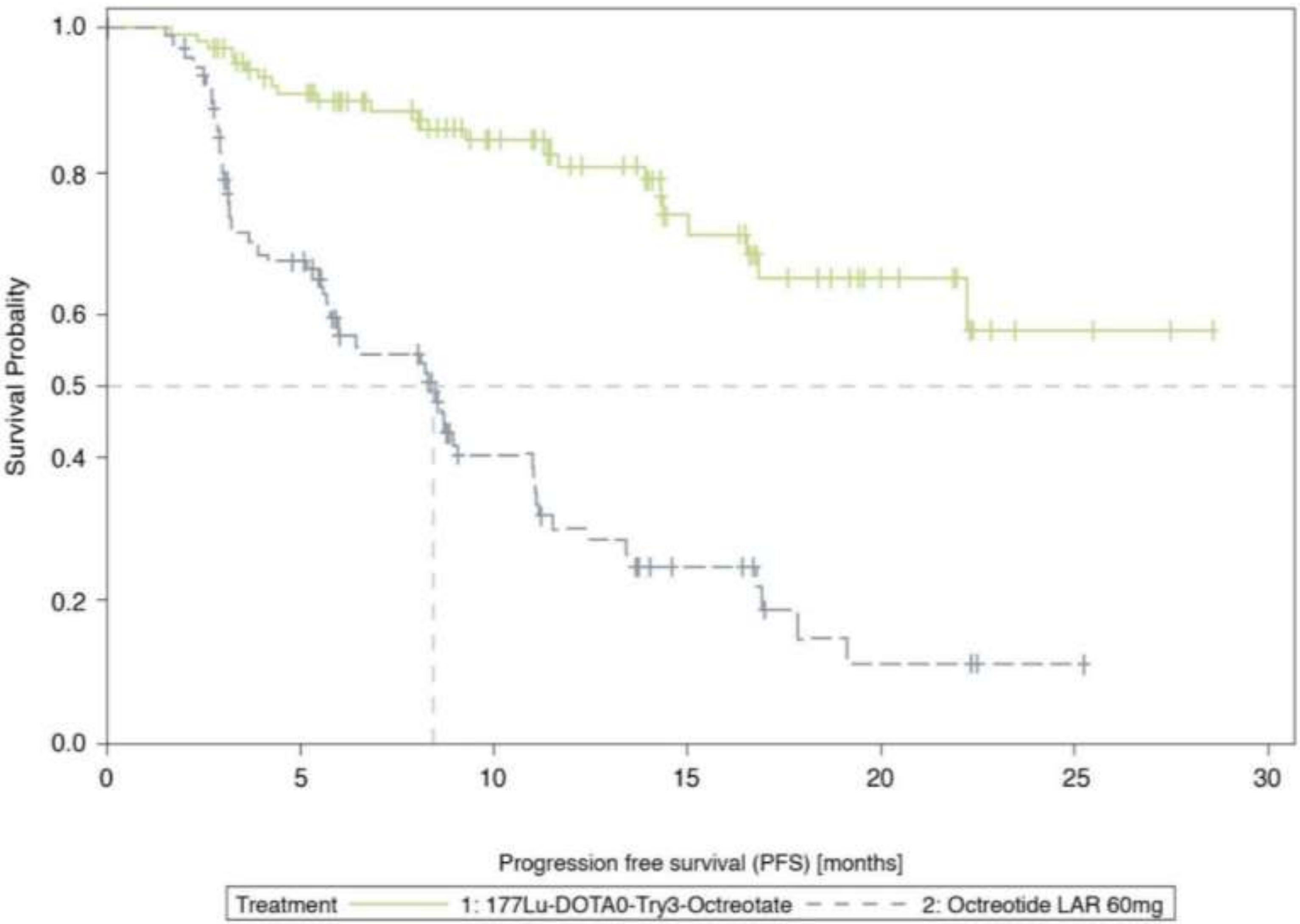
1,4,7,10-tetraazacyclododecantetraacetate

^{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.

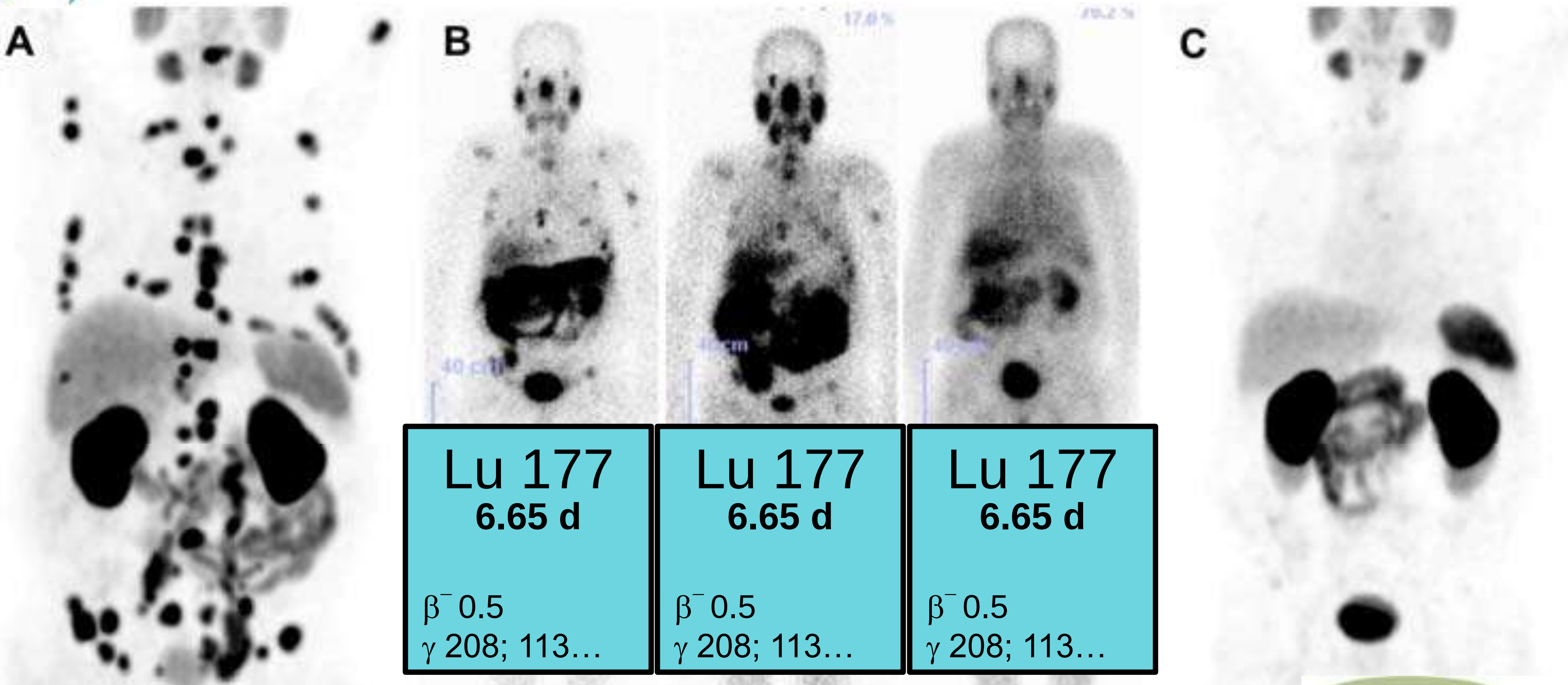
^{177}Lu-Peptide Receptor Radionuclide Therapy of midgut neuroendocrine tumors



29.1.2018
FDA Approval
of Lutathera

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

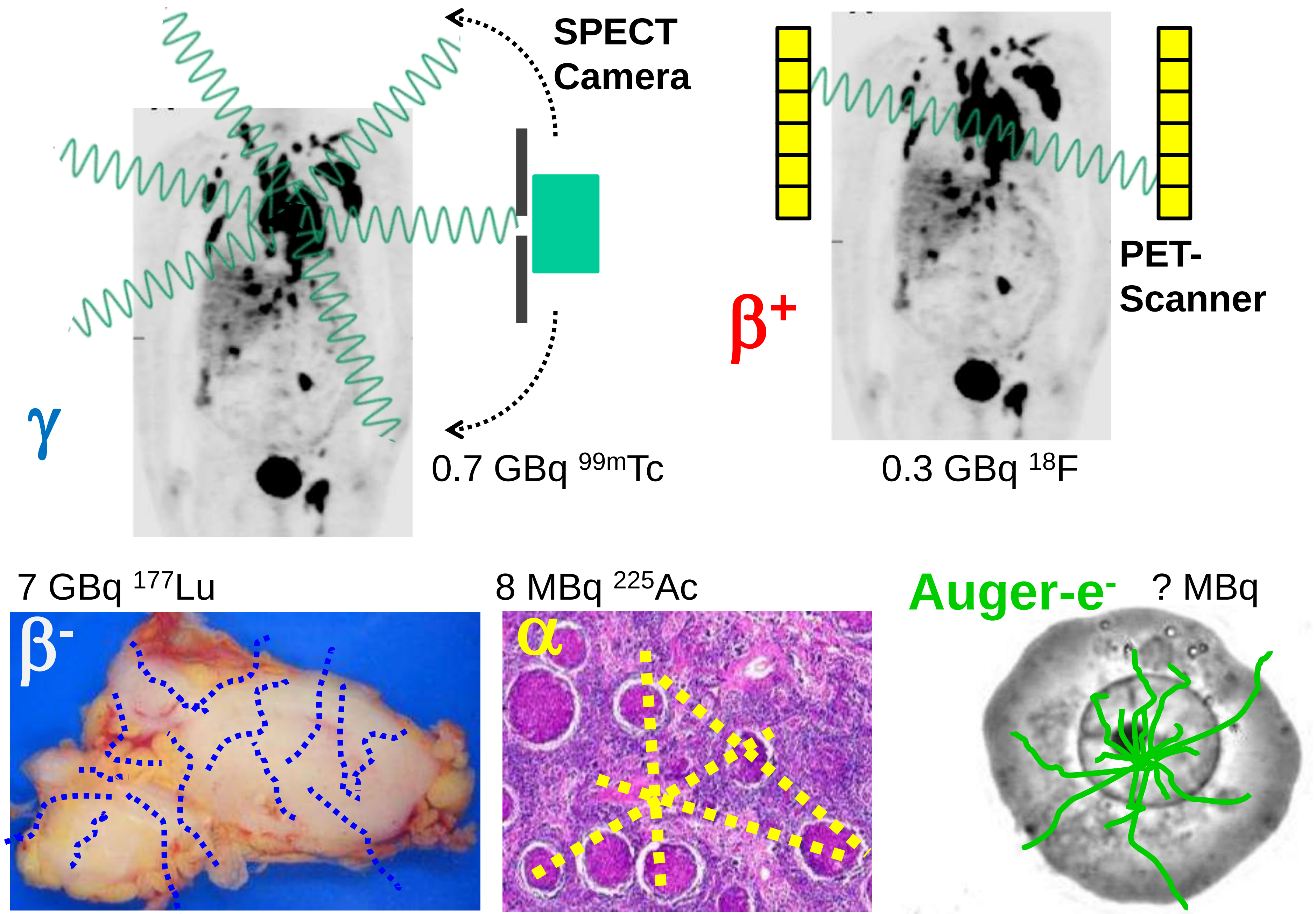
^{177}Lu-radioligand therapy of advanced prostate cancer



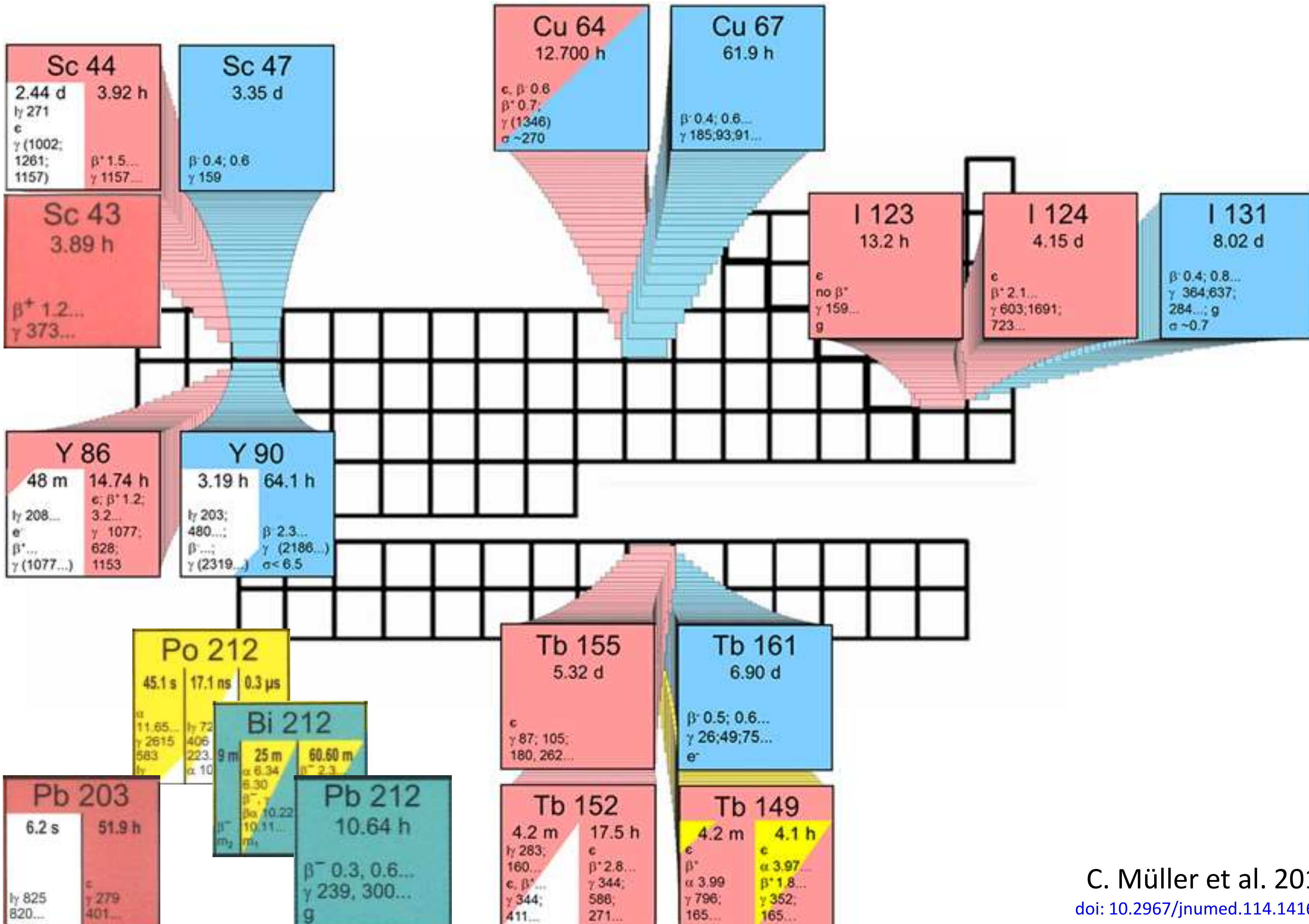
C. Kratochwil et al., Eur J Nucl Med Mol Imaging 2015;42:987.
M. Weineisen et al., J Nucl Med 2015;56:1169.
R.P. Baum et al., J Nucl Med 2016;57:1006.
C. Kratochwil et al., J Nucl Med 2016;57:1170.
K. Rahbar et al., J Nucl Med 2017;58:85.
M.S. Hofman et al., Lancet Oncol 2018;19:825.
O. Sartor et al., N Engl J Med 2021;385:1091.

Approval
23.3.2022 FDA
11.8.2022 MHRA
9.12.2022 EMA

The Nuclear Medicine Alphabet



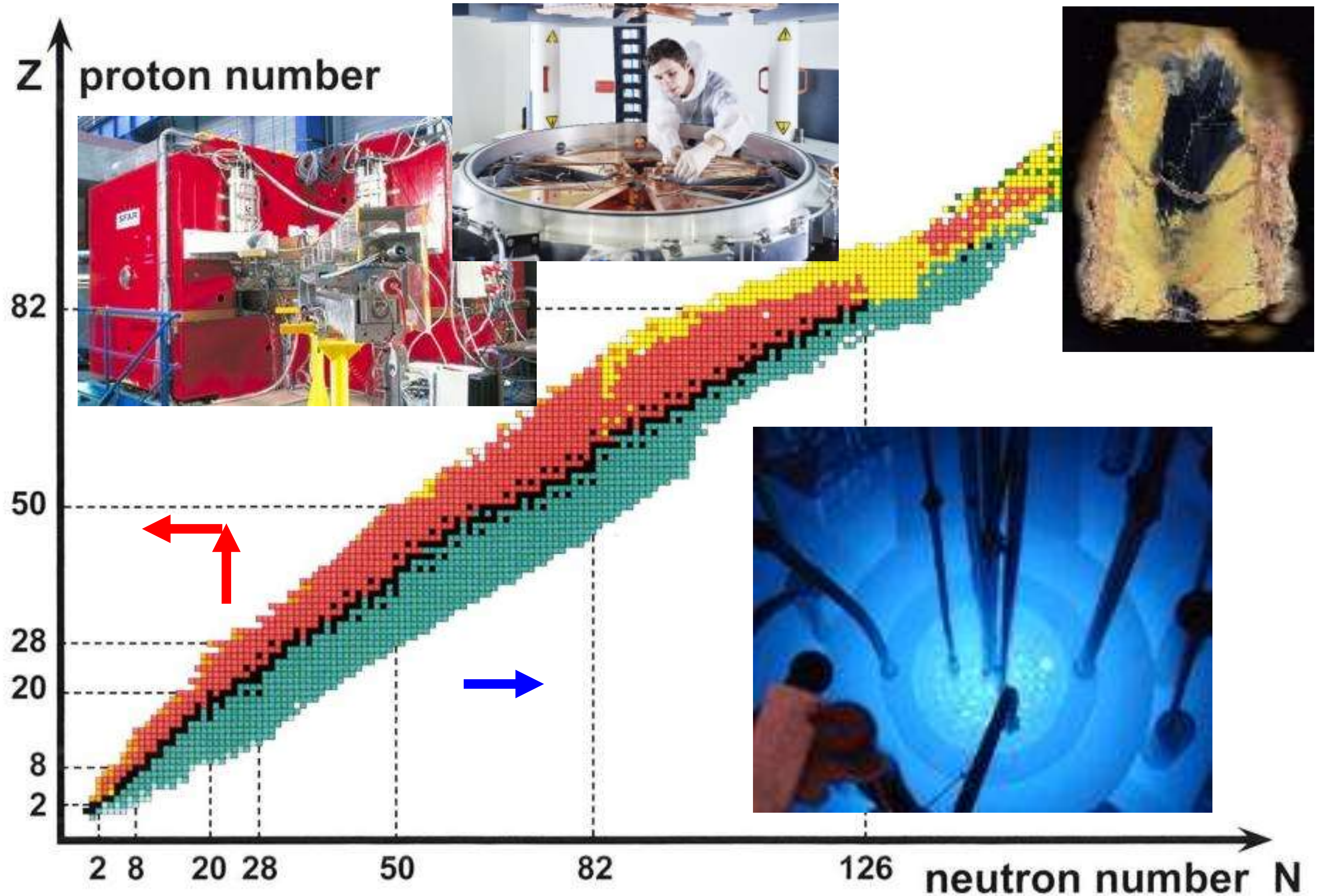
Matched pairs for theranostics



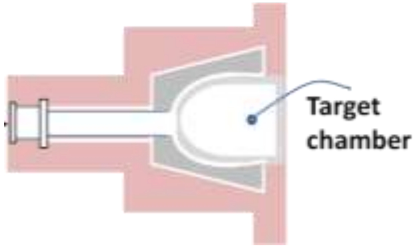
C. Müller et al. 2014

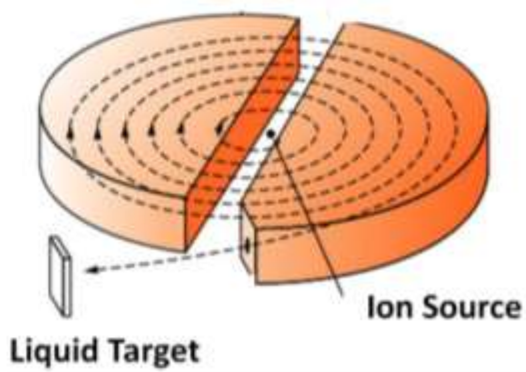
doi: 10.2967/jnumed.114.141614

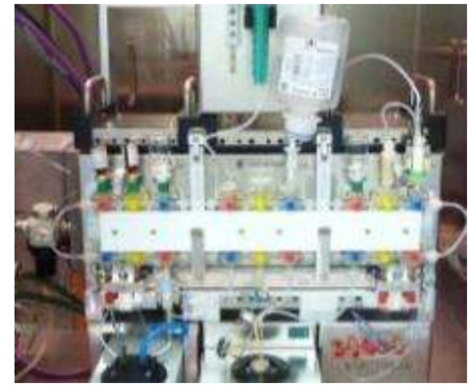
The “Alpine divide” of radionuclide production



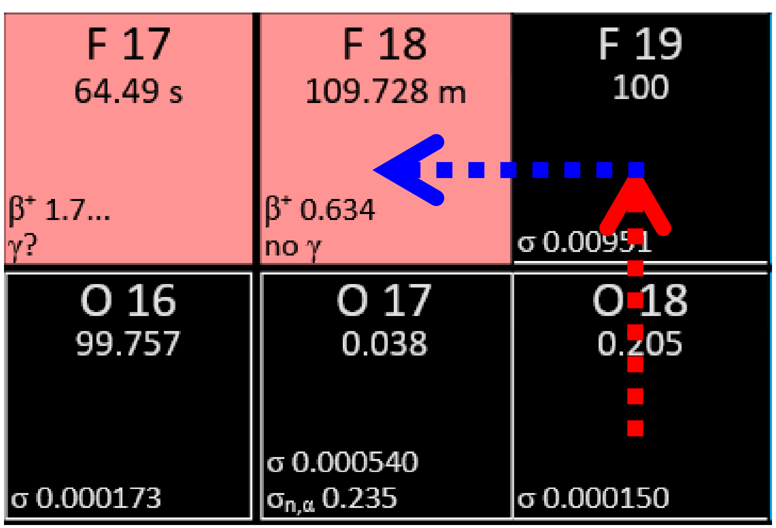
^{18}F production via $^{18}O(p,n)$

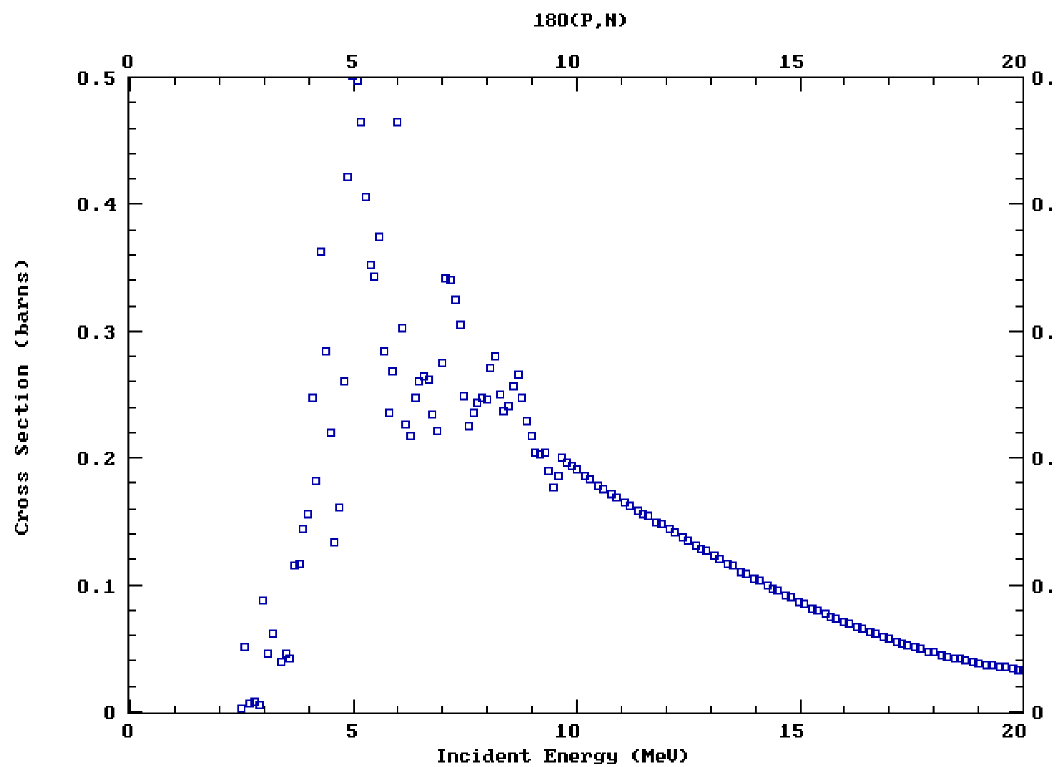






$H_2{}^{18}O$ (water) Cyclotron irradiation Transformation into FDG

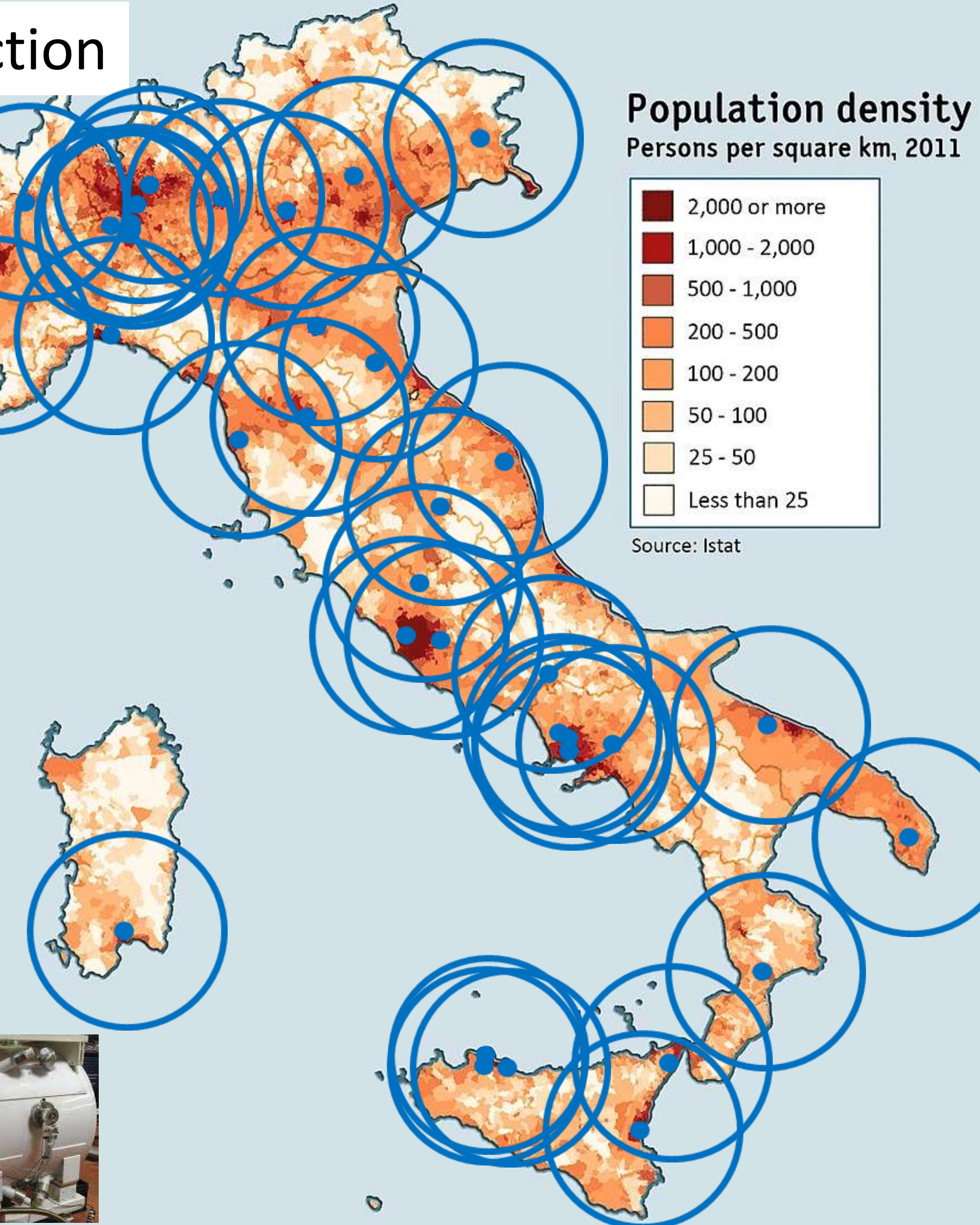




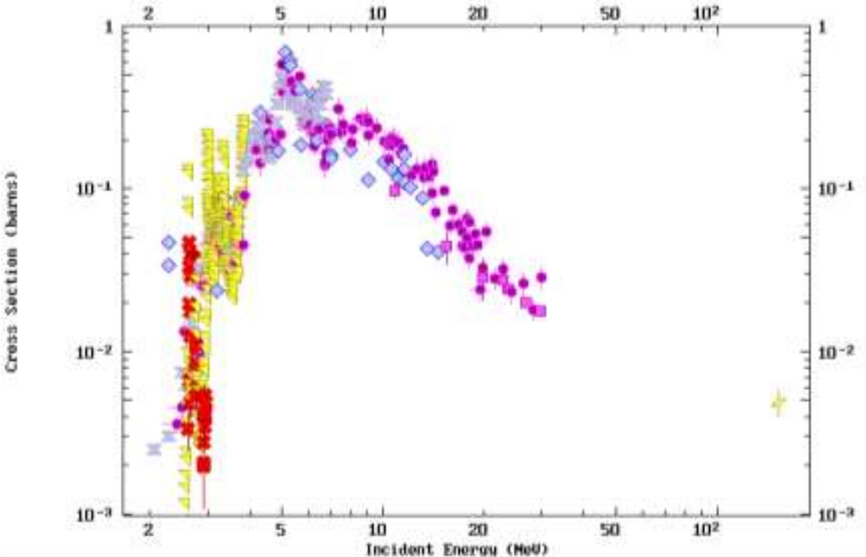
Cyclotrons for ^{18}F production

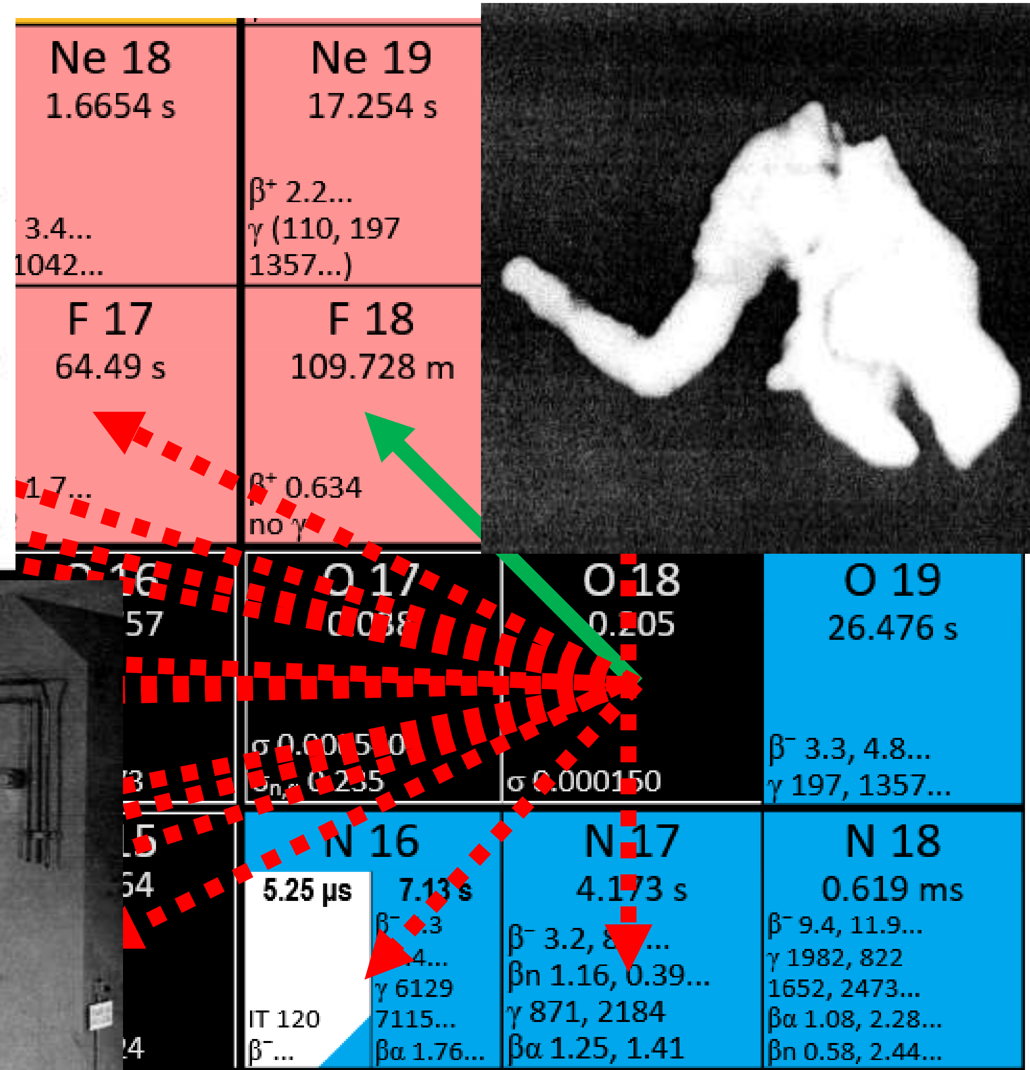
F 18
110 m
β^+ 0.633
no γ

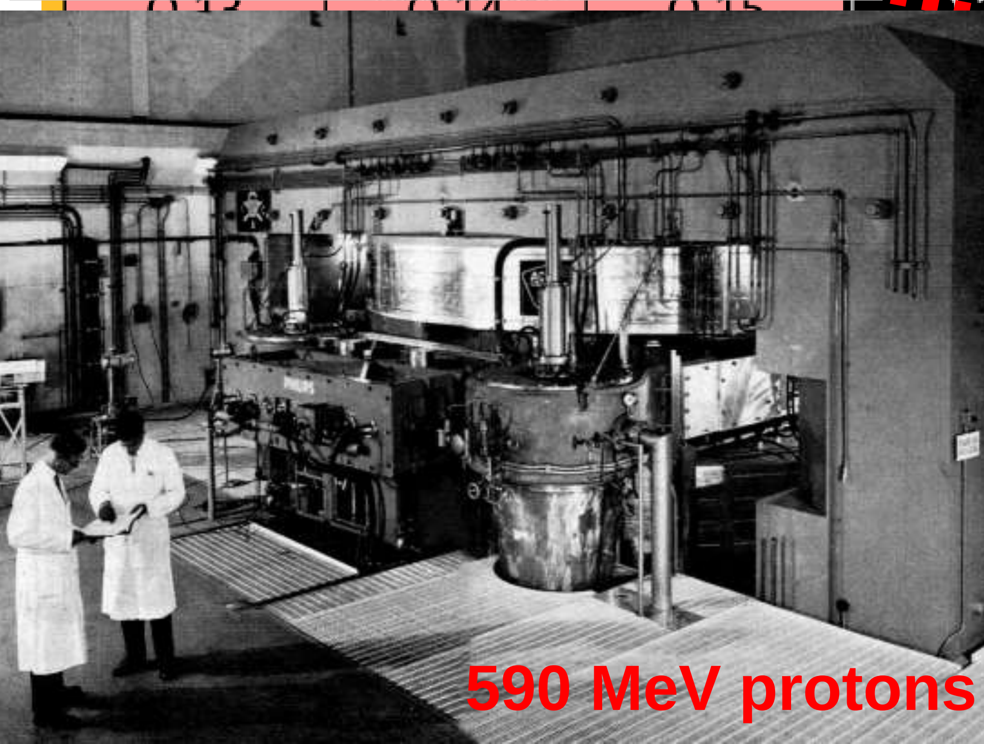
13x IBA cyclone 18
11x GE PETtrace 16.5
9x GE Minitrace 9.6
4x Siemens Eclipse 11
2x ACSI TR19
1x PMB Isotrace 12



^{18}F production via $^{18}O(p,n)$

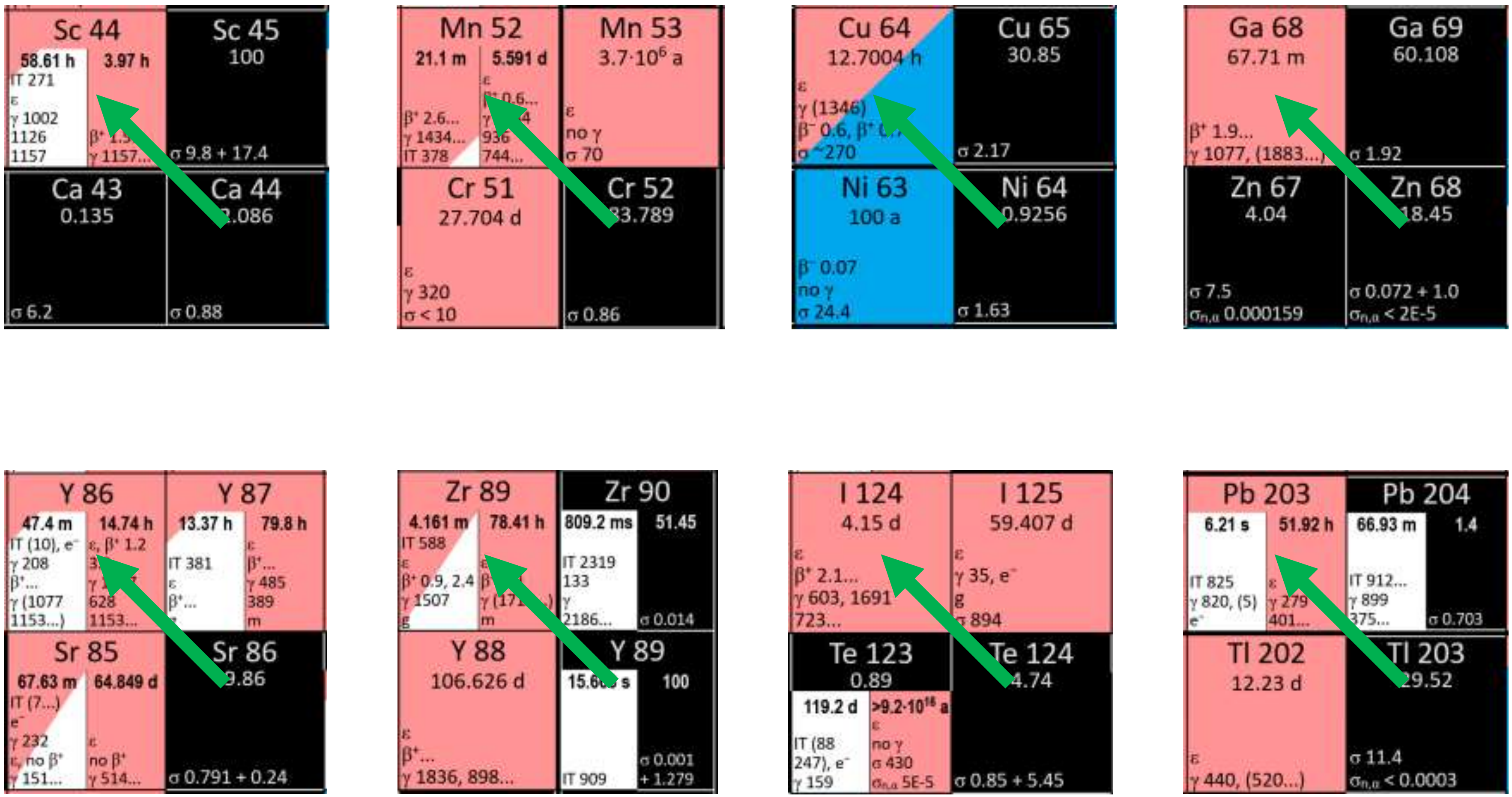






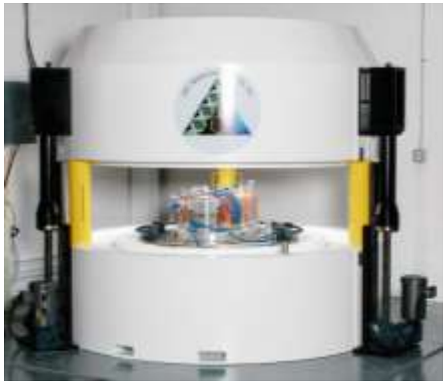
Tochon-Danguy, Townsend et al., J Fluorine Chem 1988;44:33.

(p,n) reactions



odd-odd or even-odd product nuclides

Cyclotrons for (p,n) reactions: <12 MeV




ABT BG-75
7.5 MeV, 1-5 μA

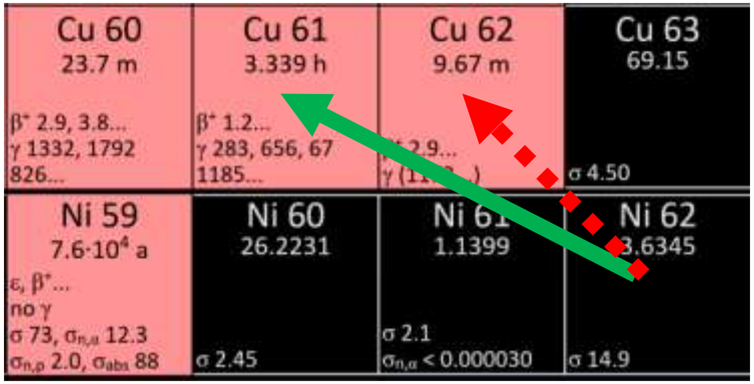
GE Minitrace
9.6 MeV, 50 μA

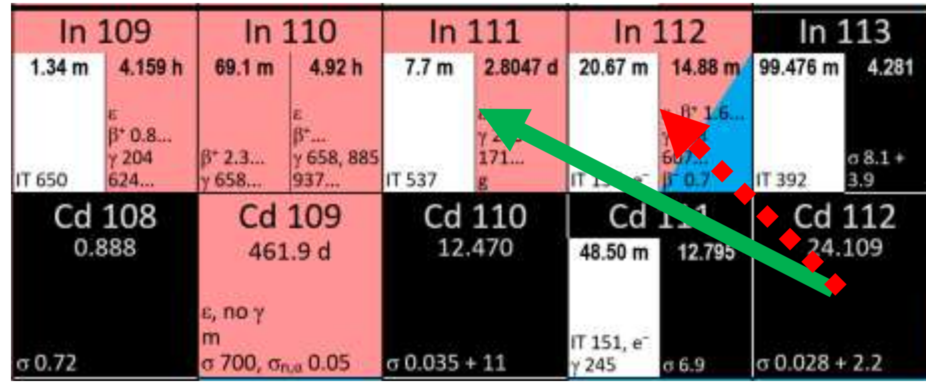
IBA Cyclone Key
9.2 MeV, 100 μA
also Cyclone 10/5
and Cyclone 11

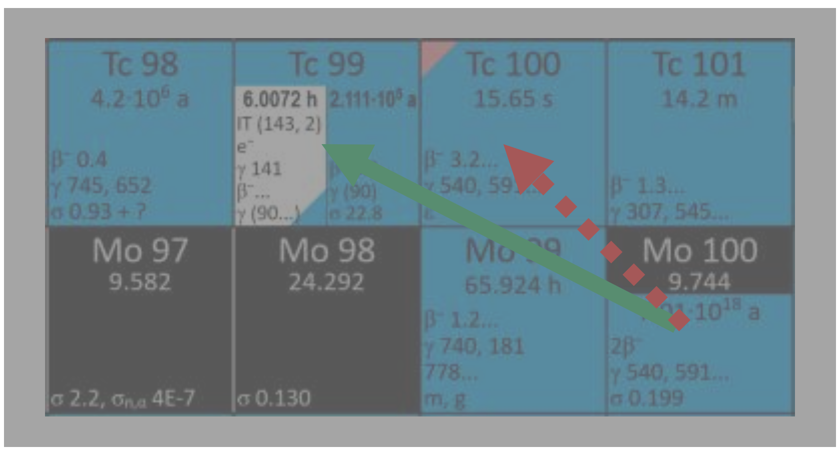
Siemens Eclipse
11 MeV, 80-120 μA

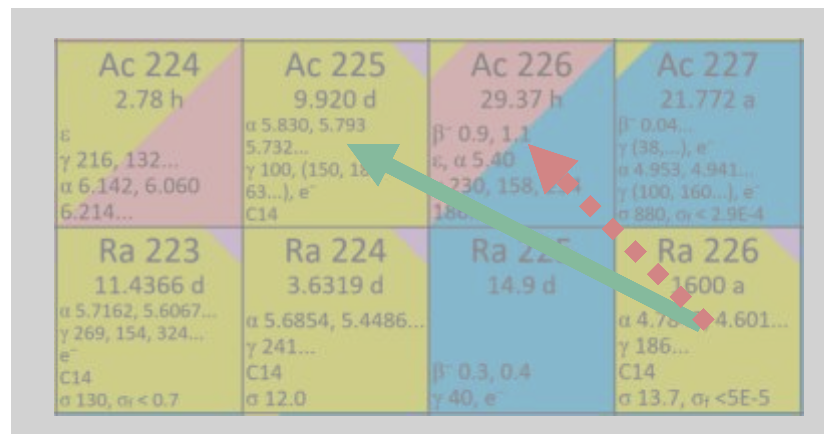
PMB-ALCEN Isotrace
12 MeV, 100 μA

(p,2n) reactions









odd-even product nuclides

(p,n) product much shorter-lived

Cyclotrons for (p,2n) reactions: 16-20 MeV

IBA Cyclone 18
18 MeV, 150 μA

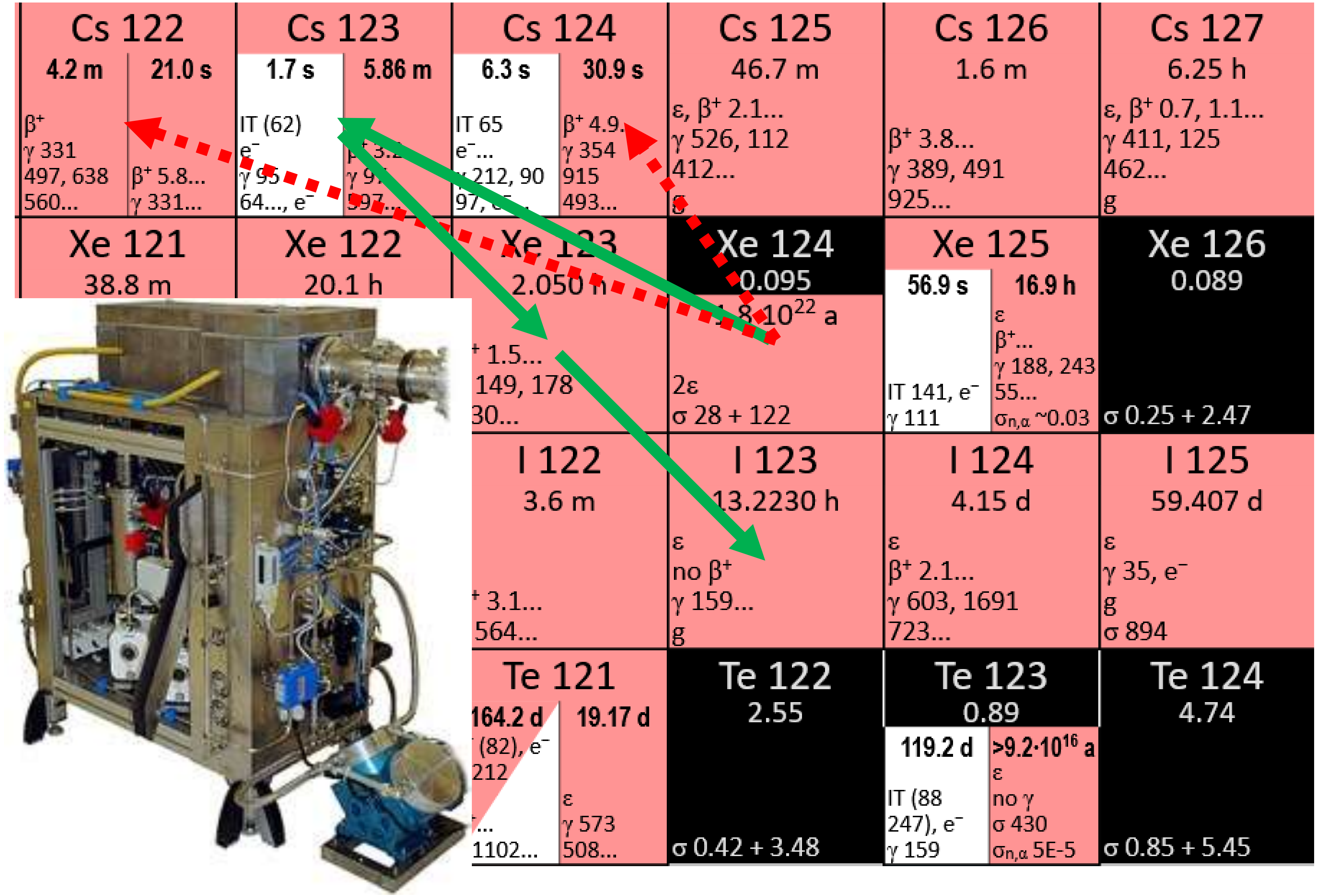
GE PetTrace
16.5 MeV, 100 μA

ASCI TR19
12-19 MeV, -400 μA

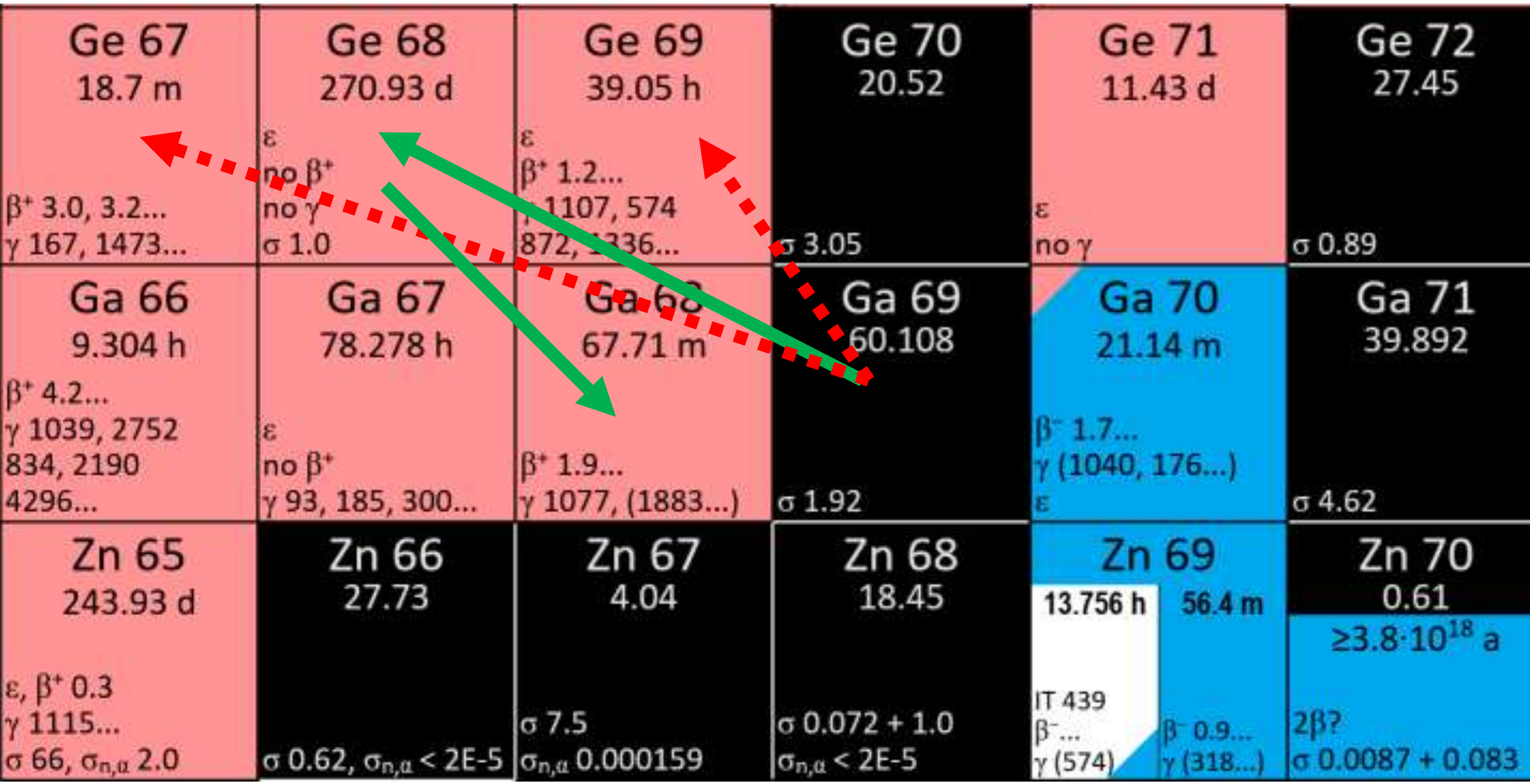
IBA Cyclone Kiube
13/14/15/18 MeV, -300 μA

ASCI TR24
12-25 MeV, 300/500/800 μA

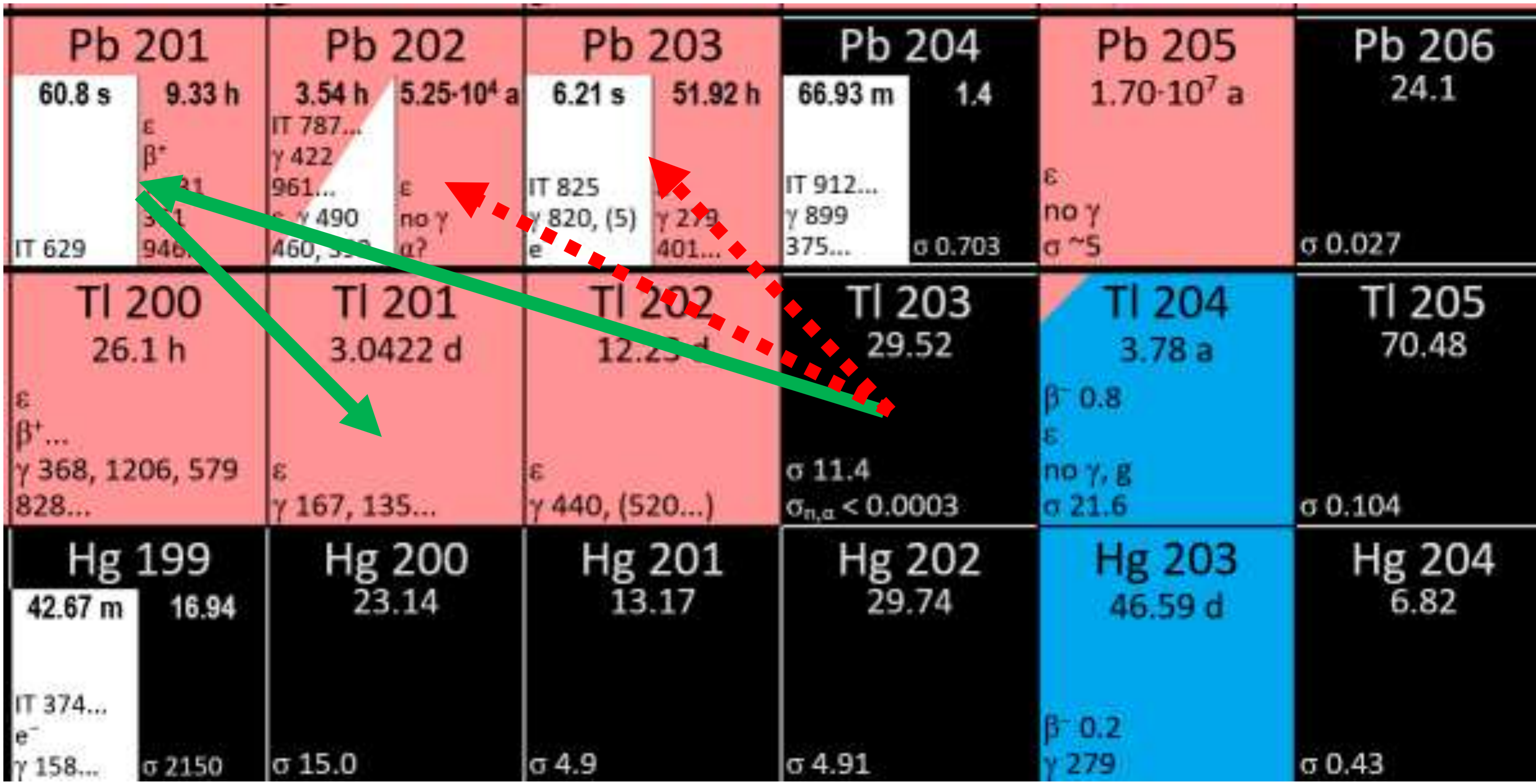
$^{124}Xe(p,2n)^{123}Cs\ (\beta^+/EC)^{123}Xe\ (\beta^+/EC)\ ^{123}I$



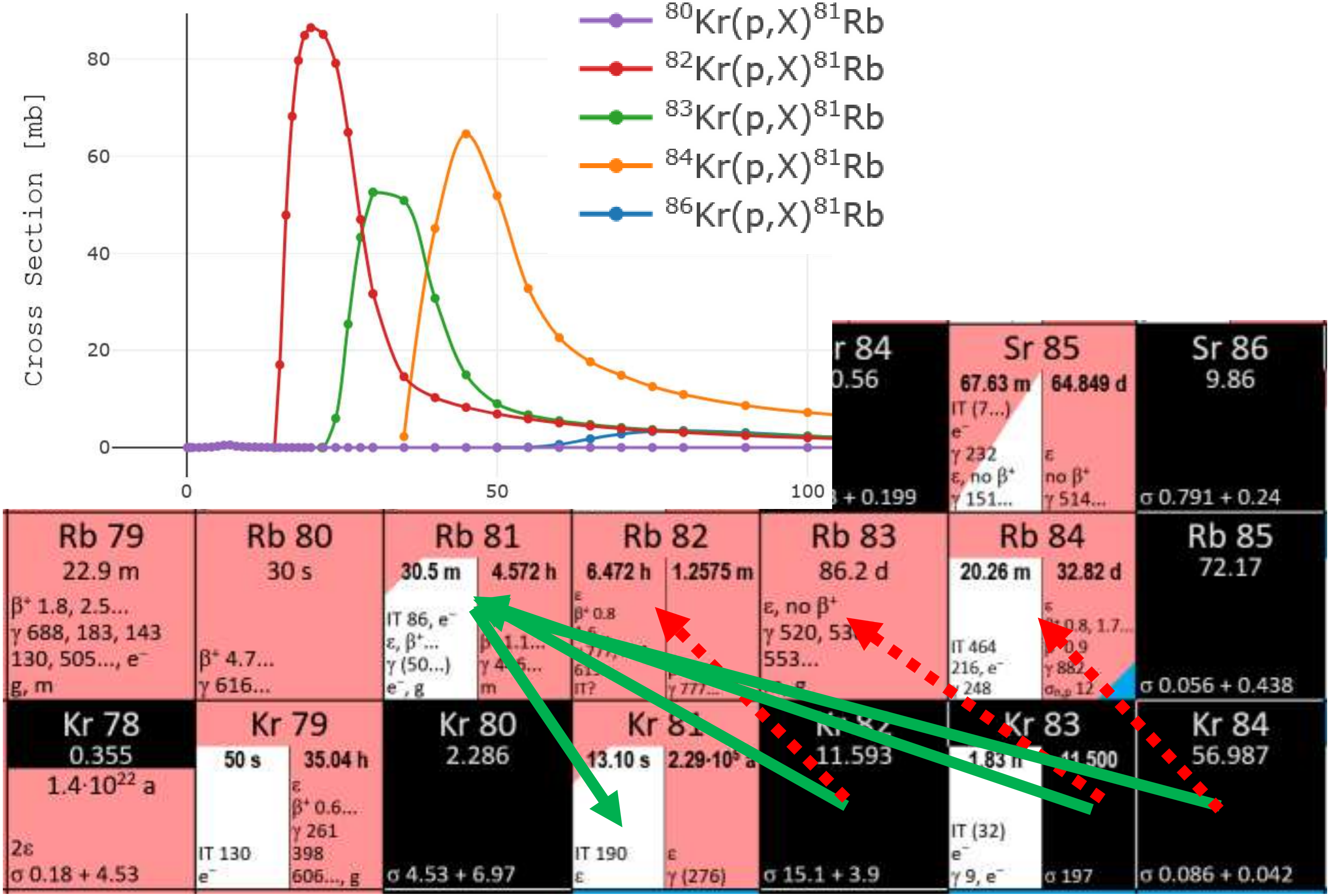
$^{69}Ga(p,2n)^{68}Ge \Rightarrow {}^{68}Ge/^{68}Ge$ generator



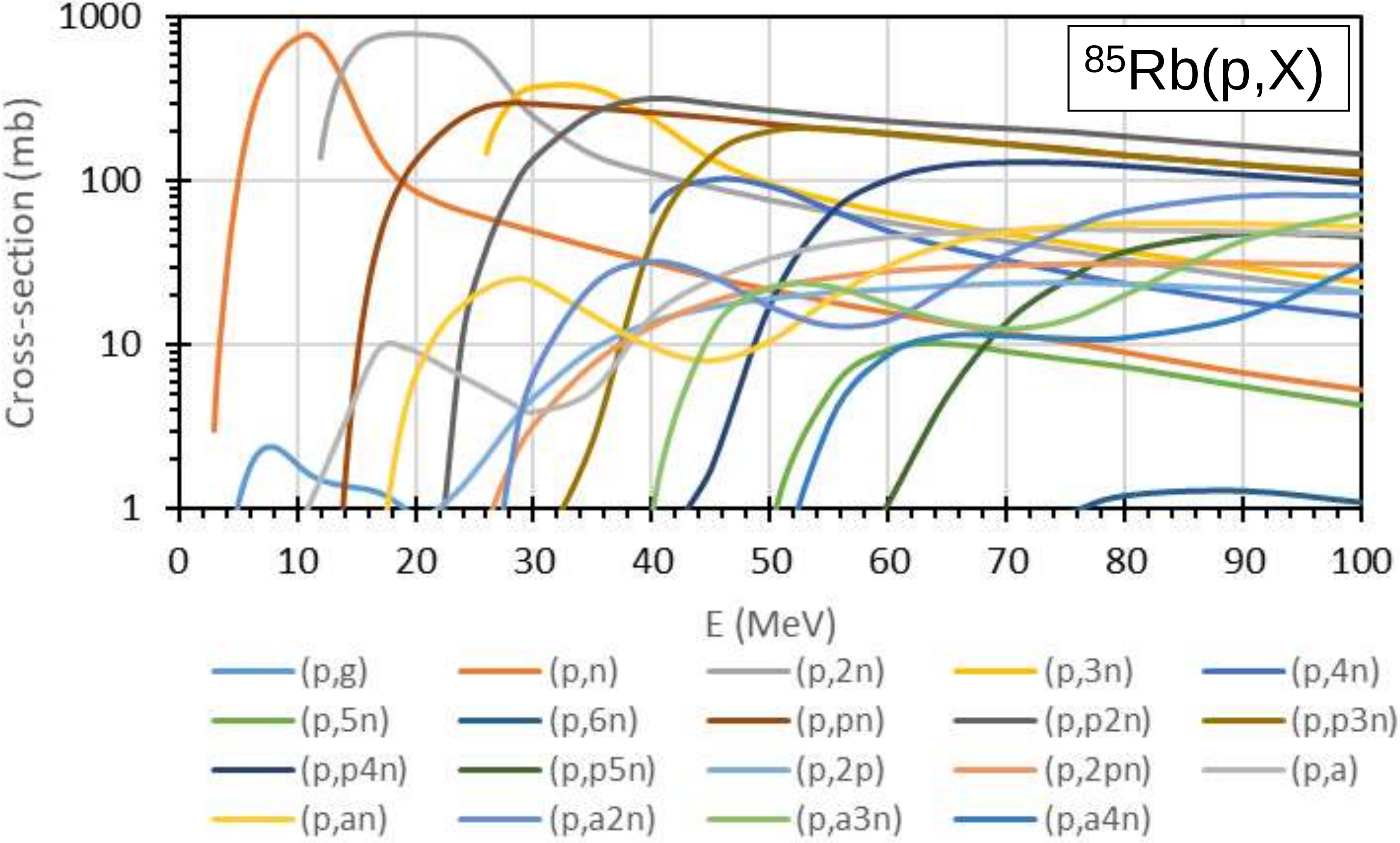
$^{203}Tl(p,3n)^{201}Pb \Rightarrow$ chem.sep. (EC)$^{201}Tl \Rightarrow$ chem.sep.



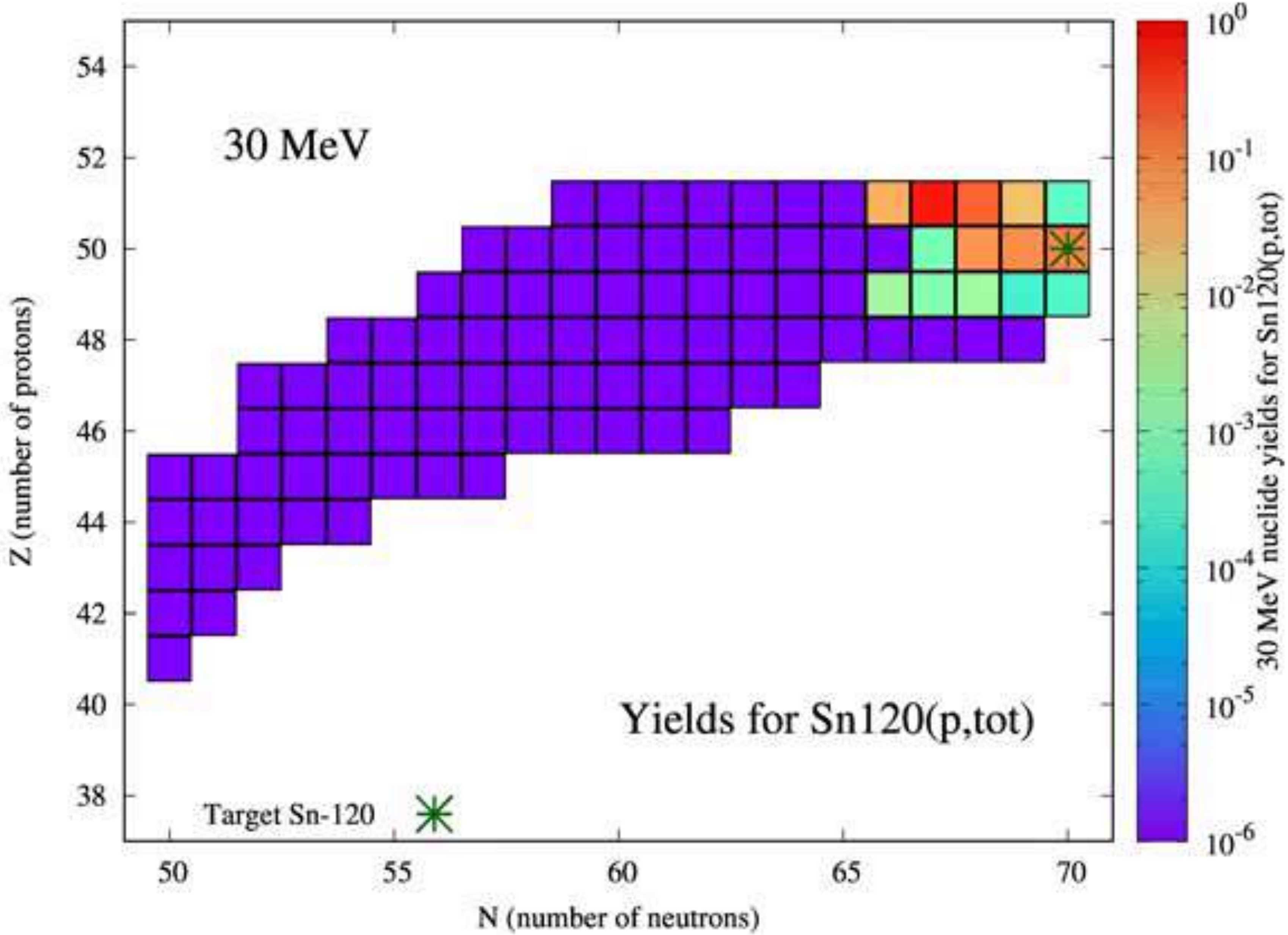
$^{nat}Kr(p,X)^{81}Rb \Rightarrow {}^{81}Rb/{}^{81m}Kr$ generator



Energy dependence of cross-sections

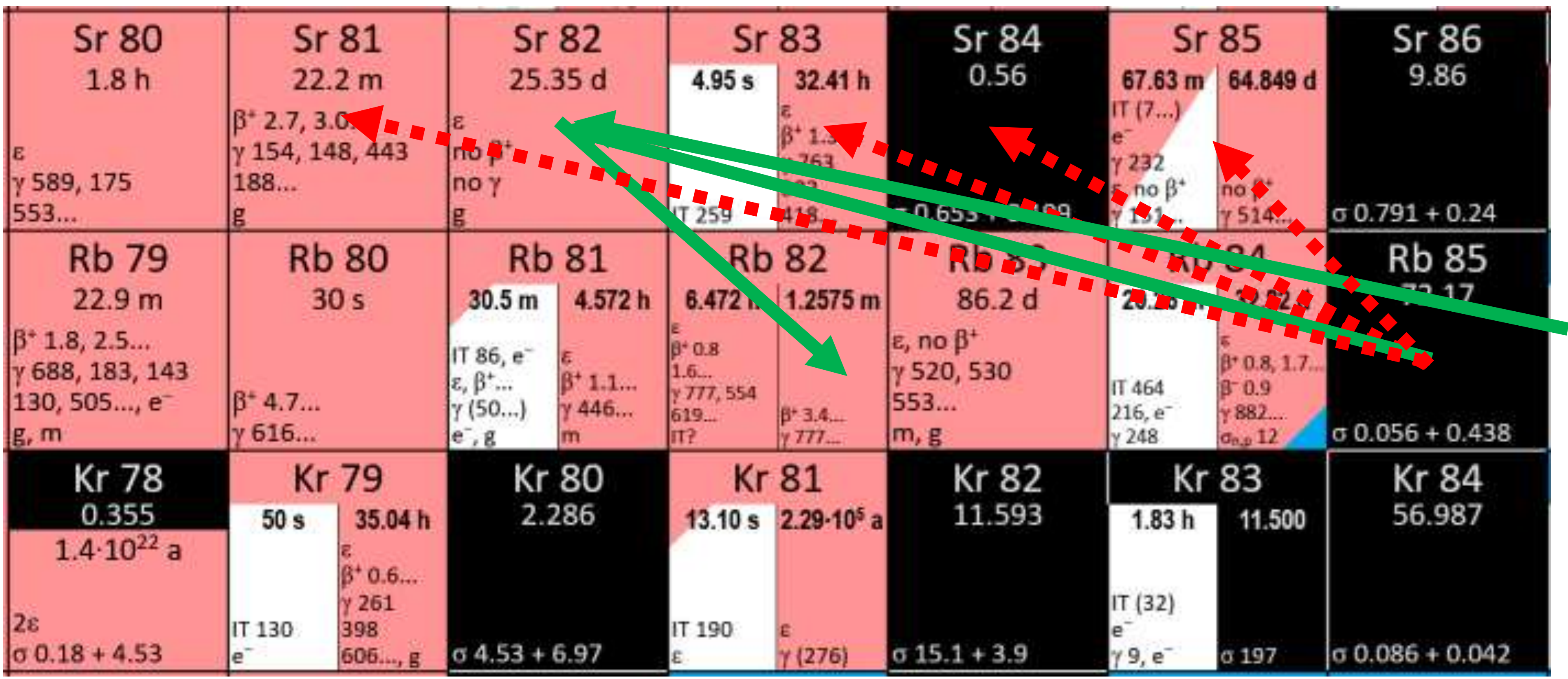


Energy dependence of cross-sections

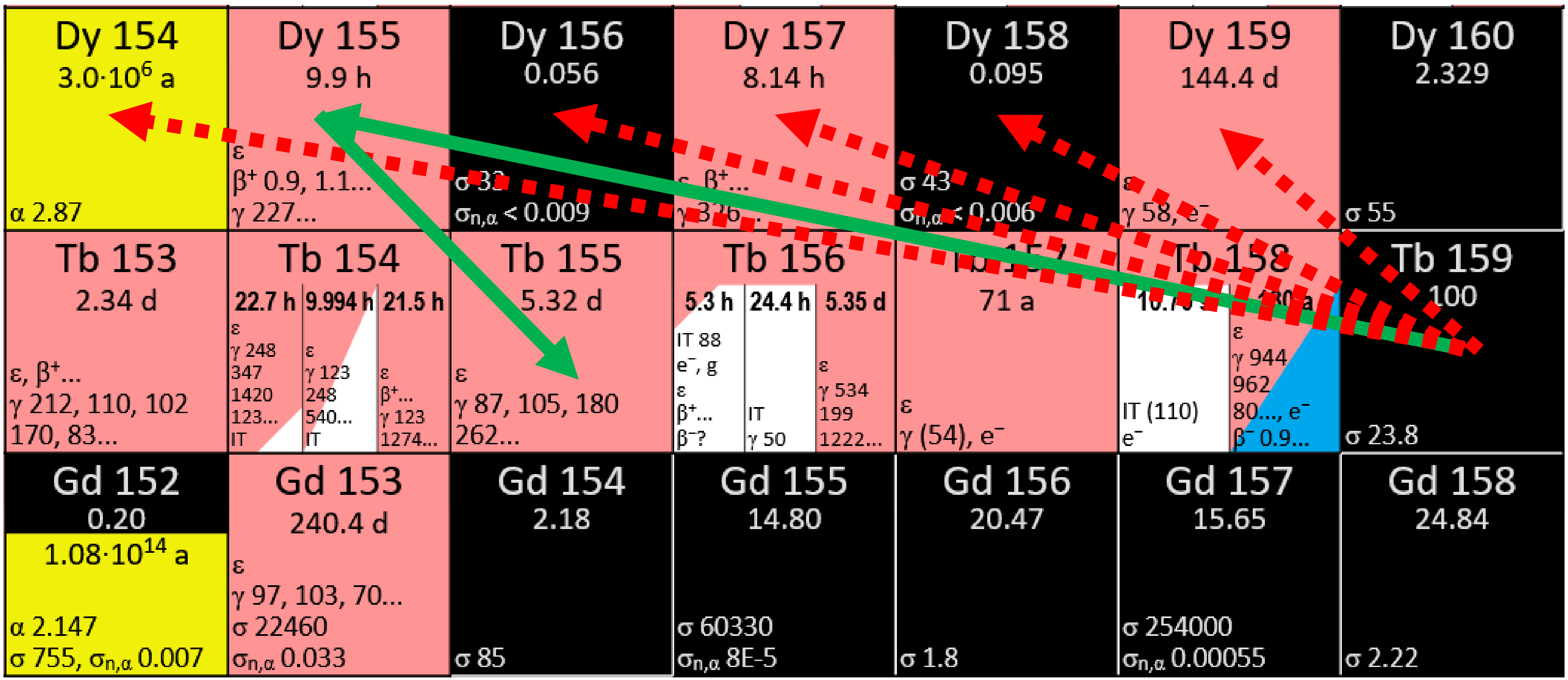


https://fispact.ukaea.uk/development/advanced-nuclear-data-forms/

$^{85/87}Rb(p,4n/6n)^{82}Sr \Rightarrow {}^{82}Rb/^{82}Rb$ generator



$^{159}Tb(p,5n)^{155}Dy \Rightarrow$ chem.sep. (EC)$^{155}Tb \Rightarrow$ chem.sep.

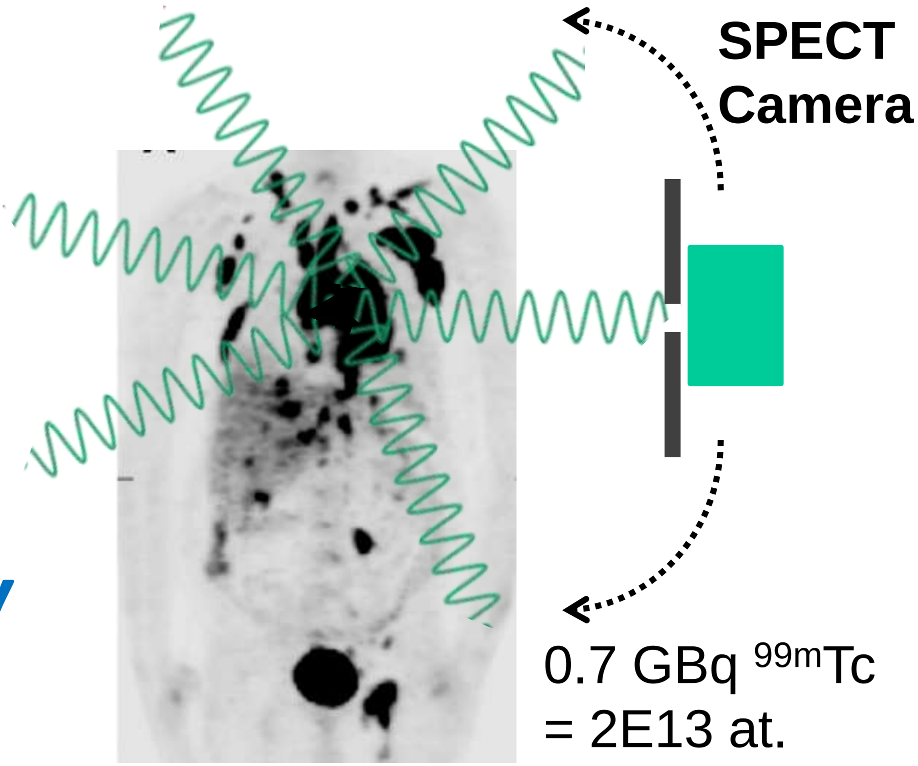


Diagnostic radionuclides

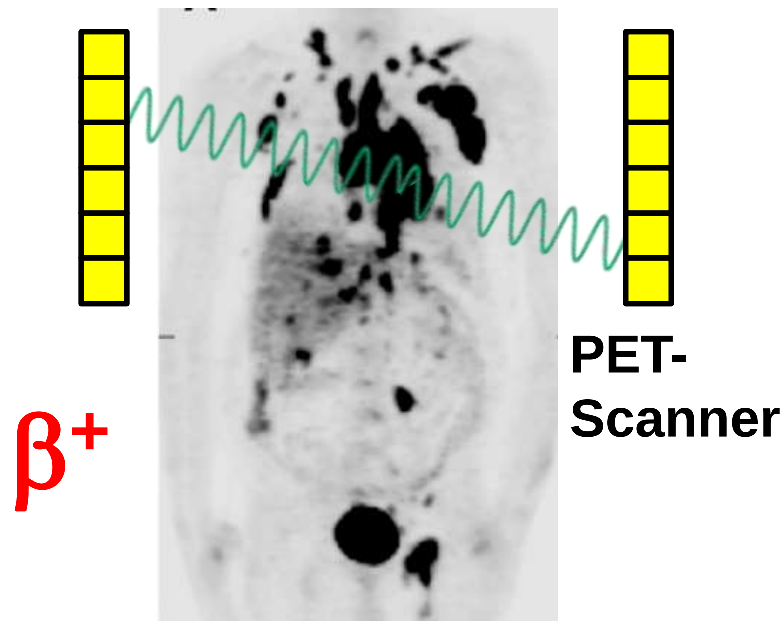
- Most short-lived: hours
  $\Rightarrow$ decentralized production network
  or generators with centralized production

- Few longer-lived: days
  $\Rightarrow$ centralized production

The Nuclear Medicine Alphabet

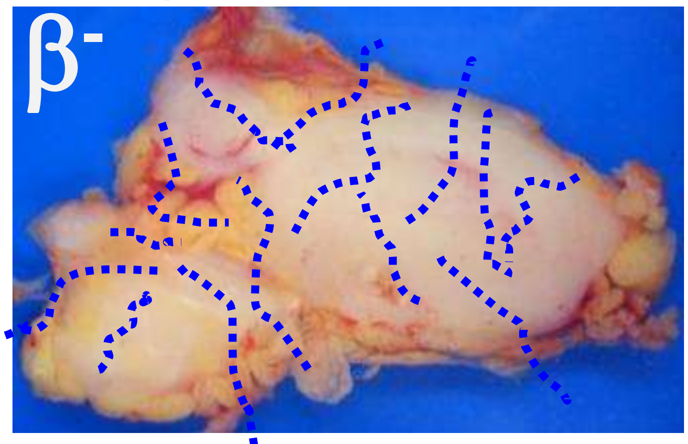


0.7 GBq ^{99m}Tc
= 2E13 at.

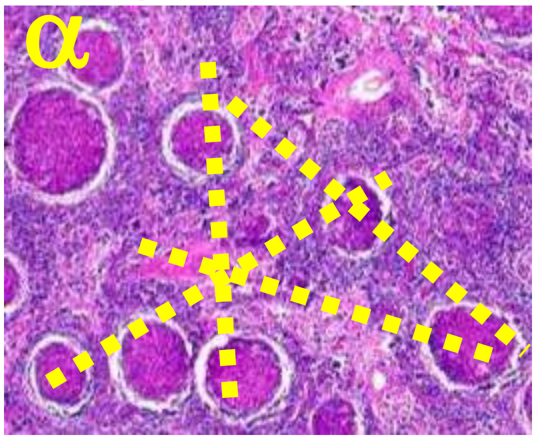


0.3 GBq ^{18}F
= 5E12 at.

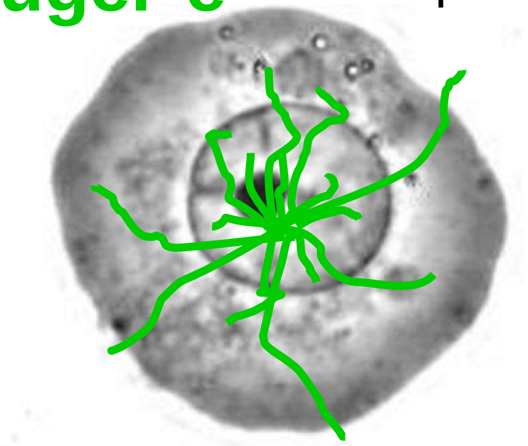
7 GBq ^{177}Lu = 6E15 at.



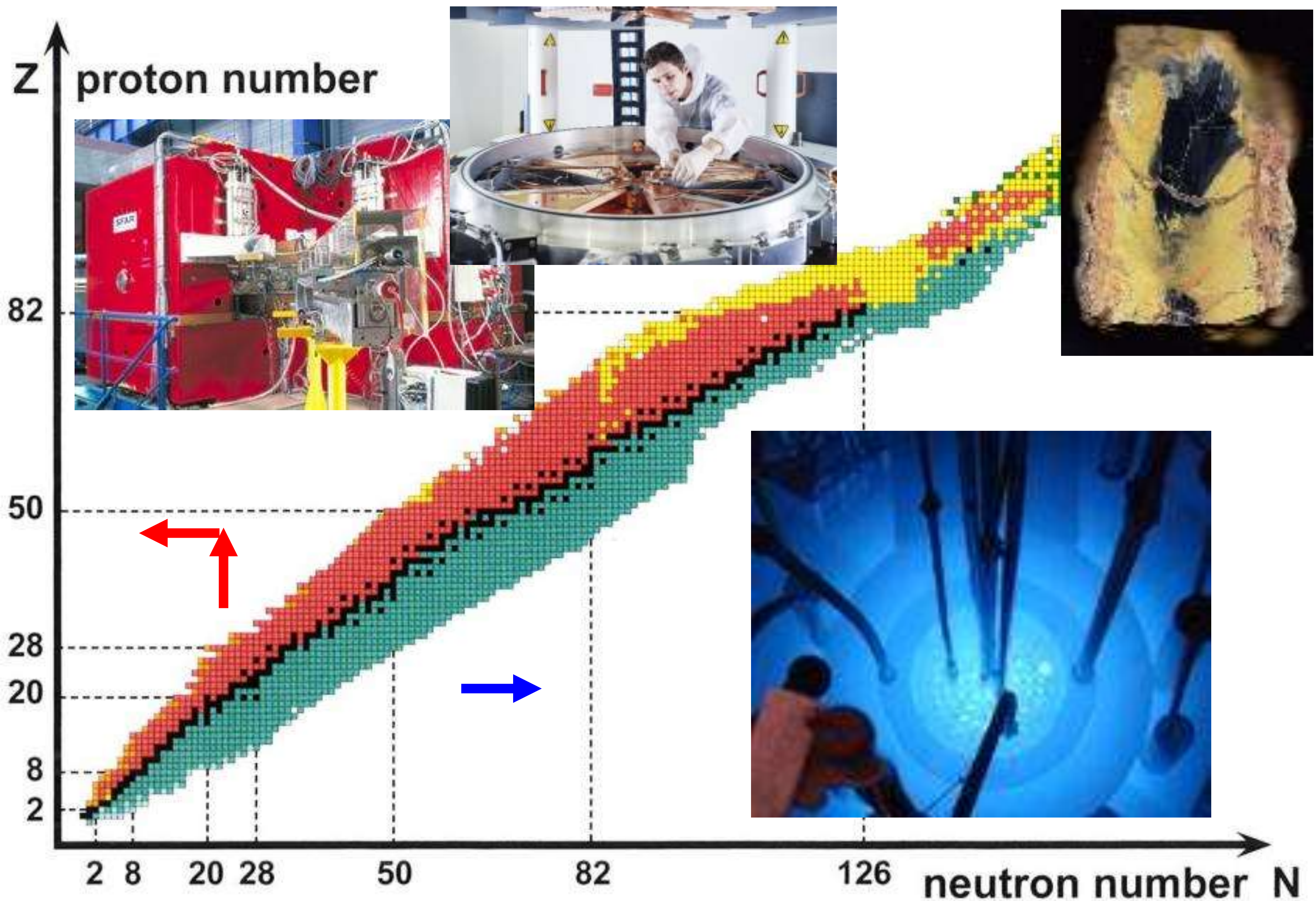
8 MBq ^{225}Ac = 1E13 at.



Auger-e⁻ ? MBq

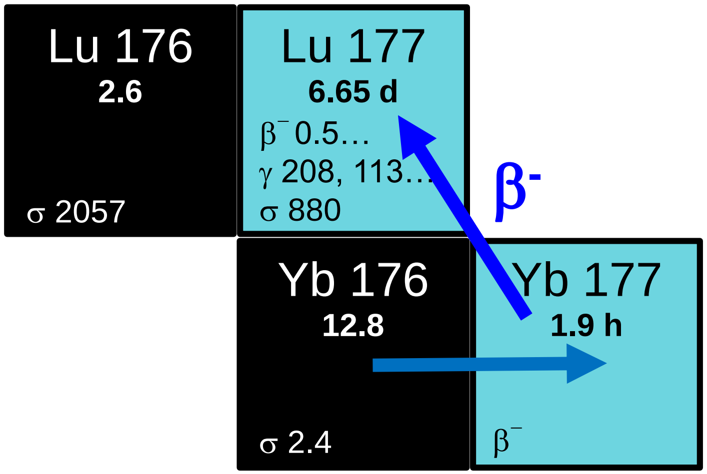


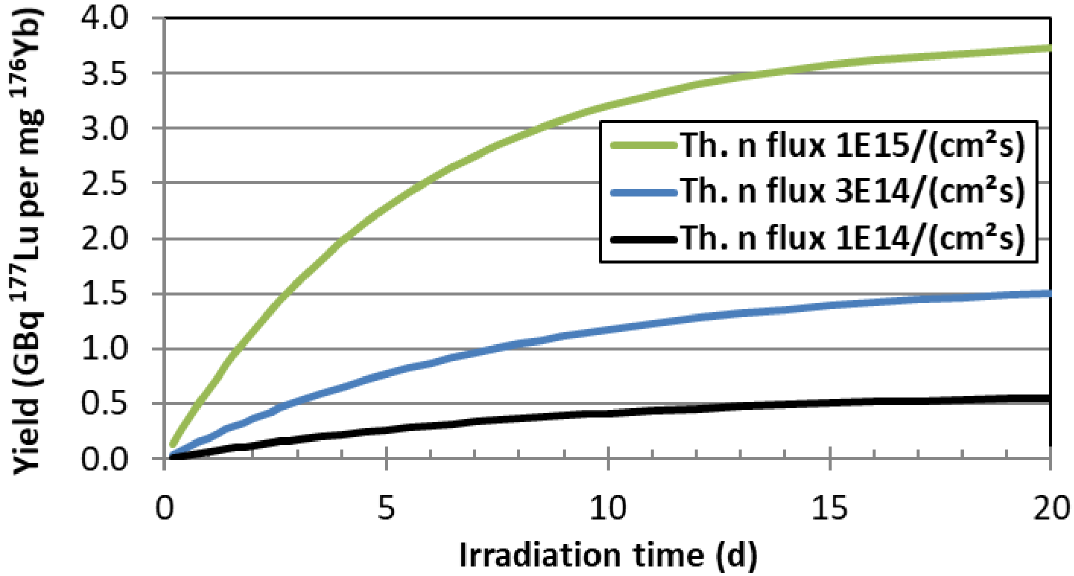
The “Alpine divide” of radionuclide production



Production of no-carrier-added ^{177}Lu

Indirect production

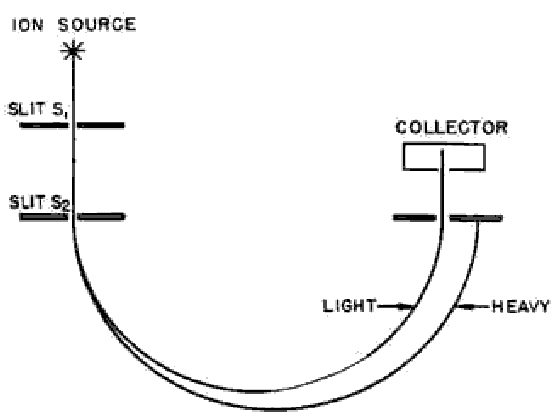




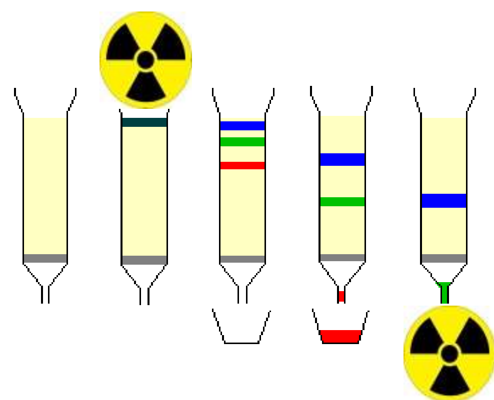
Specific activity ≈ theoretical

Yield depends on σ and Φ

Estimate for 100% enriched ^{176}Yb;
depends in reality also on neutron spectrum, self shielding, etc.



Calutron enrichment of ^{176}Yb



Radiochemical $^{177}Lu/^{176}Yb$ separation

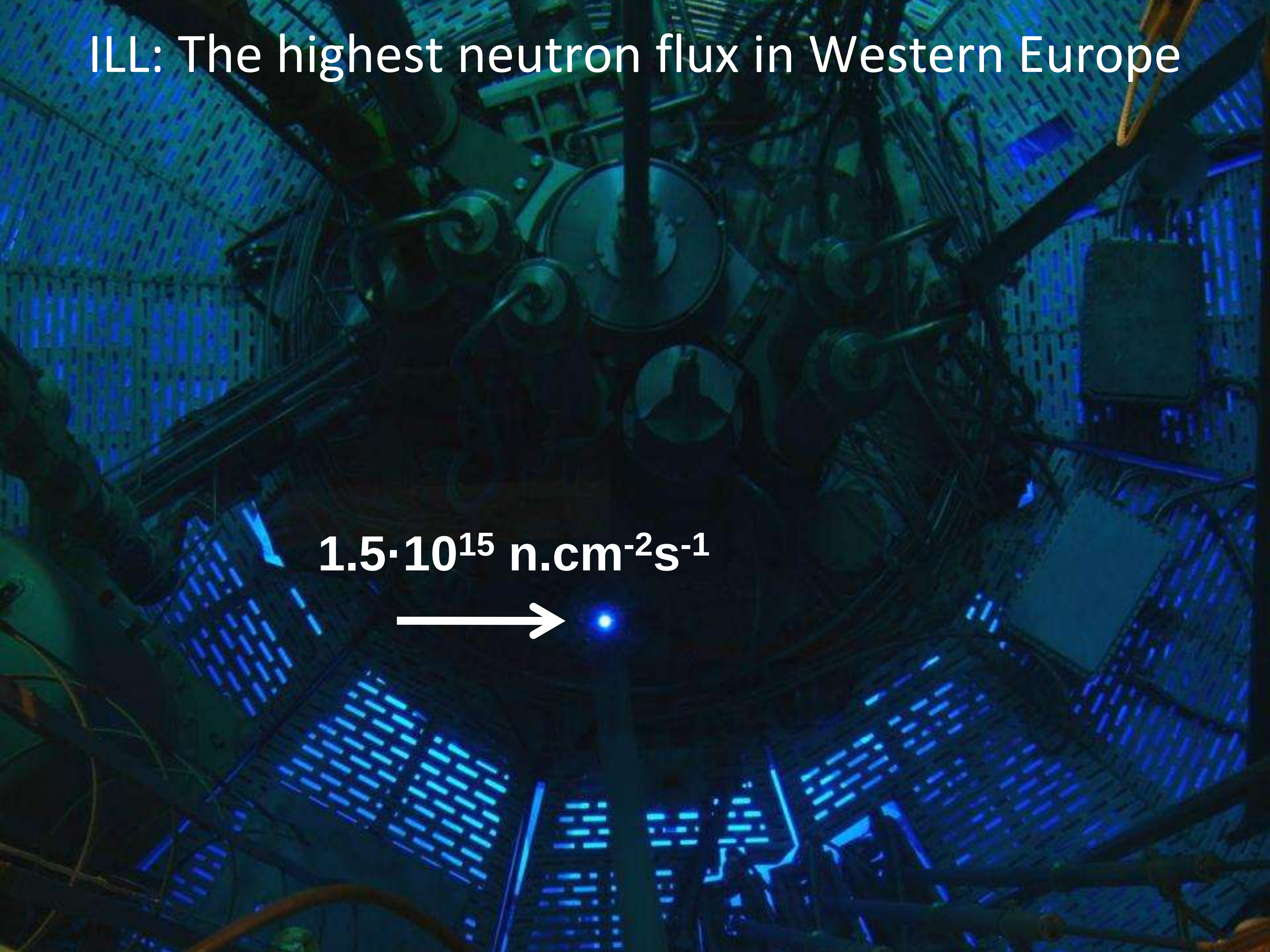
Competitive advantage of higher neutron flux

Enriched ^{176}Yb

Reactor irradiation

Radio-chemical separation

ILL: The highest neutron flux in Western Europe

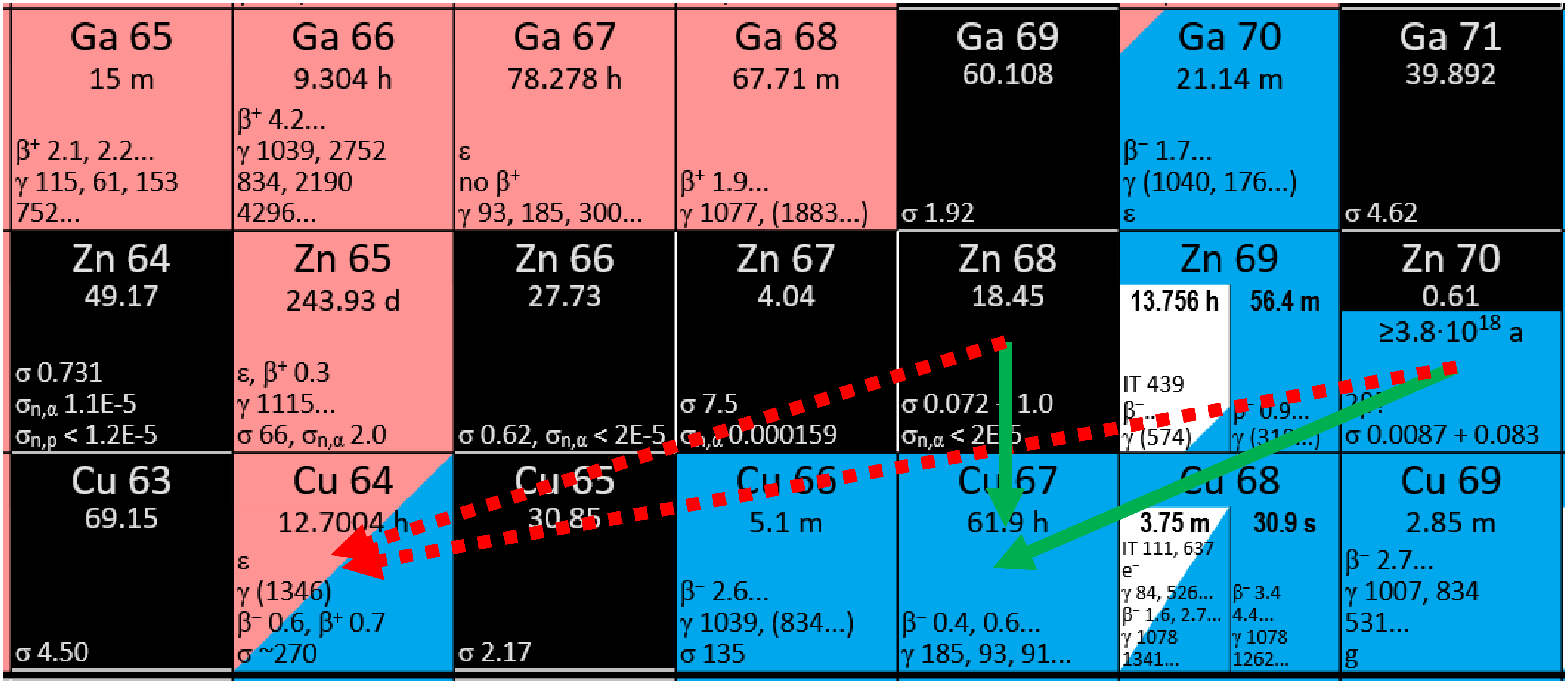


Yb 176
Lu 177
itm
endolucin
beta
NEUTRONS
FOR SOCIETY
NOVARTIS
PLUVICTO

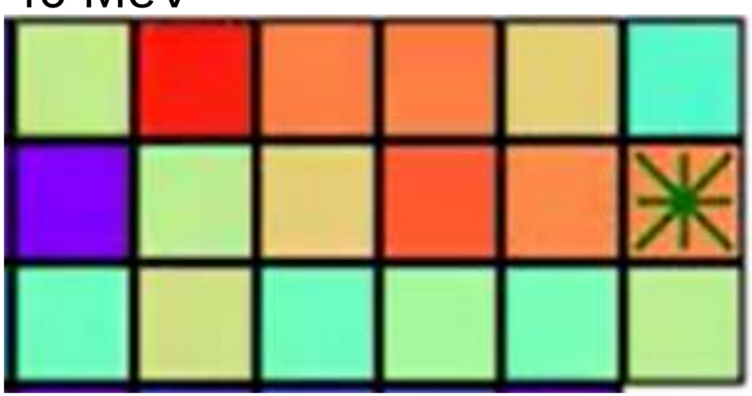
Therapeutic radionuclides

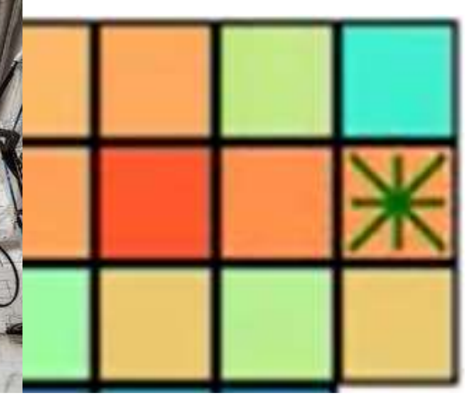
- Longer-lived: days – weeks
  $\Rightarrow$ centralized production
- Higher activity and number of atoms per patient
  $\Rightarrow$ high productivity production is essential
- High-flux reactors can provide huge activities
  of most β^- emitters (^{177}Lu, ^{161}Tb, ^{90}Y...)
- Accelerator-production may only be competitive
  for few β^- emitters not well accessible by (n,γ)

$^{68}Zn(p,2p)$ or $^{70}Zn(p,\alpha)$: $^{67}Cu/^{64}Cu$ tradeoff !

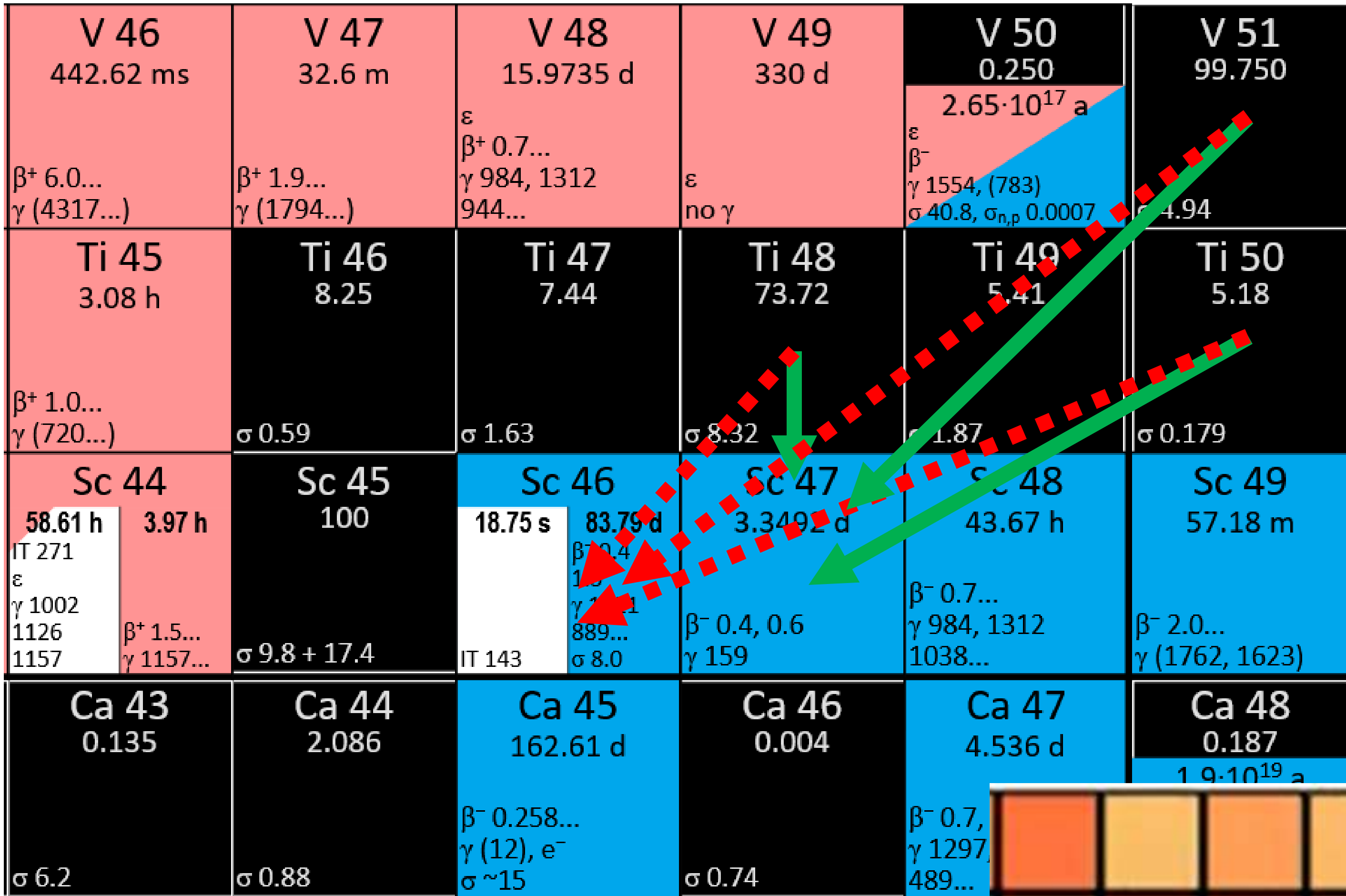


40 MeV

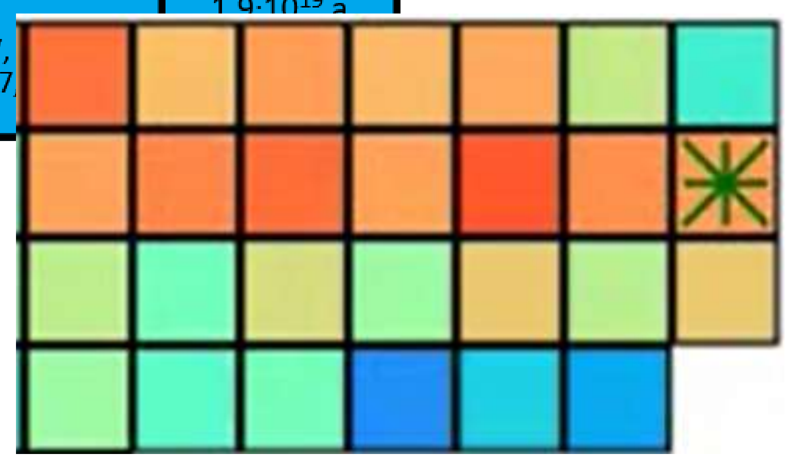




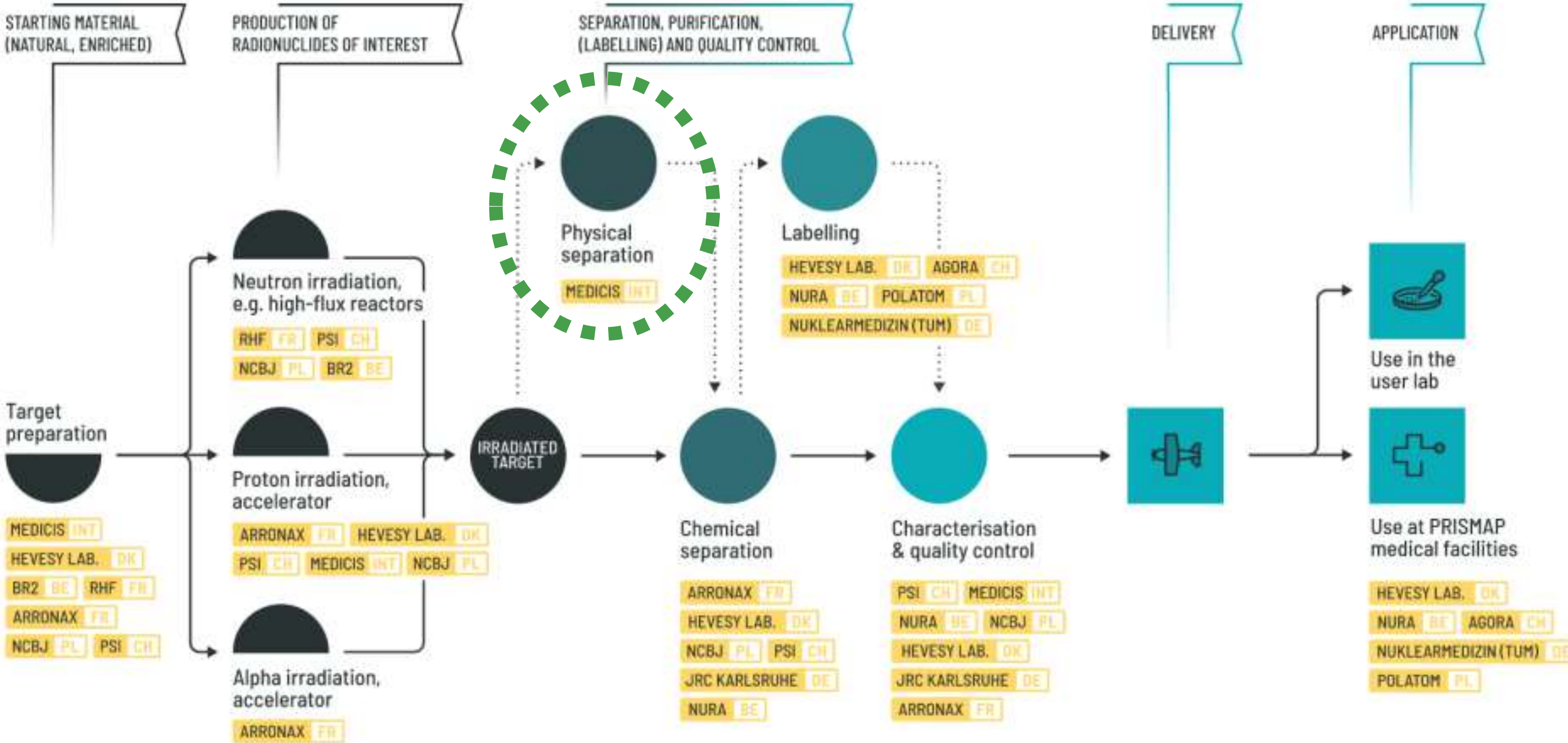
^{48}Ti(p,2p) or ^{50}Ti(p,α) or ^{51}V(p,pα): ^{46}Sc/^{47}Sc ratio !



70 MeV



PRISMAP: the European medical radionuclides programme

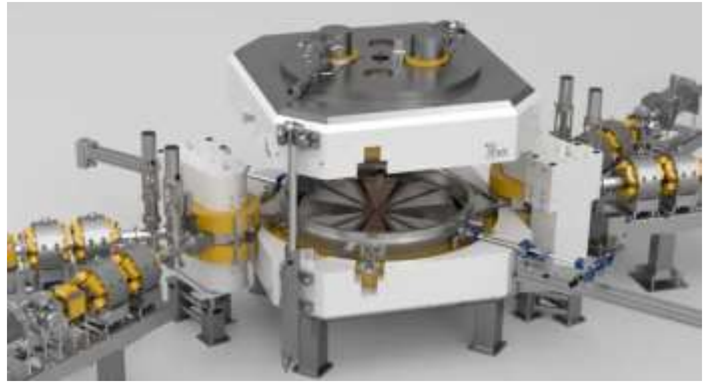


http://prismap.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008571 (PRISMAP).

Cyclotrons >=30 MeV

IBA Cyclone 30
30 MeV, 800/1500 μA



IBA Cyclone IKON
13-30 MeV, 500..1500 μA

ASCI TR30
15-30 MeV, -1500 μA

IBA Cyclone 70
30-70 MeV, 750 μA

BSC 70p
35-70 MeV, 750 μA

What to do with a 70 MeV cyclotron ?

- Commercial production: ^{82}Sr, ^{68}Ge

- Potential commercial production: ^{81}Rb, ^{123}I

- "R&D towards production" and
  "production for (pre-)clinical R&D":
  ^{67}Cu, ^{47}Sc, ^{155}Tb, ^{152}Tb, Auger e^- emitters, etc.
  radiotracers of noble metals/Pt group metals