LNF Mini-Workshop Series:

Rewarding Science

Premio « Francesco Resmini » CSN5 - 2014

Radioisotopes Production via Accelerator for Nuclear Medicine Applications

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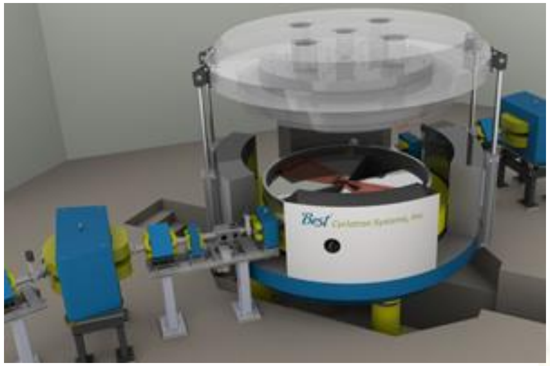
Coordinatore PhD: Prof. Vincenzo Guidi

Direttore Sezione INFN di Ferrara: Prof. Diego Bettoni

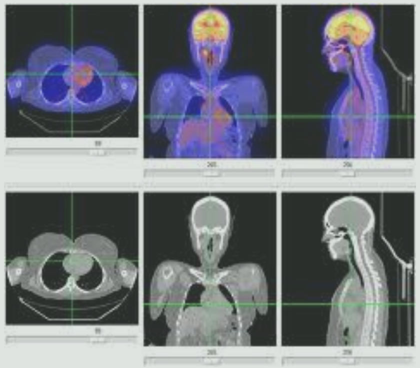
SPES:
Selective Production of Exotic Species (LNL)



BEST Cyclotron:
E_P =70 MeV ; I_P = 1 mA

Study of neutron rich nuclides

LARAMED



Research and production of RadioIsotopes for medicine

Accelerator based neutron source

LARAMED
LAboratorio di Radionuclidi per la MEDicina

- Aim : Production and research on radionuclides (SPES cyclotron)
- « Premium Project 2012 » by MIUR , co-financed with 7 M€
- Research of fundings is ongoing (laboratories, beam lines, staff..)

10/03/2014 , PhD in Physics

07/04/2015 , Premio Resmini

From website LNL : web.infn.it/spes

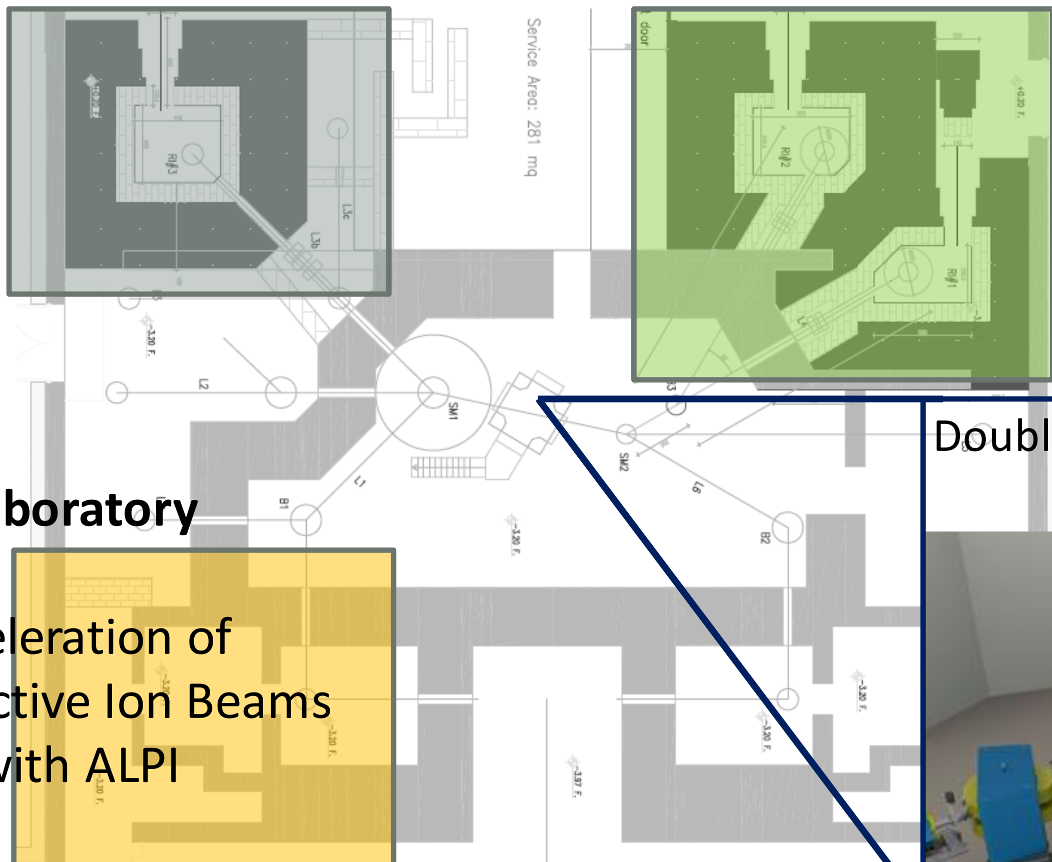
LARAMED
LAboratorio di Radionuclidi per la MEDicina

Cyclotron installation, May 2015

A multi-purpose facility

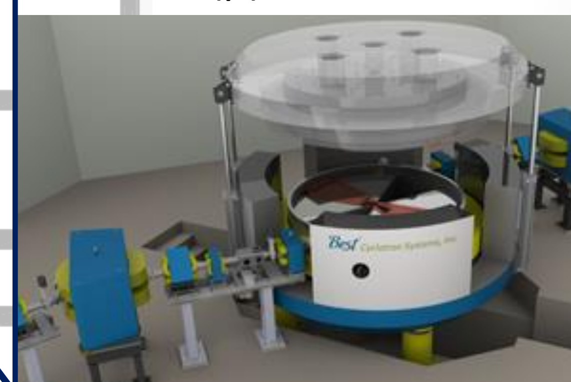
Research laboratory
(INFN, CNR)
^{99m}Tc
^{64}Cu
^{67}Cu

Production Facility
(INFN, Private Partner)
^{82}Sr (^{82}Sr/ ^{82}Rb)
^{68}Ge (^{68}Ge/ ^{68}Ga)



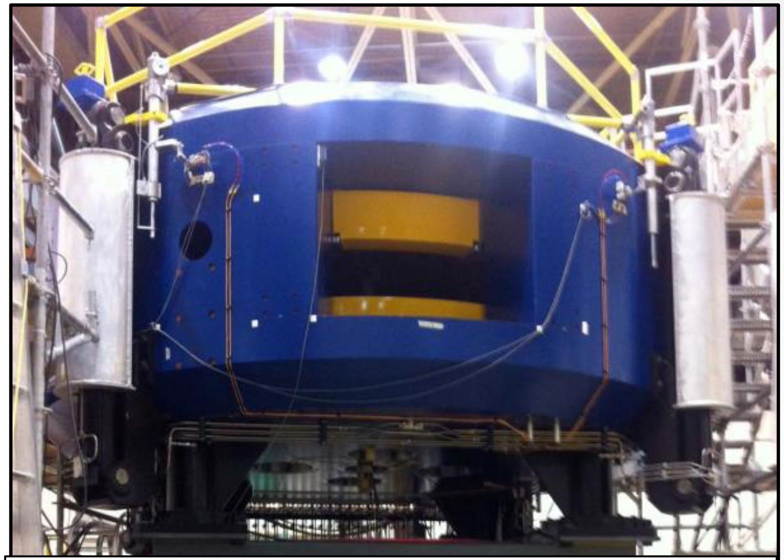
SPES Laboratory
(INFN)
Re-acceleration of
Radioactive Ion Beams
(RIBs) with ALPI

Double Extraction Cyclotron
E(p)=70MeV I=1mA



The cyclotron 70p

1° beam (H^-) :
E_{MAX} = 40 MeV ; I_{MAX} = 200 µA (upgrade to 500 µA)
→Nuclear physics research RIBs: **SPES project**

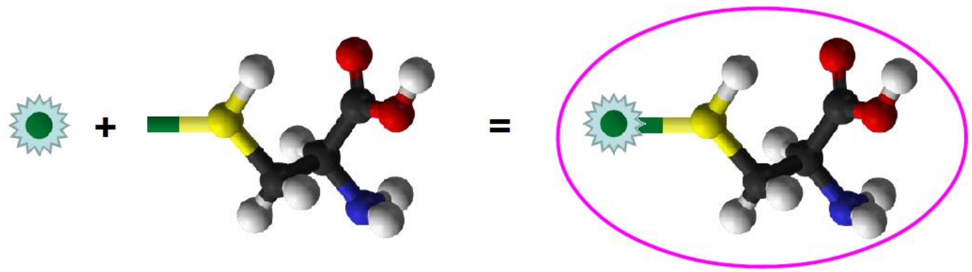

BEST Cyclotron

2° beam (H^-) :
E = 35-70 MeV ; I_{MAX} = 300 µA
(upgrade to 500 µA)
→Applications: **LARAMED project** ,
Development of intense neutron source

Why Radioisotopes & Medicine ?

- Earlier stages DIAGNOSIS
- More specific THERAPY

Variety of Radionuclides !



The radiation emitted in the decay of the nuclide can be used for :

- Diagnostics : γ-rays for SPECT ; β^+ for PET
- Therapy : Auger e^-, α and β^- radiation

Theragnostics !

TOPICS
of my PhD work

- Production of ^{99}Mo and ^{99m}Tc
  - Analysis of the proton-induced reactions ^{100}Mo(p,x)
  - Measurement of the alpha-induced reaction ^{96}Zr(α,n)^{99}Mo @ ARRONAX

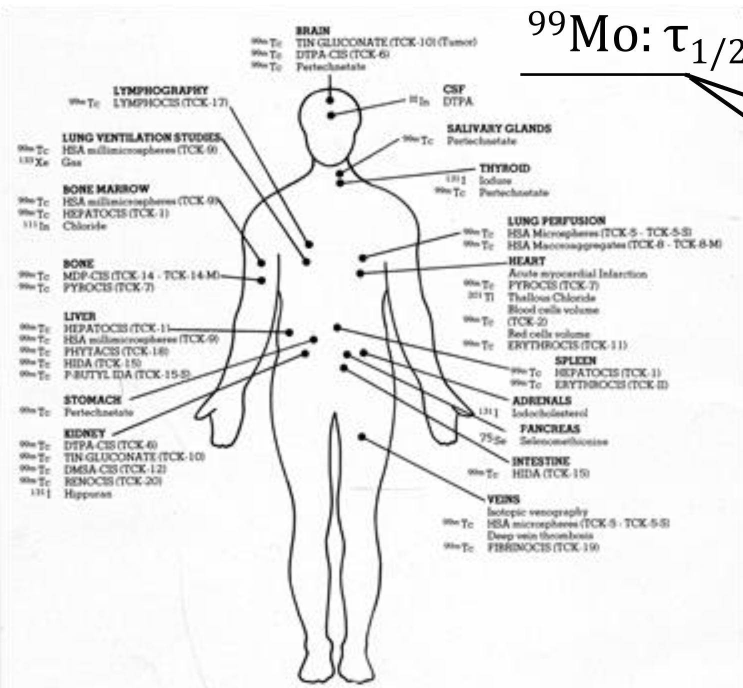
- Production of ^{67}Cu
  - Measurement of the proton-induced reaction ^{68}Zn(p,2p)^{67}Cu @ ARRONAX

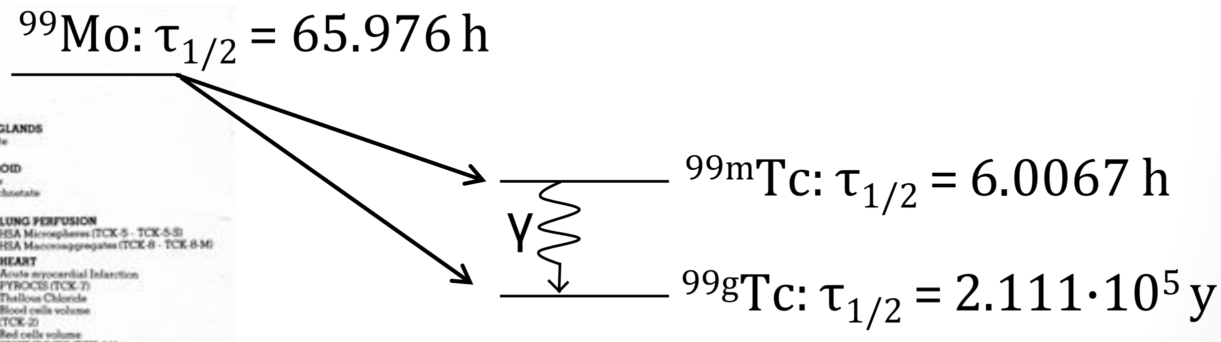
Technetium-99m & Molybdenum-99

- ^{99m}Tc : most important nuclide in nuclear medicine (> 90%)

  (> 30 millions SPECT diagnostic procedures worldwide yearly*)

- ^{99m}Tc : available in hospitals *via* the ^{99}Mo/^{99m}Tc generator system



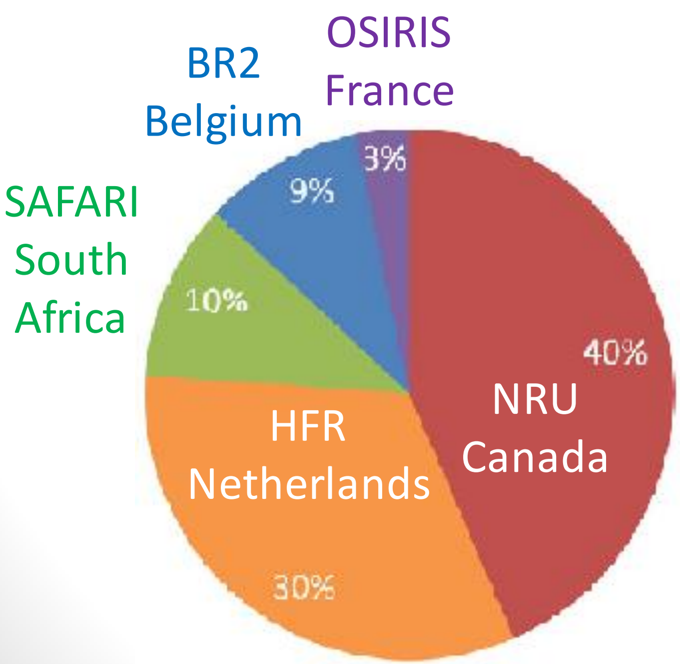


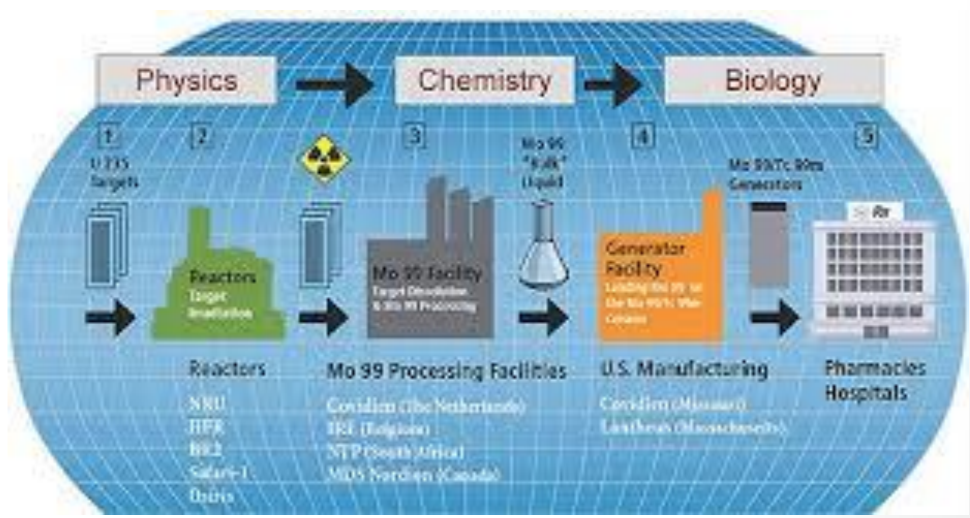
^{99m}Tc radiation**: $\begin{cases} E(\gamma) = 140.511\ \text{keV} \\ I(\gamma) = 89\% \end{cases}$

* NEA and OECD, (2010) IAEA-TECDOC-1601; ** NNDC, http://www.nndc.bnl.gov/exfor/exfor.htm.

Technetium-99m supply:
Production of the parent nuclide ^{99}Mo

- ^{99m}Tc distribution chain relies on ^{99}Mo production
- ^{99}Mo : currently produced in nuclear reactors by n-induced fission of Highly Enriched ^{235}U (HEU) targets (weapon grade matrial)





* J Esposito et al., Hindawi Publ. Corp. (2013) ID 972381

** NEA and OECD, (2010) IAEA-TECDOC-1601

Technetium-99m supply:
Production with particle accelerators

- ^{99m}Tc shortening* : long shutdowns of two facilities (≈ 70% total ^{99}Mo)
- New ideas about ^{99}Mo and ^{99m}Tc supply - Short term solutions**:

➢ Reactors: LowEU ^{235}U(n,f)^{99}Mo & ^{98}Mo(n,γ)^{99}Mo

➢ Particle accelerators

APOTEMA project (INFN-CSN5 2012-2014)

Accelerator-driven Production Of TEchnetium/Molybdenum for medical Applications

- ^{100}Mo(p,x)^{99}Mo,^{99m}Tc
- ^{96}Zr(α,n)^{99}Mo

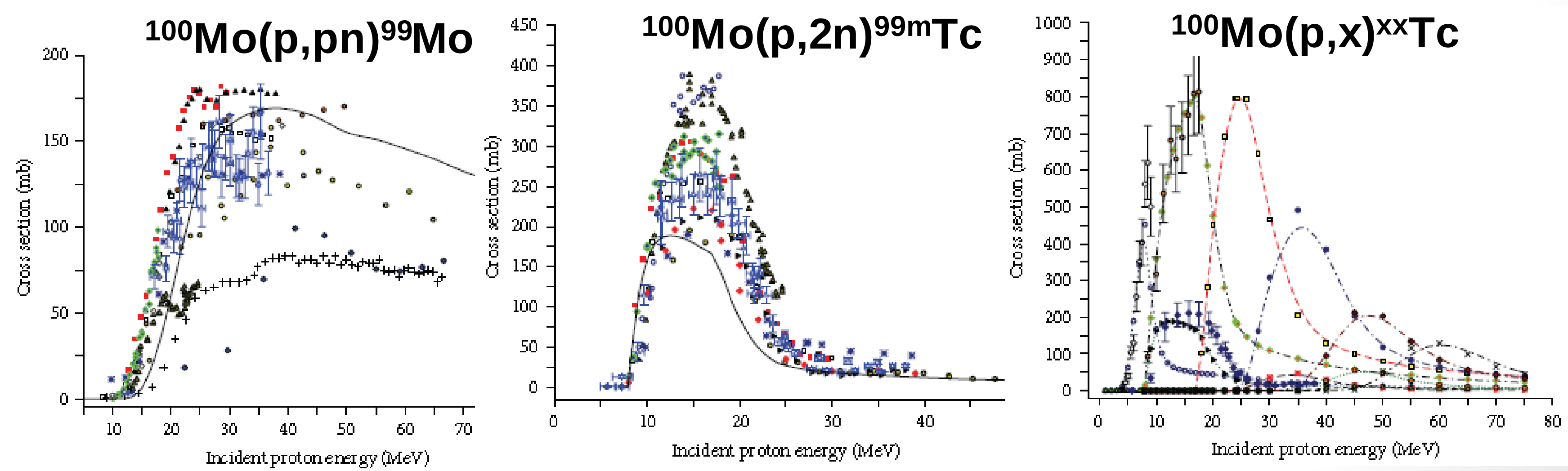
TECHN-OSP project (INFN-CSN5 2015-2017)

* J Esposito et al., Hindawi Publ. Corp. (2013) ID 972381

** NEA and OECD, (2010) IAEA-TECDOC-1601

APOTEMA
The $^{100}Mo(p,x)^{99}Mo$, ^{99m}Tc nuclear reactions*

- Analysis of measured $^{100}Mo(p,x)$ cross sections
- Calculation of optimal irradiation conditions, considering the incoming 70 MeV cyclotron @ LNL



* J Esposito et al., Hindawi Publ. Corp. (2013) ID 972381

APOTEMA

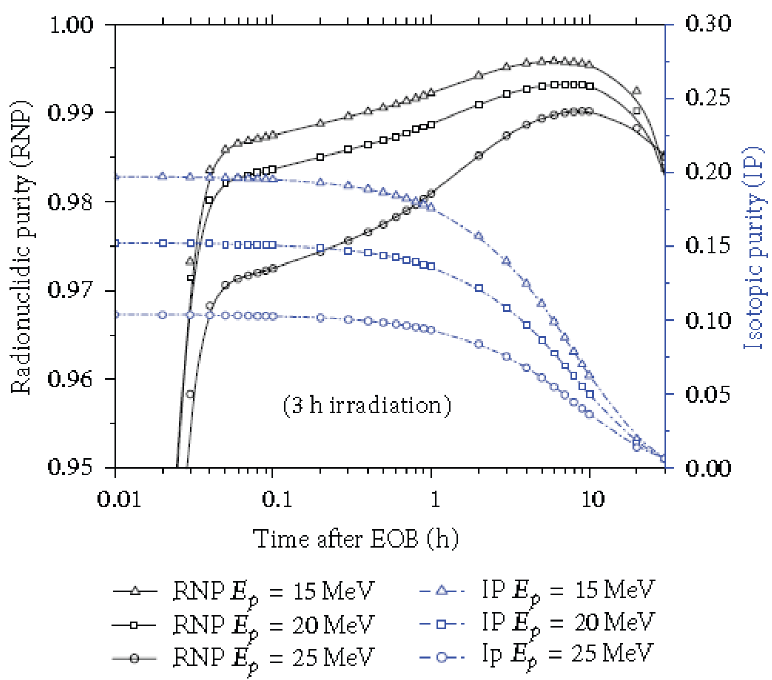
Production of ^{99}Mo, ^{99m}Tc with protons*

- ^{99}Mo production : NOT favourable solution* , LOW Specific Activity
  → *alternative* generator systems

- **^{99m}Tc direct production** : RadioNuclidic (RNP) and Isotopic Purity (IP) values comparable with generator-produced ^{99m}Tc

✓ Best irradiation conditions :
- Highly enriched ^{100}Mo targets
- $E_P \leq 20$ MeV
- Short irradiation times ($t_{IRR} \leq 3$ h)

⚠ **No Pharmacopoeia !**

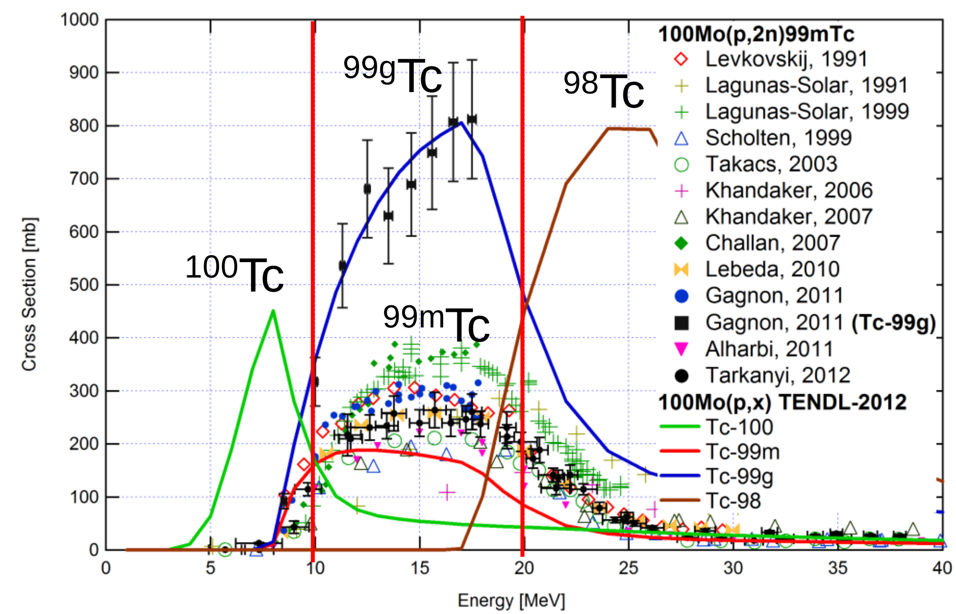


* J Esposito et al., Hindawi Publ. Corp. (2013) ID 972381

APOTEMA

Direct production of ^{99m}Tc: isotopic impurities

- Tc-contaminants can NOT be chemically removed from ^{99m}Tc
- Appropriate irradiation conditions ($E_P \leq 20$ MeV, $t_{IRR} \leq 3$ h) reduce the presence of Tc-isotopes as much as possible



The production of the long-lived ($\tau_{1/2} \approx 10^5$ y), pure β-emitter isomer **^{99g}Tc** can NOT be avoided by choosing appropriate protons' energy range

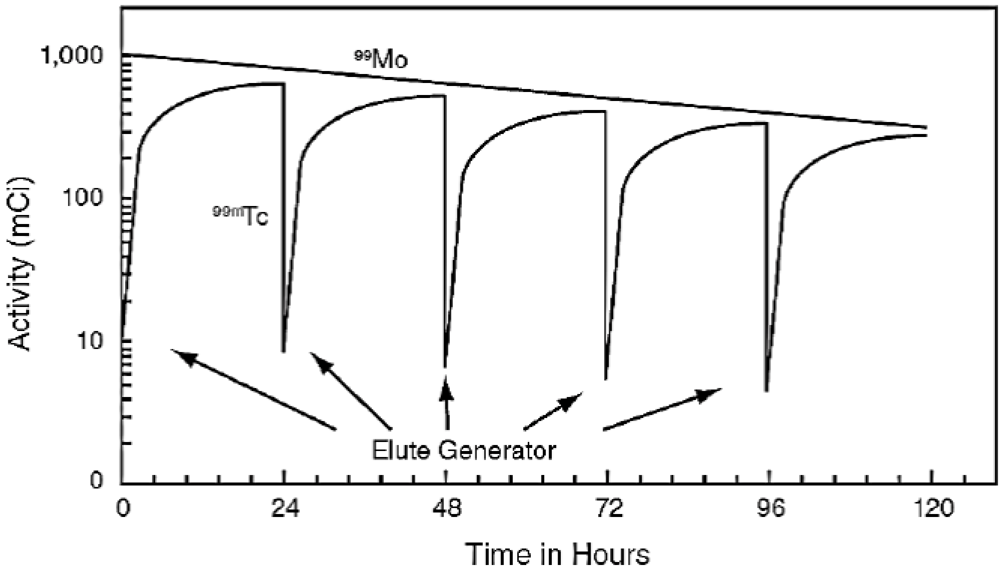
* J Esposito et al., Hindawi Publ. Corp. (2013) ID 972381

APOTEMA

Direct production of ^{99m}Tc: isomeric impurity ^{99g}Tc

- Investigation of possible influence of **^{99g}Tc** on radiopharmaceuticals (RP) by using commercial $^{99}Mo/^{99m}Tc$ generator systems * :
  - ✓ RadioChemical Purity (RCP)
  - ✓ Stability

$$R = \frac{N(^{99g}Tc)}{N(^{99m}Tc)}$$



Elutions taken at 24 hours intervals (max ^{99m}Tc activity) : R (*24 h*) = 2.5

* L Uccelli et al., Hindawi Publ. Corp. (2013) ID 379283

APOTEMA

Possible influence of ^{99g}Tc on ^{99m}Tc-RP

- Quality Control tests* on elutions with R = 2.5 -11.8 :

✔ Agreement with Italian and European Pharmacopoeia requirements

- Same elutions (R = 2.5 -11.8) used to label commercial RP kits :

Name	Radiopharmaceutical
Neurolite (Brystol-Myer Squibb)	^{99m}Tc-ECD (^{99m}Tc-Bicisato)
Cardiolite (Brystol-Myer Squibb)	^{99m}Tc-SESTAMIBI
Stamicis (IBA)	^{99m}Tc-SESTAMIBI
Technemibi (Mallinckrodt)	^{99m}Tc-SESTAMIBI
TechneScan (Mallinckrodt)	^{99m}Tc-MAG3
Pentacis (IBA)	^{99m}Tc-DTPA
Medronato II (GE Healthcare)	^{99m}Tc-MDP
Osteocis (IBA)	^{99m}Tc-HMDP
Nanocoll (GE Healthcare)	^{99m}Tc-nanocolloids
Renocis (IBA)	^{99m}Tc-DMSA

✔ No variations in RP quality and stability up to R = 11.8 !

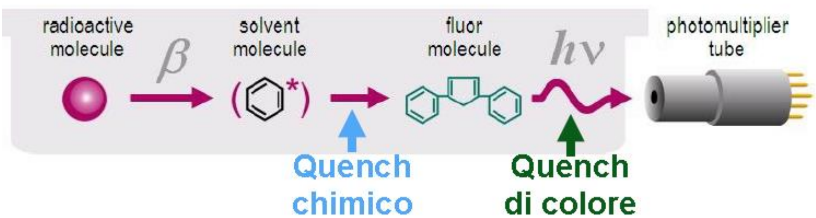
✔ Preliminary imaging tests with YAP-(S)-PET scanner: NO variations in image quality up to R = 15.2 !

* L Uccelli et al., Hindawi Publ. Corp. (2013) ID 379283

APOTEMA

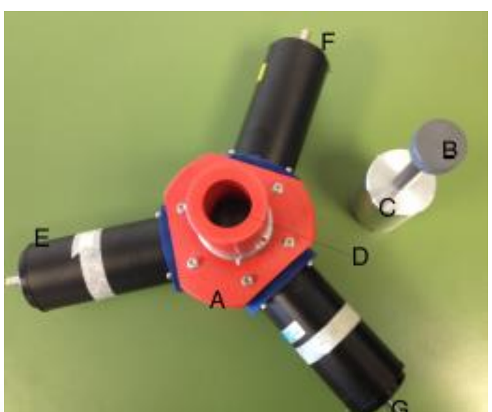
The β-spectrometer for ^{99g}Tc activity measurements

- Development of a β-spectrometer* based on liquid scintillation techniques and **Triple to Dual Coincidence Ratio (TDCR)** method



$$m(E) = \int_0^{E_{max}} \frac{L\,dE}{1 + kB(\frac{dE}{dx})}$$

Set-Up of the β-spectrometer: A. Optical Chamber; B. Piston; C. Cylinder for vial insertion; D. Shutter; E,F,G. Photomultiplier Tubes; H. CAEN Digitizer DT5720; I. PC.



* L. Fornasini, Bachelor Thesis in Physics at UNIFE (2013)
A. Scarpelli, Bachelor Thesis in Physics at UNIFE (2014)

APOTEMA

The β-spectrometer for ^{99g}Tc activity measurements

Sample ^{99g}Tc	K value	Results of ^{99g}Tc Activity (Bq)			
		TDCR Simplified	TDCR Software*	TriCarb β-counter	Expected
0.1 ml	0.927 ±0.008	3850 ± 15	3880 ± 40	3840 ± 80	3700 ± 185
0.4 ml	0.927 ±0.002	14870 ± 65	14910 ± 150	14860 ± 295	14800 ± 740

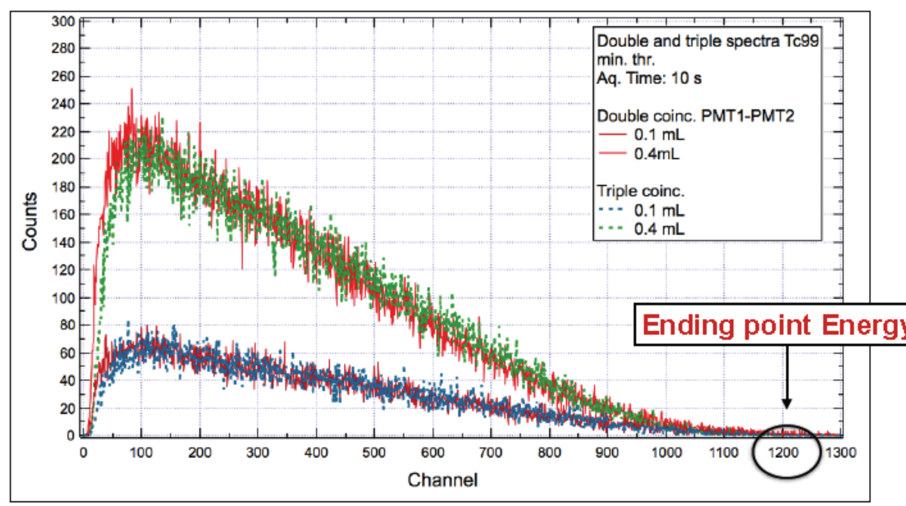
Reference samples prepared as aliquot of calibrated ^{99g}Tc liquid source :

187 kBq, 5% uncertainty, 5 ml volume

^{99g}Tc calibrated liquid source

Reference sample

Reconstructed ^{99g}Tc Spectra



* Lab. National Henri Becquerel, TDCR07 Software, url: http://www.nucleide.org/ICRM_LSC_WG/icrmtdcr.htm

TOPICS of my PhD work

- Production of ^{99}Mo and ^{99m}Tc
  - $^{100}Mo(p,x)^{99m}Tc$ (^{99g}Tc, ^{xx}Tc, ^{99}Mo) ; TDCR β-spectrometer
  - $^{96}Zr(\alpha,n)^{99}Mo$ @ ARRONAX
- Production of ^{67}Cu :
  - $^{68}Zn(p,2p)^{67}Cu$ @ ARRONAX

2010. Agreement for scientific collaboration: INFN & GIP ARRONAX

ARRONAX
Accelerator for Research in Radiochemistry and Oncology at Nantes Atlantique (France)

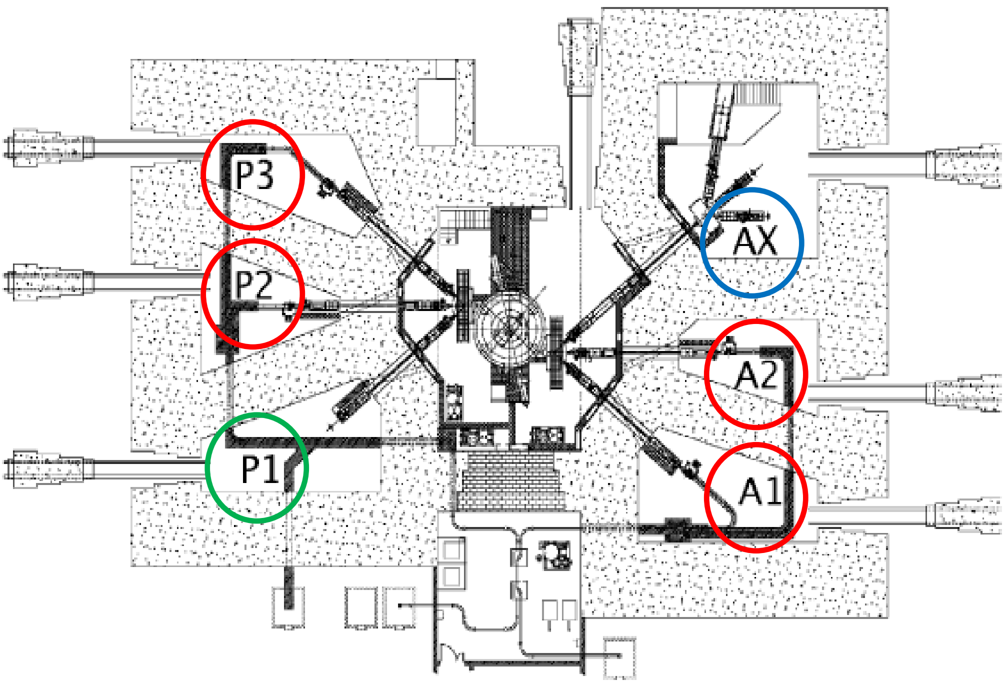
- Facility for production and research on radionuclides (2007)

Beam	Energy [MeV]	Intensity [µA]
Protons	30-70	< 350 (x2)
Deuterons	15-35	50
Alphas	68	< 35

* F. Haddad et al., Eur J Nucl Med Mol Imaging (2008)

ARRONAX : The facility layout

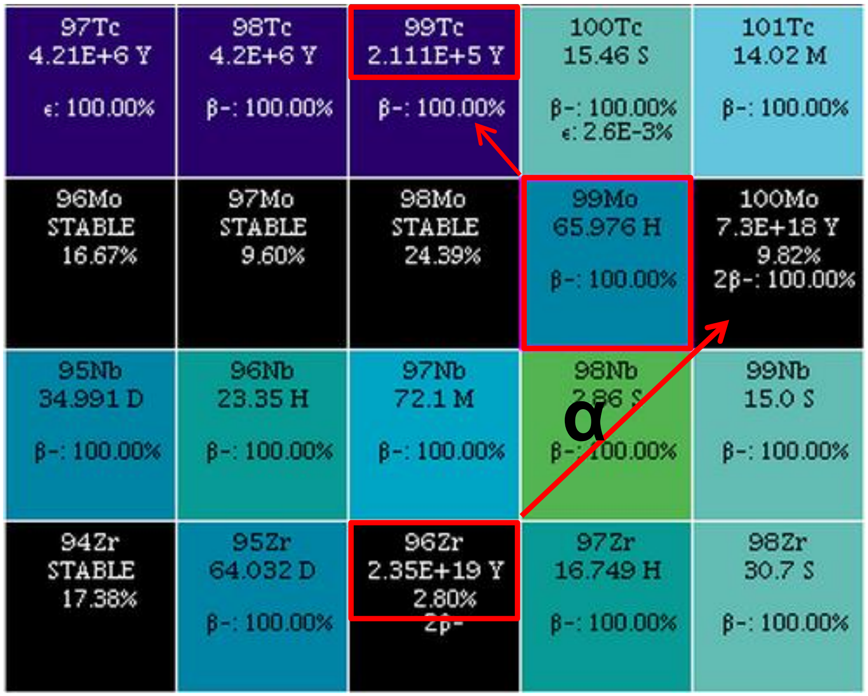
- A1, A2, P1, P2 vaults : Production (^{82}Sr, ^{64}Cu, …)
- P1 vault : Neutron activator system (Collaboration with *AAA*)
- AX vault : Experiments (physics, radiolysis and radiobiology)

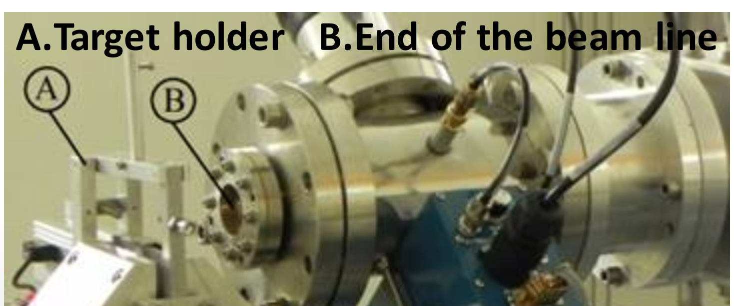


* F.Haddad et al., Eur J Nucl Med Mol Imaging (2008) – AAA, Advanced Accelerator Applications

The $^{96}Zr(\alpha,n)^{99}Mo$ nuclear reaction

NNDC, http://www.nndc.bnl.gov





IBA Cyclone 70

Beam	Energy Range [MeV]	Intensity [μA]
Protons	30-70	< 350 (x2)
Deuterons	15-35	50
α-particles	68	< 35

Irradiation details:

$E = 68$ MeV, $I \approx 200$ nA, $t_{IRR} \approx 4$ h

Target : highly pure (99.9%) ^{nat}**Zr**

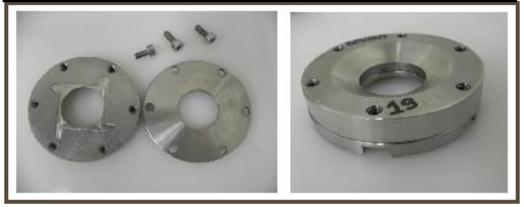
Results : rescaled to 100% ^{96}Zr since (α,n) is the only open channel for ^{99}Mo production on ^{nat}Zr

* G. Pupillo et al., J Radioanal Nucl Chem (2014)

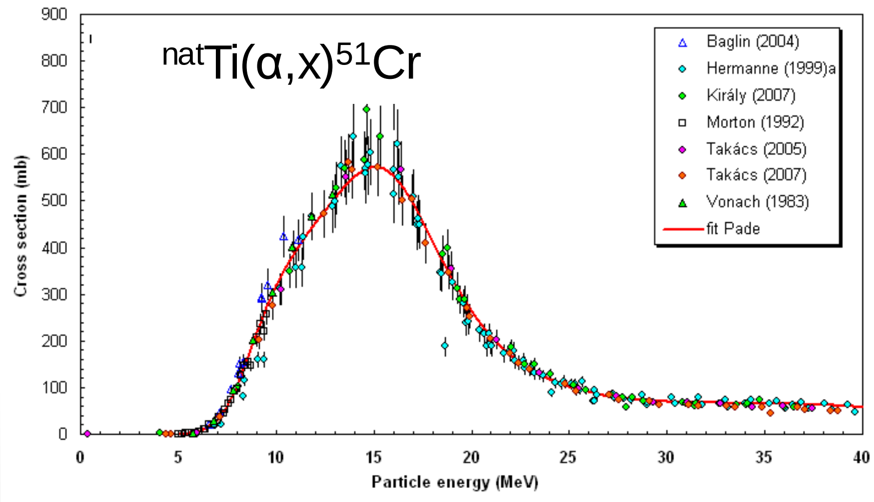
The $^{96}Zr(\alpha,n)^{99}Mo$ nuclear reaction

- Cross section measurement of the ^{96}**Zr(α,n)**^{99}**Mo** reaction
  - ✓ Stacked-foil targets have been used

Stacked-foil holder



  - ✓ Monitor reaction* $^{nat}Ti(\alpha,x)^{51}Cr$



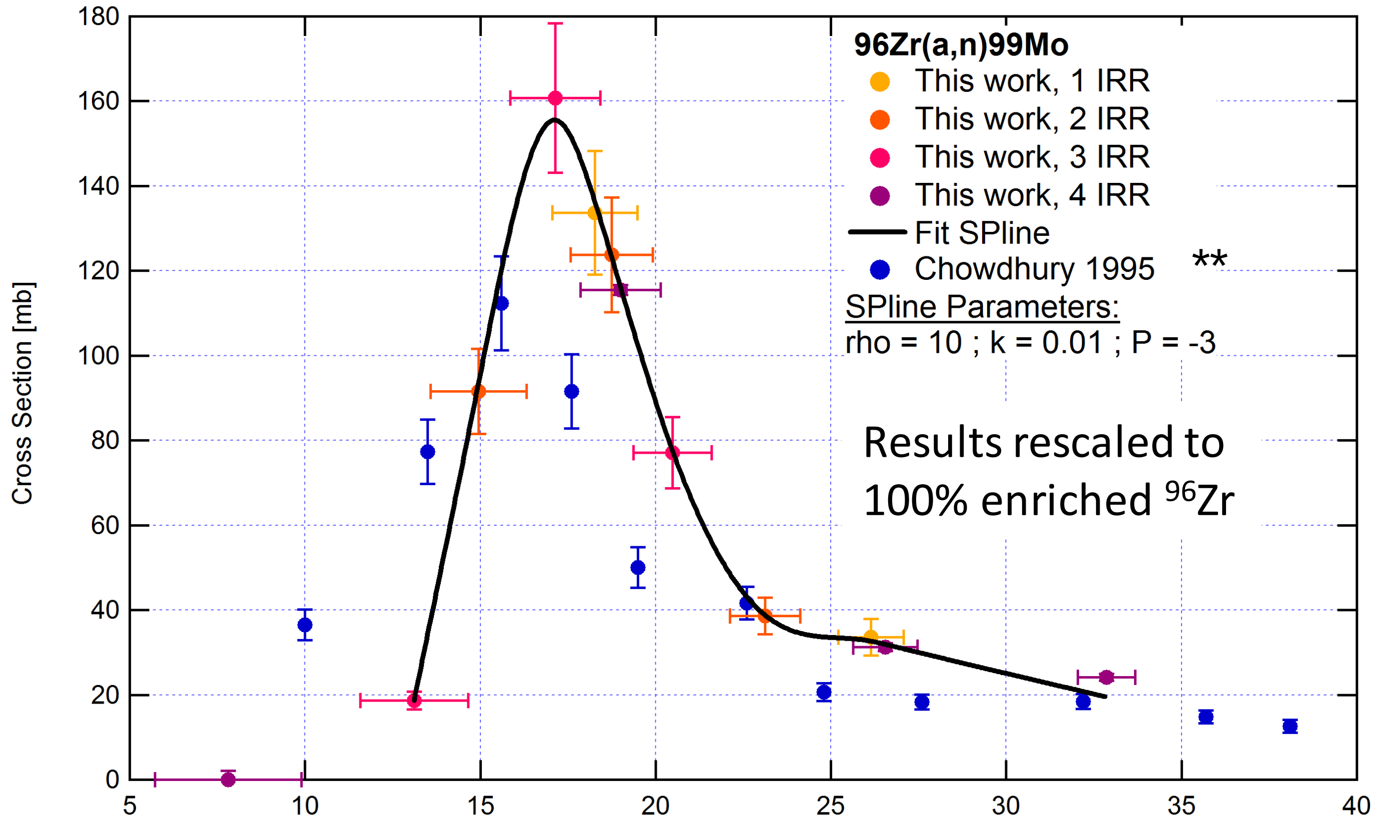
  - ✓ γ-spectrometry (DT < 6%)
  - ✓ Recoil estimation:
    ^{51}Cr activity in ^{nat}Zr foils ≈ 10%

→ $Act_{TOT} = Act(^{nat}Ti) + Act(^{nat}Zr)$

$\sigma(Act_{TOT}) = \sigma(Act_{Ti}) + \sigma(Act_{Zr})$

* International Atomic Energy Agency (IAEA) http://www-nds.iaea.org/medical/monitor_reactions.html

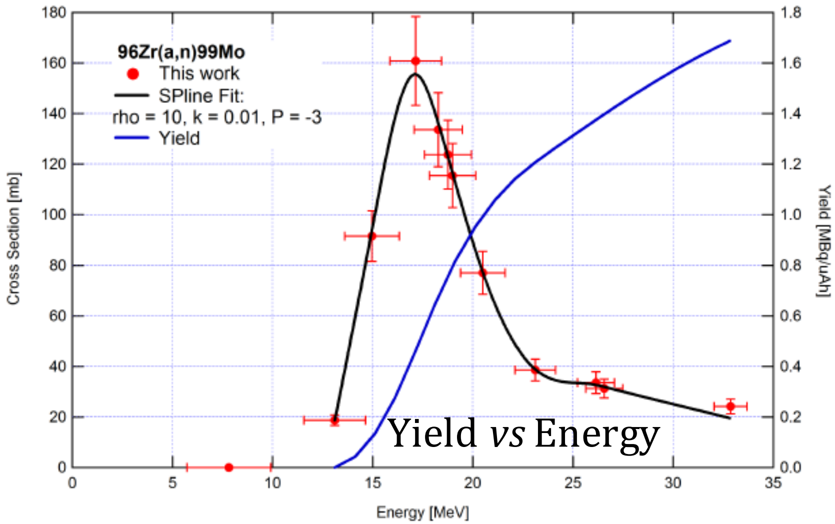
The $^{96}Zr(\alpha,n)^{99}Mo$ nuclear reaction

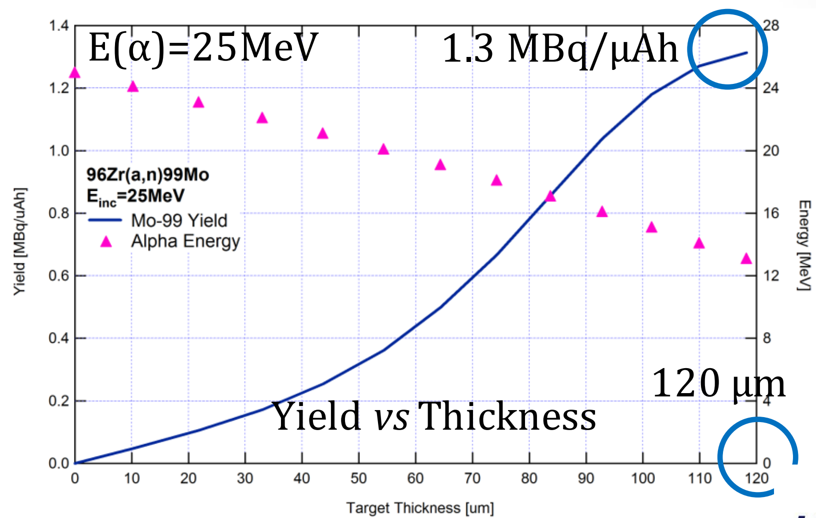


- Perfect agreement in results from different irradiation runs
- Good agreement on the trend with *Chowdhury et al.* (1995), but higher peak value (≈45%) and a shift of about 2MeV towards higher energies

* G. Pupillo et al., J Radioanal Nucl Chem (2014) ** D.P. Chowdhury et al., NIMB, 103 (1995) 261-266

^{99}Mo yield *





VERY HIGH ^{99}Mo Specific Activity (SA) : fabrication of standard ^{99}Mo/^{99m}Tc

Available α-beam (35 μA) : too low current to produce adequate ^{99}Mo yield

The development of intense α-sources is ongoing (10-100 mA)**

*G. Pupillo et al, J Radioanal Nucl Chem (2014)

**GB. Rosenthal et al. (2014) Topical Meeting on Mo99 Technological Development

^{67}Cu and ^{64}Cu Physical Characteristics*

Cu-67
61.83 h

β- : 100 %
(Zn-67)

γ-ray [keV]	γ-ray [%]	β energy [keV]	β int [%]	Auger [keV]	Auger [%]
		THERAPY			
184.6 (SPECT)	48.7	51.0	1.11	0.99	19.14
209.0	0.115	121	57	7.53	6.87
300.2	0.797	154	22.0	83.652	12.09
393.5	0.220	189	20.0	Mean β- : 141 keV	

Cu-64
12.701 h

ε : 61.5 %
(Ni-64)

γ-ray [keV]	γ-ray [%]	β+ energy [keV]	β+ int [%]	Auger [keV]	Auger [%]
				THERAPY	
1345.77	0.475	278.21 (PET)	17.60	0.84	57.7
				6.54	22.51

β- : 38.5 %
(Zn-64)

THERAPY

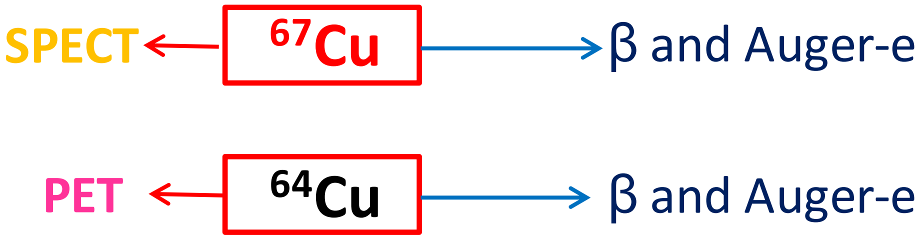
β energy [keV]	β int [%]
190.70	38.5

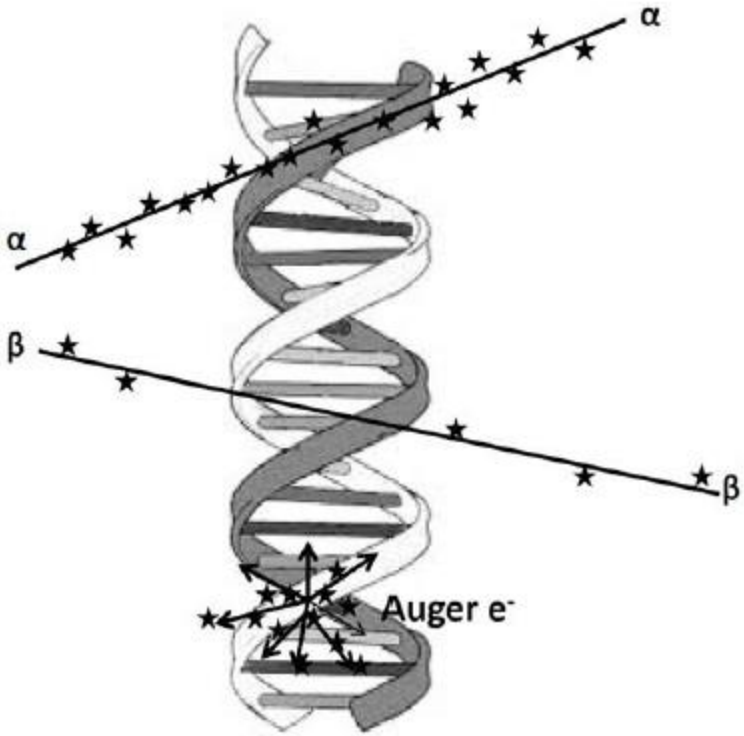
* NuDat 2.6 database (2013) - NNDC

^{67}Cu and ^{64}Cu: novel theranostic radionuclides

Theranostic = Therapy + Diagnostic

^{67}Cu and ^{64}Cu as «single» radioisotope or ^{64}Cu/^{67}Cu as «pair»





Advantage:

- Pre-therapy information for dosimetry
- Information about critical organ/tissue
- Knowledge of maximum tolerated dose

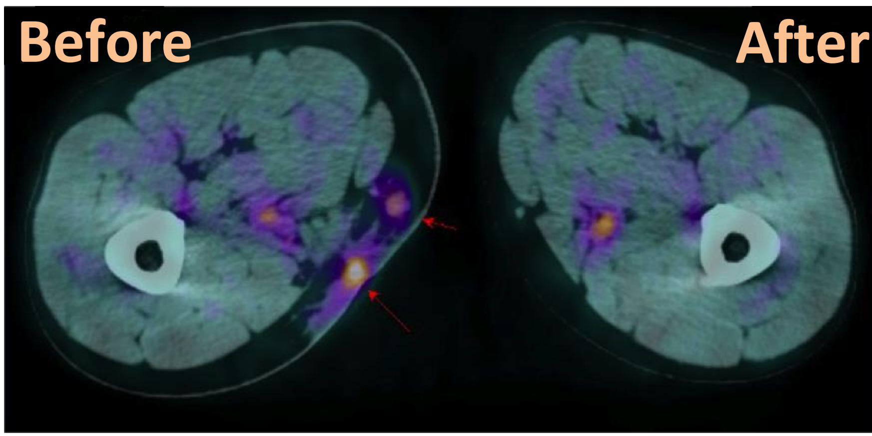
↓

Selection of patients **prior** therapy !

Schematic illustration of ionization densities , from A. Dash et al., *Current Radiopharmaceuticals* (2013)

Copper-67 (and Copper-64) in medicine

- ^{64}**Cu** is ALREADY used in nuclear medicine for PET (diagnosis)
- ^{64}**Cu** seems to provide excellent results also in THERAPY



Injection
100 mCi
^{64}**Cu**Cl_2

- ^{67}**Cu** is a promising nuclide in RAdio Immuno Therapy (RAIT)
- ^{67}**Cu**'s limiting factor: LOW availability

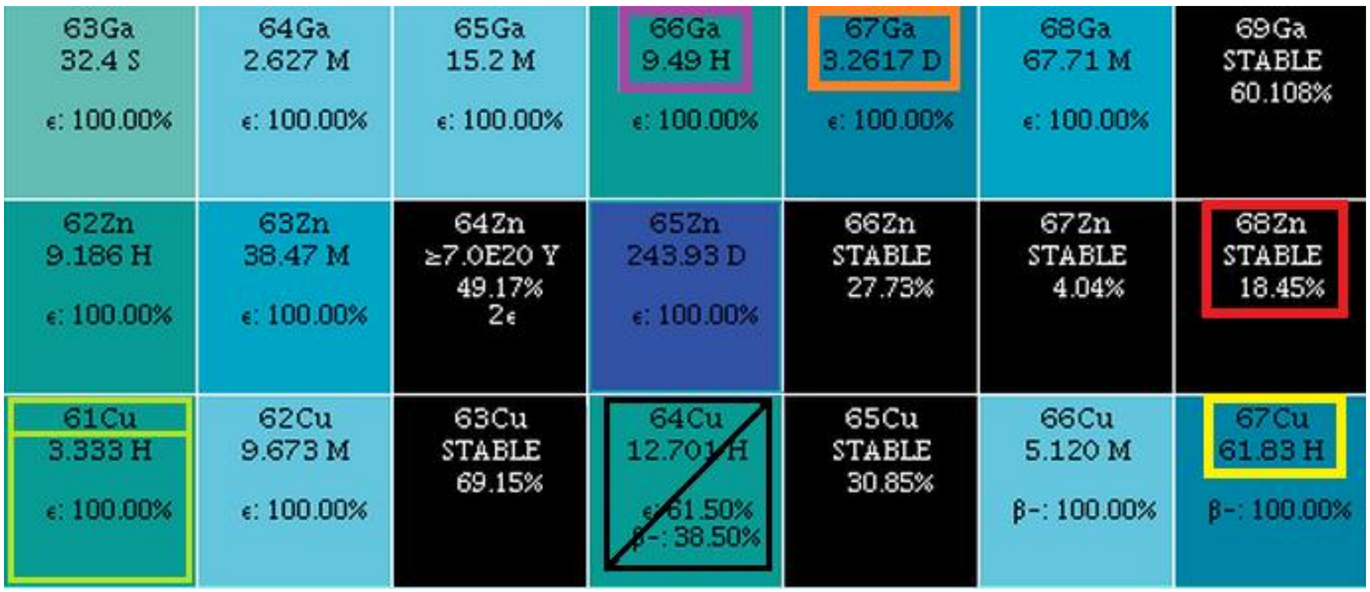
  Worldwide Production per month : 100 mCi (≈ 1 patient dose)

→ ^{67}**Cu** production: Goal for LARAMED and ARRONAX !

The $^{68}Zn(p,2p)^{67}Cu$ nuclear reaction

$^{68}Zn(p,2p)^{67}Cu$

NNDC, http://www.nndc.bnl.gov



Co-production: **^{64}Cu, ^{61}Cu** ^{67}Ga, ^{66}Ga, ^{65}Zn

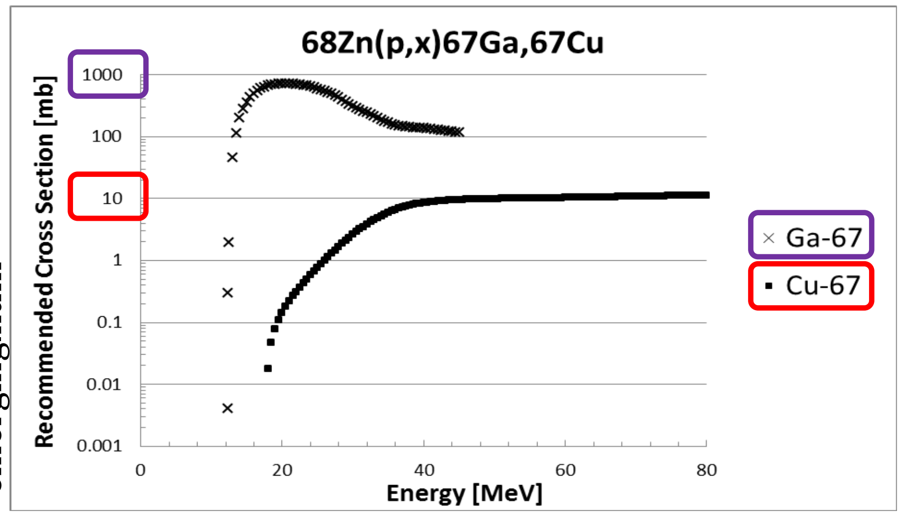
* I Novak-Hofer and PA Schubiger, Eur J Nucl Med, 29 (2002) 489-505

The ^{68}Zn(p,2p)^{67}Cu nuclear reaction: ^{67}Ga co-production

- ^{67}**Ga** has similar half-life of ^{67}**Cu** and much higher cross section

^{67}**Ga** ($t_{1/2}$ = 78.24 h)
^{67}**Cu** ($t_{1/2}$ = 61.83 h)

IAEA http://www-nds.iaea.org/radionuclides/emerging.html



- ^{67}**Ga** has the same γ-lines of ^{67}**Cu** (both decay to ^{67}Zn)

NNDC,http://www.nndc.bnl.gov

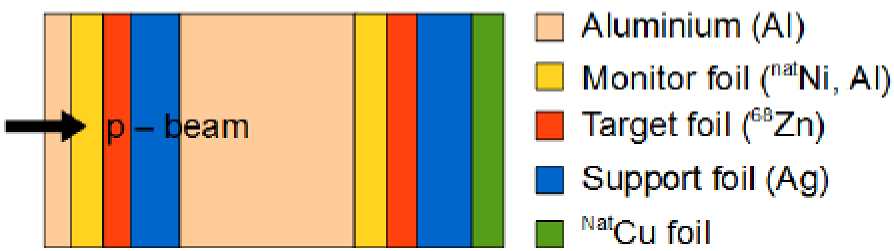
Energy [keV]	Cu-67 Int. [%]	Ga-67 Int. [%]
184.6	**48.7 3**	**21.41 1**
209.0	0.115 5	2.46 1
300.2	**0.797 11**	**16.64 12**
393.5	0.220 8	4.56 24

A chemical separation **Cu**/**Ga** is mandatory !!

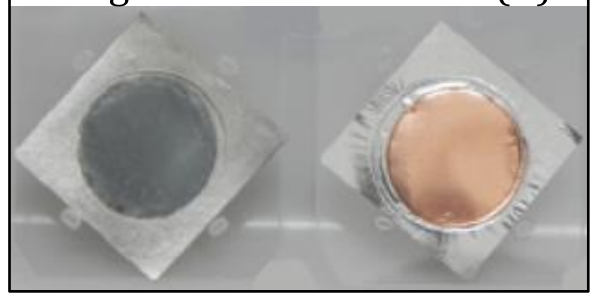
The $^{68}Zn(p,2p)^{67}Cu$ nuclear reaction: Cross section measurement

- ✓ Irradiation details: E_P=43.3-70.4 MeV, I ≈ 100-230 nA, t_{IRR} ≈ 1-1.5 h
- ✓ Stacked-foil targets: Enriched **^{68}Zn** powder (98.78%), electrodeposited on silver (Ag) support

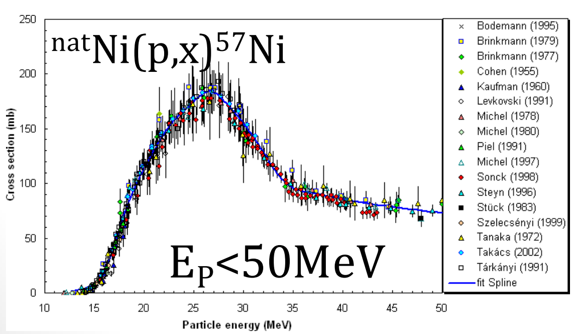
Stacked foil structrure

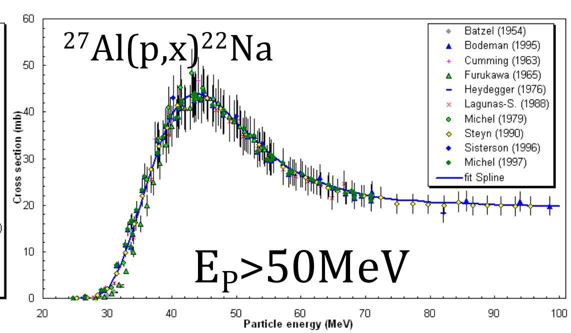


Target foil pictures:
^{68}Zn electrodeposited on Ag (L)
Target with monitor foil (R)



- ✓ Monitor reactions:

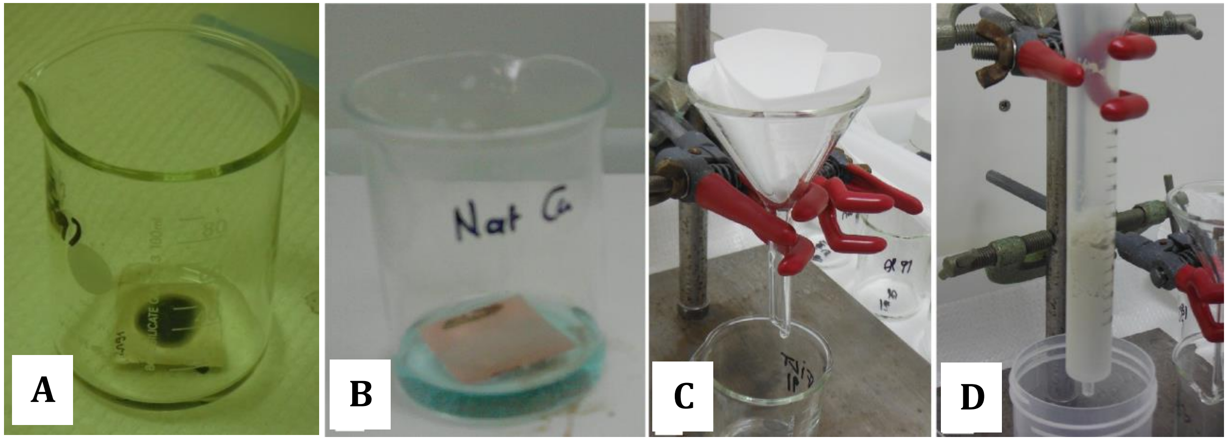




* Work performed in collaboration with Thomas Sounalet

The ^{68}Zn(p,2p)^{67}Cu nuclear reaction: Chemical procedure

- Chemical procedure for Cu/Ga separation (resin)



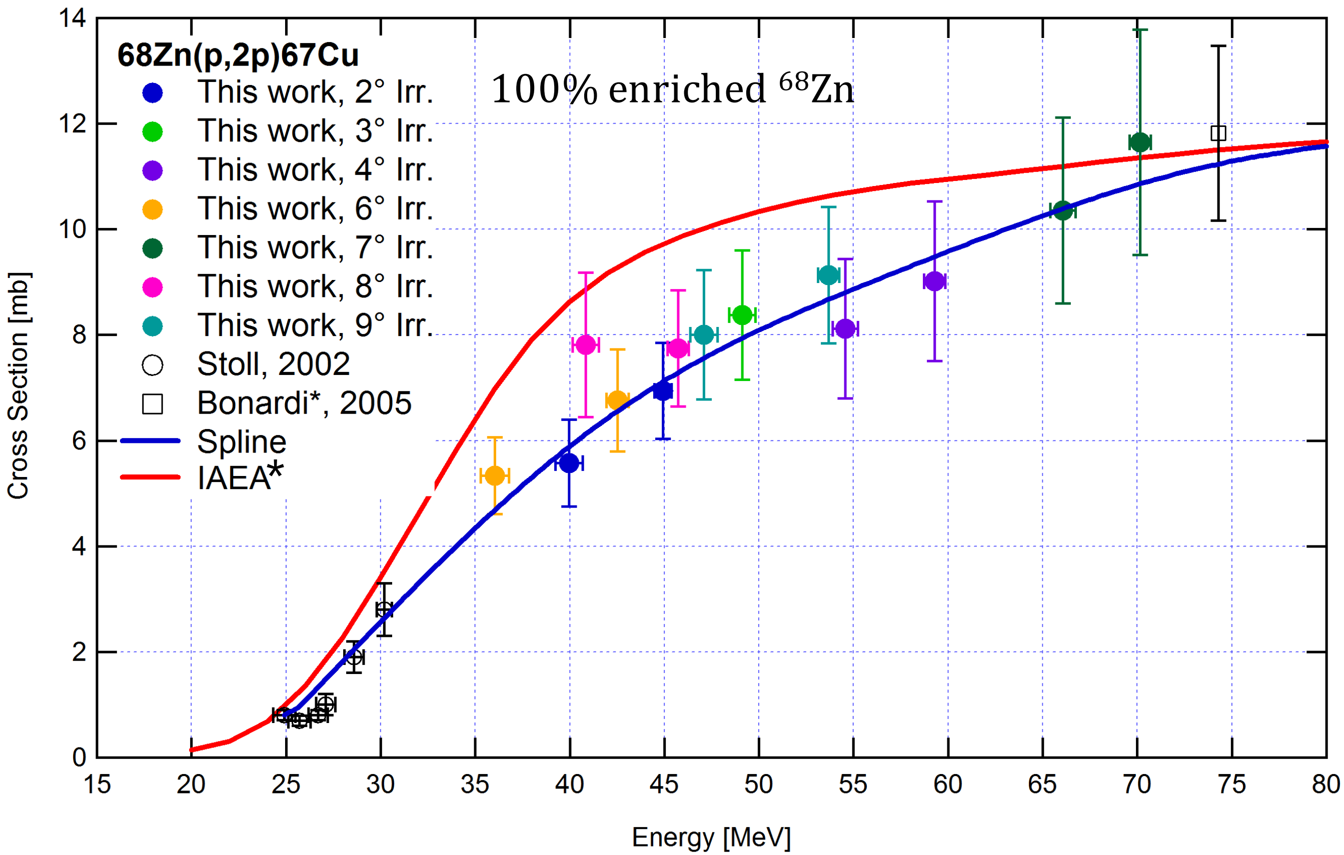
A. ^{68}Zn dissolution ; B. ^{nat}Cu dissolution ; C. Filtration ; D. Separation (resin)

- Two *tracer-isotope* have been used:

Cu-61 (produced in ^{nat}Cu foil) ; $t_{1/2}$ = 3.333 h
Ga-66 (co-produced in ^{68}Zn) ; $t_{1/2}$ = 9.49 h

- γ-spectrometry analysis (HPGe detector, DT < 10%)

The ^{68}Zn(p,2p)^{67}Cu nuclear reaction: Results

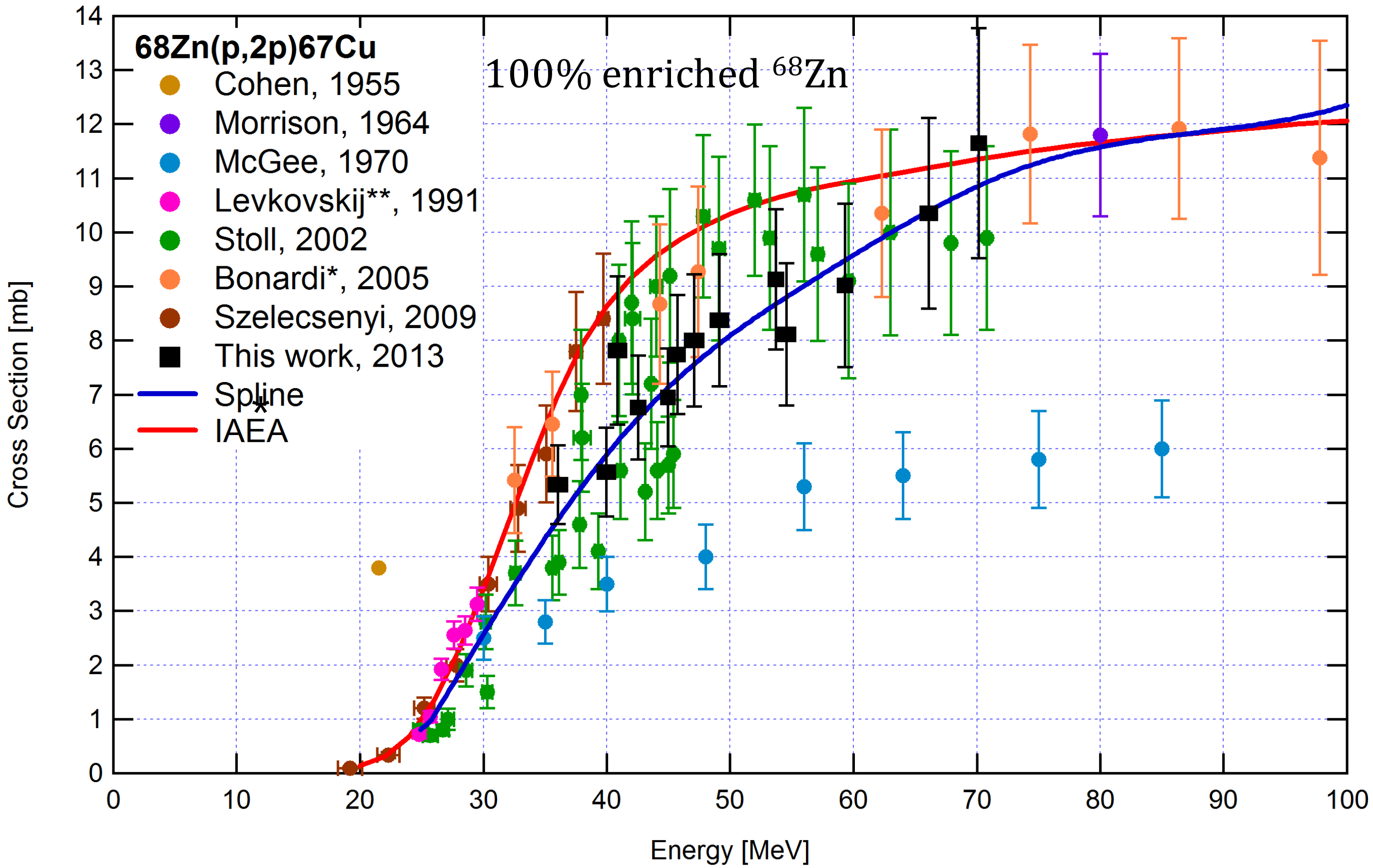


Good agreement in results from different irradiation runs !

Good agreement with recommended xs (IAEA) for $E_P > 50$ MeV !

* IAEA http://www-ds.iaea.org/radionuclides/emerging.html

The $^{68}Zn(p,2p)^{67}Cu$ nuclear reaction: Comparison

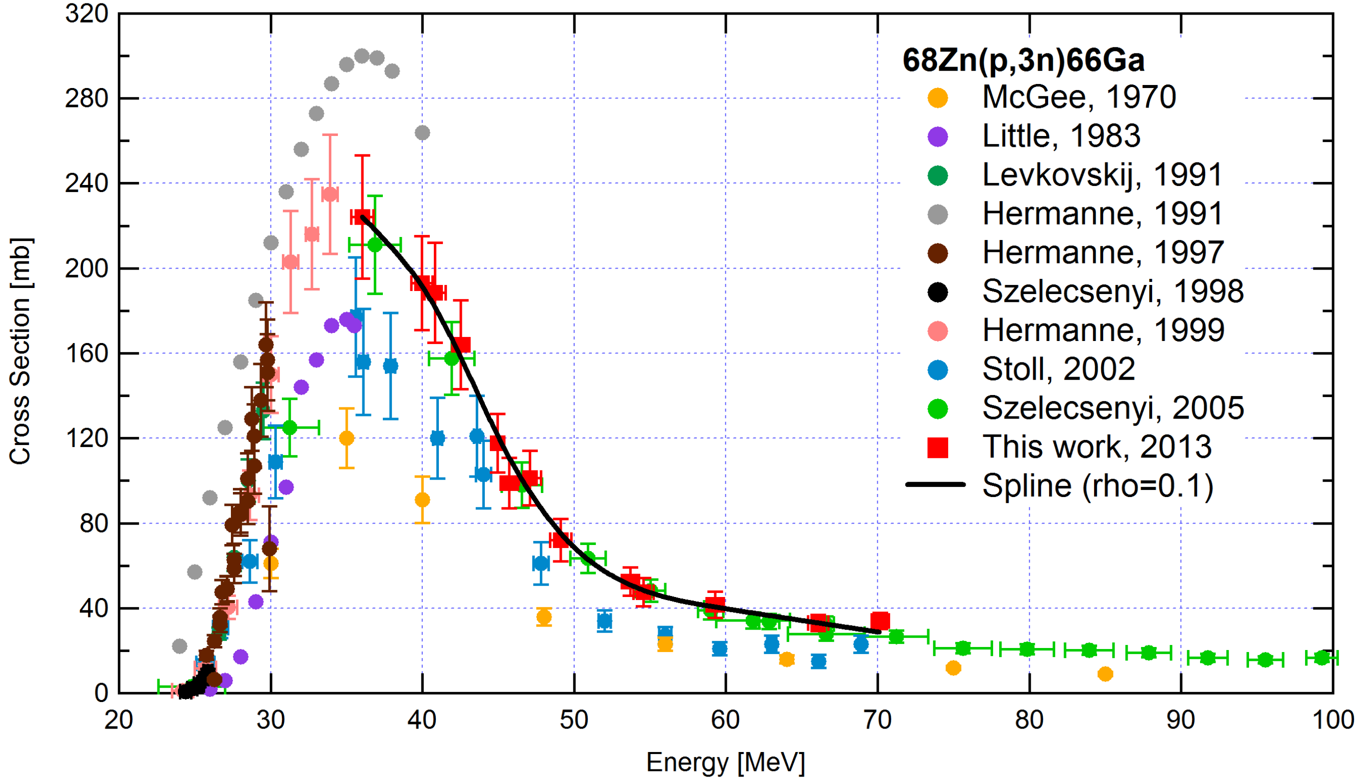


For E_P < 50 MeV : discrepancy in comparison with IAEA xs* (20-30%), but good agreement with Stoll et al. (2002) : two series of values !

For E_P > 50 MeV : agreement with IAEA and Bonardi et al. (2005) !

* IAEA http://www-ds.iaea.org/radionuclides/emerging.html

The $^{68}Zn(p,3n)^{66}Ga$ nuclear reaction



- Perfect agreement in results from different irradiation runs !
- Perfect agreement in comparison with previous results (entire energy range) !

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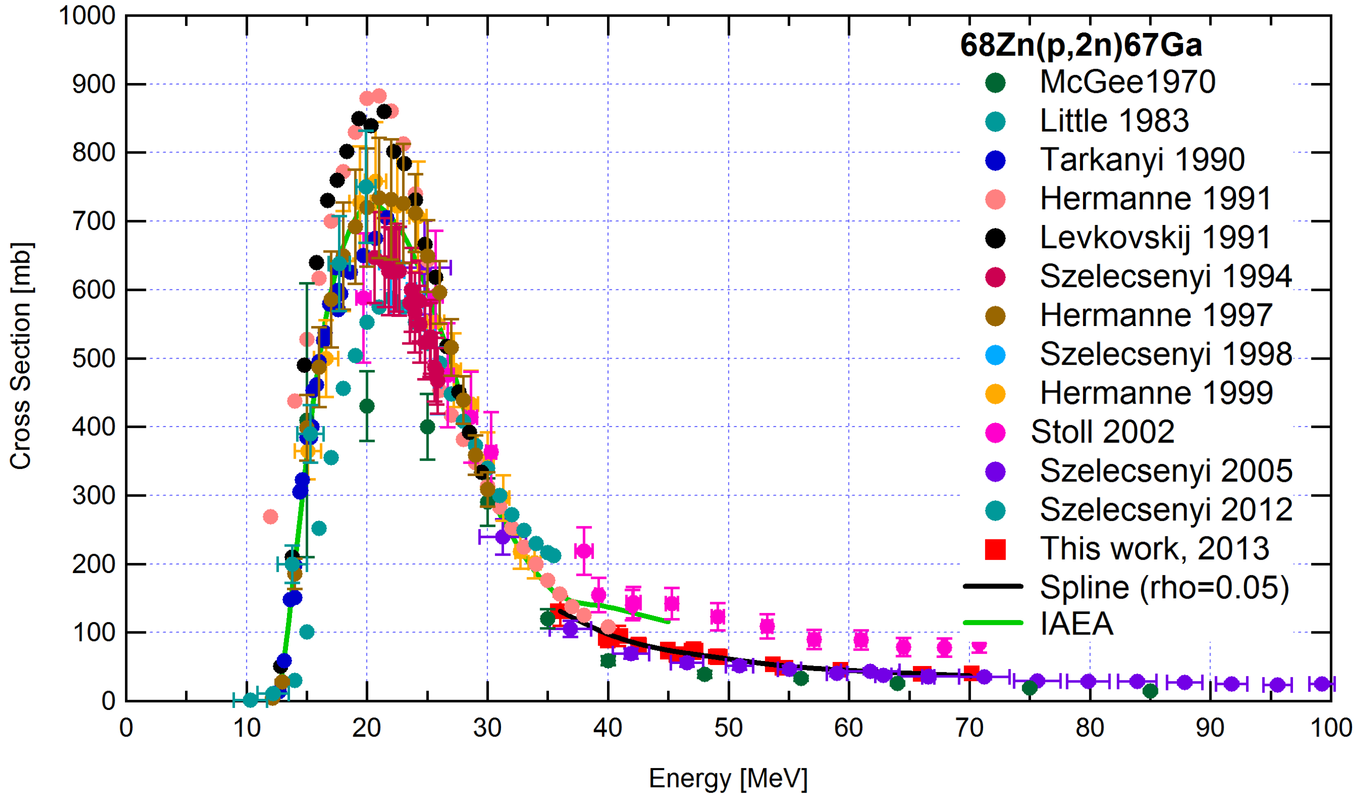
The $^{68}Zn(p,2n)^{67}Ga$ nuclear reaction

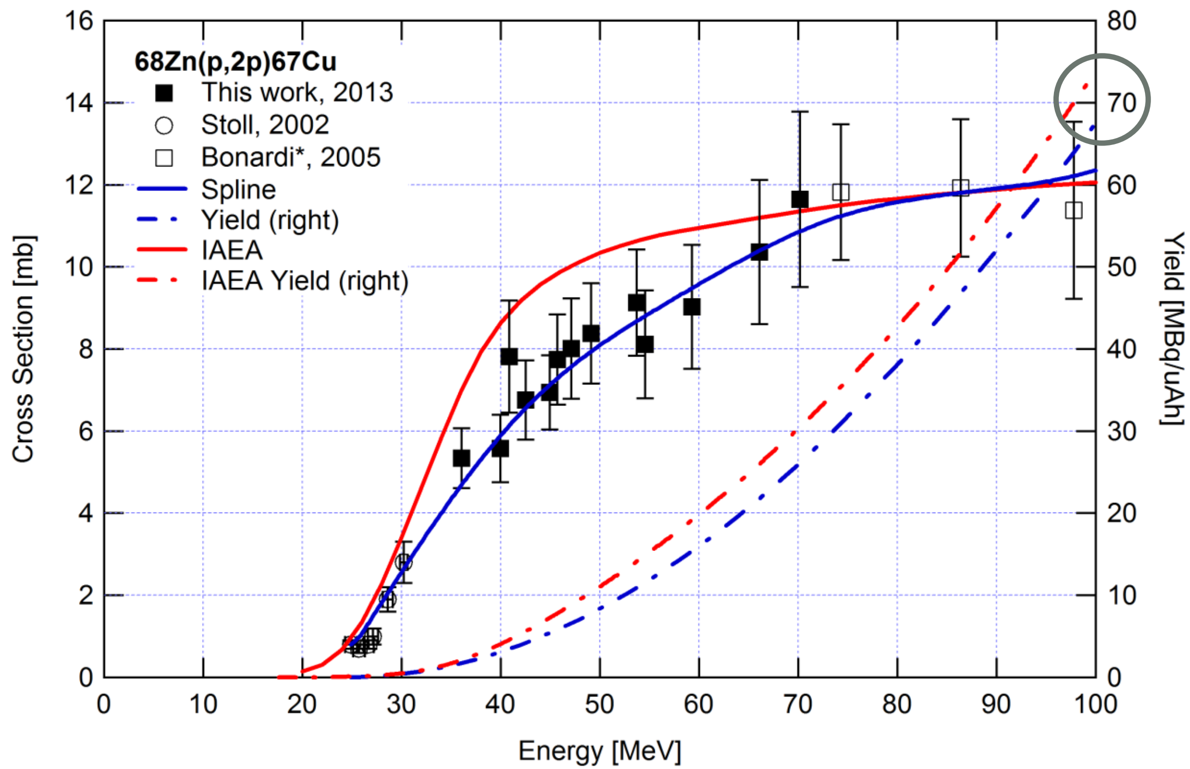


LARAMED

- ✅ Perfect agreement in results from different irradiation runs !
- ✅ Good agreement in comparison with previous results (entire energy range) !

* IAEA http://www-ds.iaea.org/radionuclides/emerging.html

^{67}Cu yield



- Discrepancy on the yield*,** ≈ 13%
- Issue of ^{64}**Cu** co-production: in order to have *pure* ^{67}**Cu** (RNP>99%) , ^{64}**Cu** must decay → decay-time ≈ 140 h → ^{67}**Cu** activity ≈ 20% !

*F. Haddad, S. David, E. Garrido (2009) ** IAEA http://www-ds.iaea.org/radionuclides/emerging.html

CONCLUSIONS

- *Radioisotope Production via Accelerator for Nuclear Medicine Application*

- Collaboration with ARRONAX facility (8 months):

  RaMe project (5x1000 UniFE) : 3 months + 1 month, 2012

  Erasmus Placement (EU) : 4 months , 2013

- INFN projects (CSN5) : APOTEMA & TECHN-OSP

  Coord. Nazionale : Ing. Juan Esposito

  - $^{100}Mo(p,x)^{99}Mo/^{99m}Tc$ & TDCR β-spectrometer
  - $^{96}Zr(\alpha,n)^{99}Mo$ @ ARRONAX facility

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CONCLUSIONS

- *Radioisotope Production via Accelerator for Nuclear Medicine Application*

- Study of ^{67}Cu production (collaboration with T. Sounalet)
  - ^{68}Zn(p,2p)^{67}Cu @ ARRONAX facility
  - *Hopefully* new INFN project (CSN3) – 2016 :
    CoMe – Copper Measurement , for innovative production via the ^{70}Zn(p,2p+2n)^{67}Cu nuclear reaction

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Grazie !

Thank you !!

Merci beaucoup !!!

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.. *grazie* !