Cyclotron-based production of innovative radionuclides for medicine

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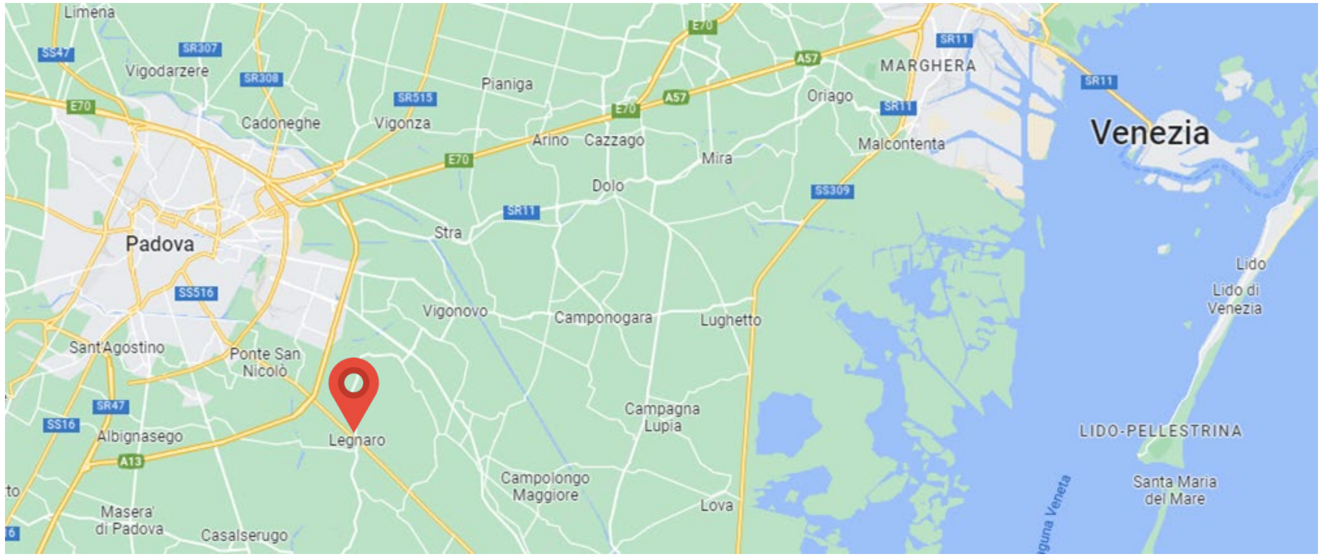
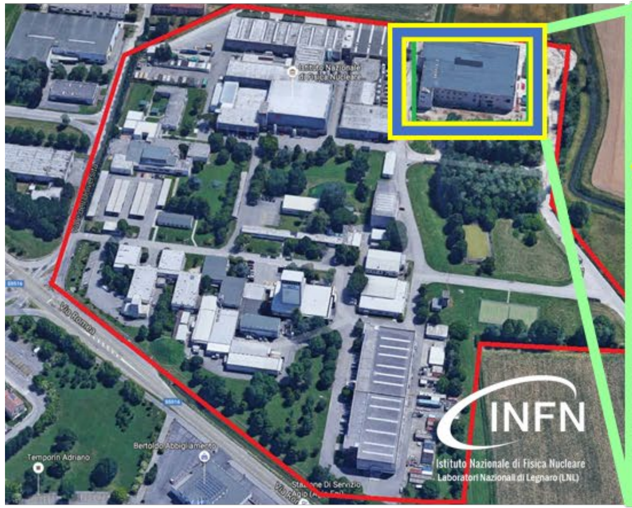
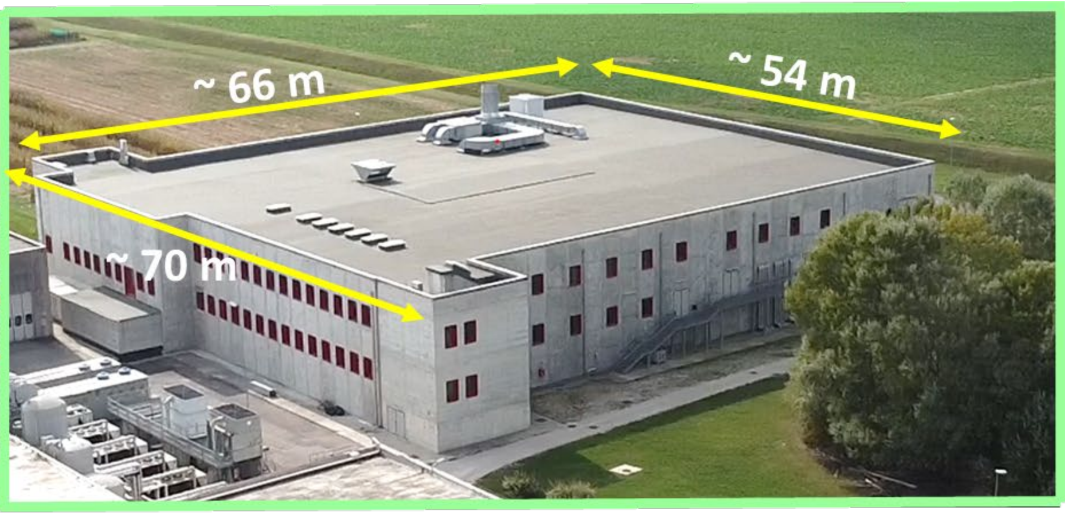
INFN-LNL are close to Padova and Venice



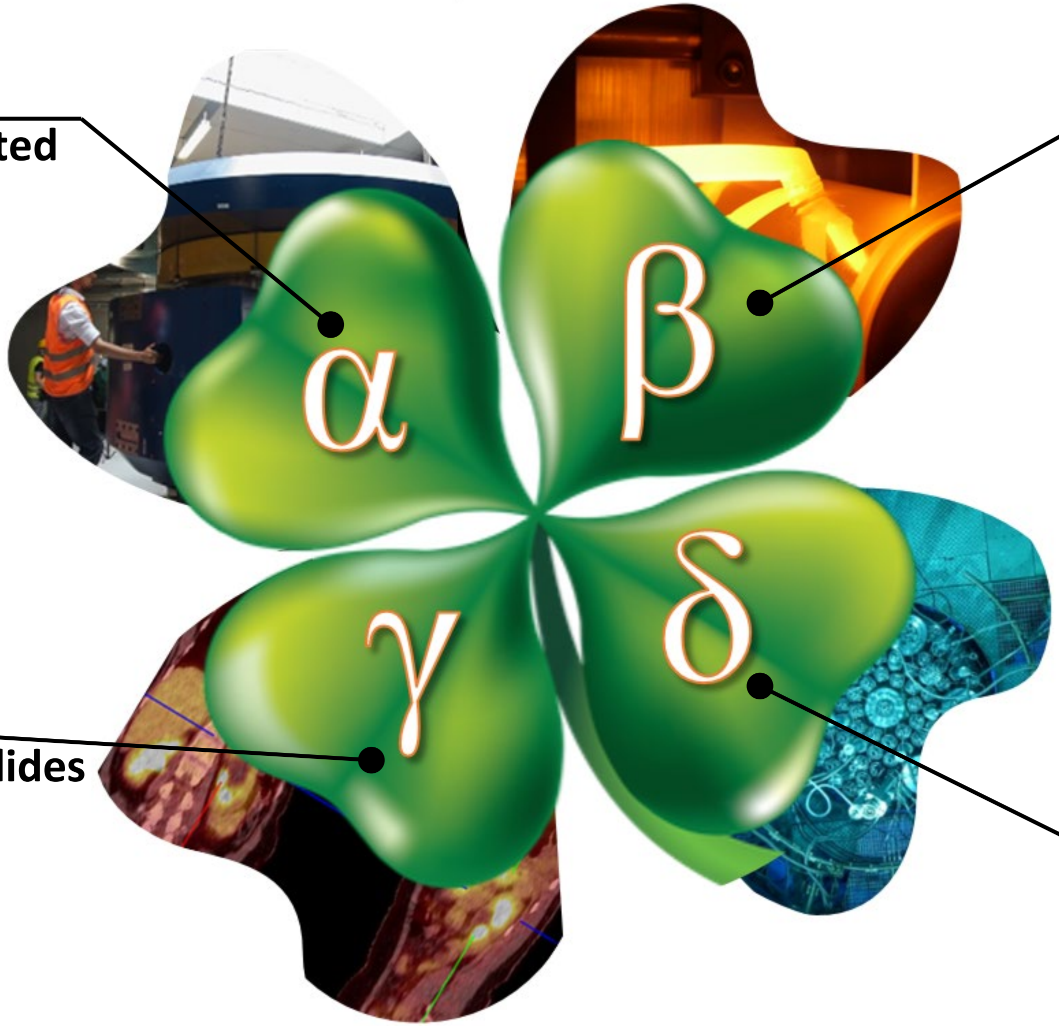




The SPES project

SPES-α
The cyclotron and related infrastructure.

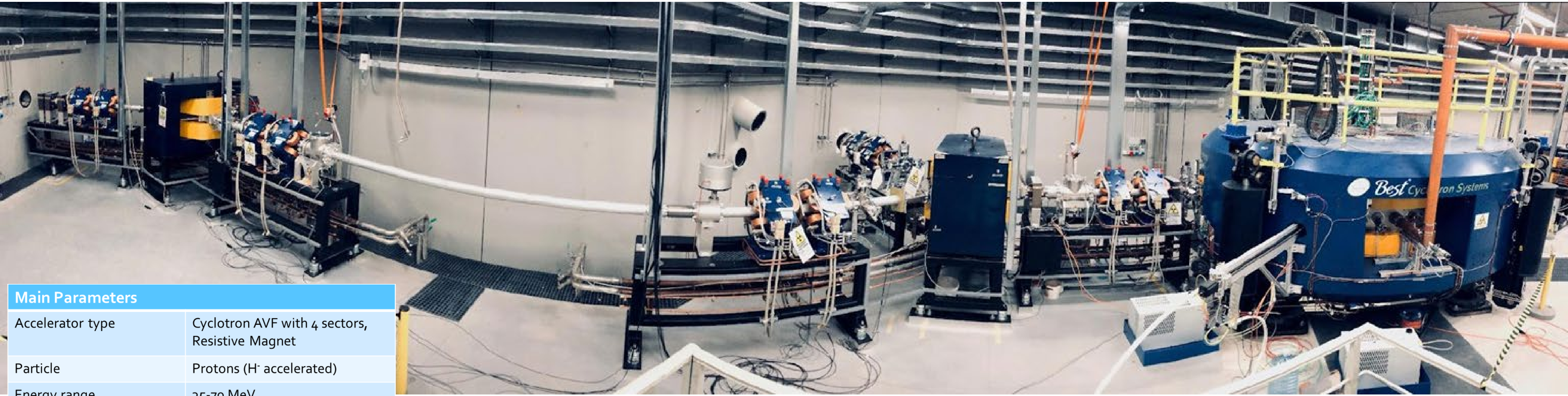
SPES-β
The ISOL facility and the acceleration of neutron-rich unstable nuclei.



SPES-γ
The production of radionuclides for applications.

SPES-δ
The multidisciplinary neutron sources.

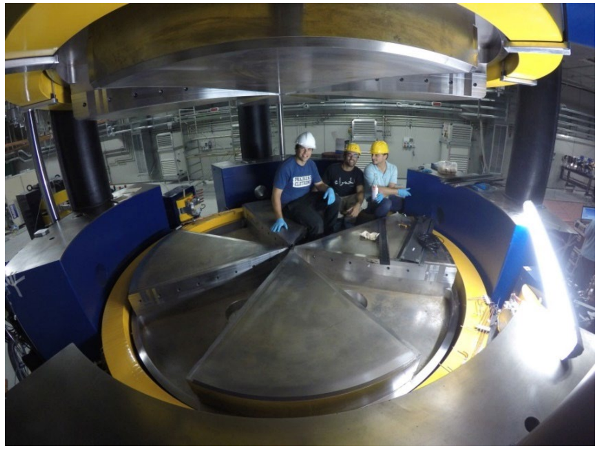
The SPES cyclotron



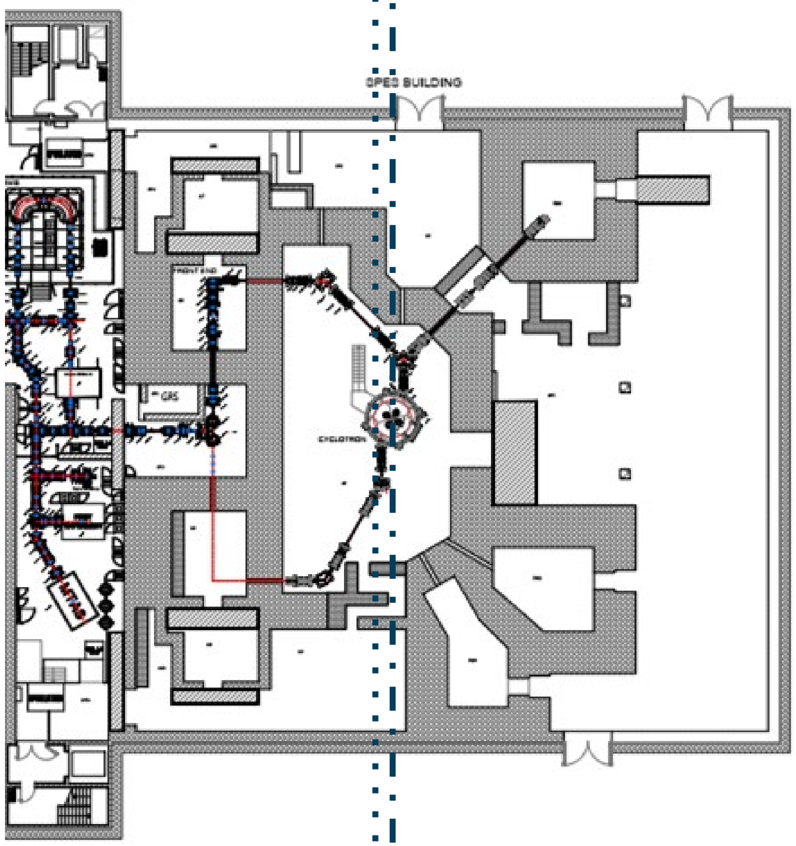
Main Parameters	
Accelerator type	Cyclotron AVF with 4 sectors, Resistive Magnet
Particle	Protons (H^- accelerated)
Energy range	35-70 MeV
Max Current Intensity	700 µA (variable within the range 1µA-700µA)
Extraction	Dual stripping extraction
Max Magnetic Field	1.6 T (Bo = 1 T)
RF System	nr. 2 delta cavities; harmonic mode=4; f_{RF} =56 MHz; 70 kV peak voltage; 50 kW RF power (2 RF amplifiers)
Ion Source	Multi-cusp volume H^- source; I_{ext} =8mA; V_{ext}=40 kV; axial injection
Dimensions	Φ=4.5 m, h=2 m, W=190 tons

Tunable energy: 70 – 35 MeV
High output current: 500 µA

Dual extraction ⇒ Fundamental & Applied research



Medical radionuclides production



ISOLPHARM
SPES exotic beams for medicine

ISOL technique
A. Andrighetto
Resp. ISOLPHARM

https://isolpharm.pd.infn.it/web/

LARAMED

Direct activation
J. Esposito
Resp. LARAMED

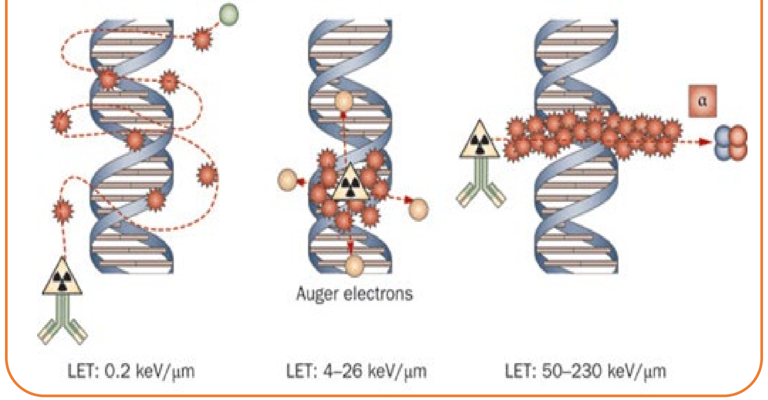
https://www.lnl.infn.it/en/spes-laramed-range

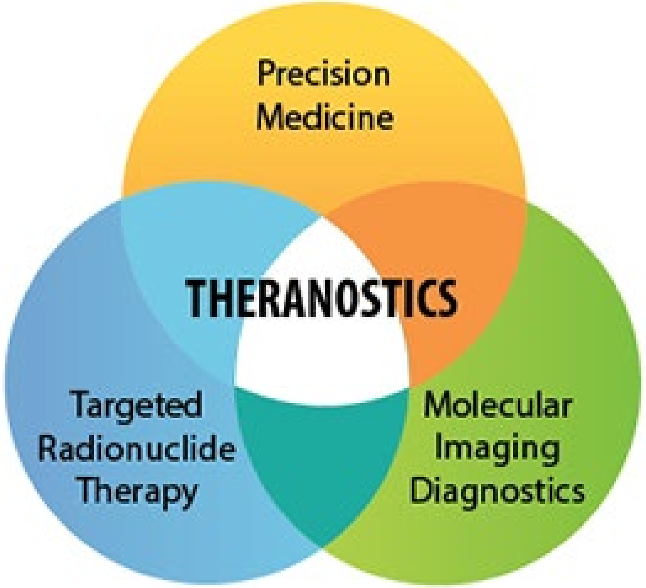
SPES-γ
The production of radionuclides for applications.

PRISMAP Medical Radionuclides

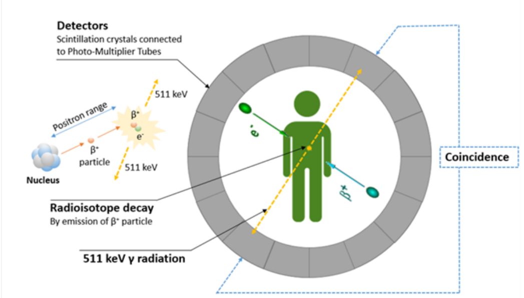
WHY?

THERAPY

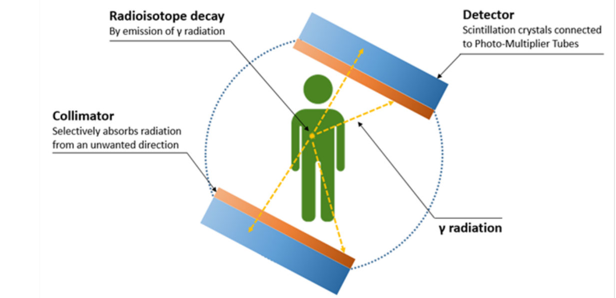




PET
Positron Emission Tomography



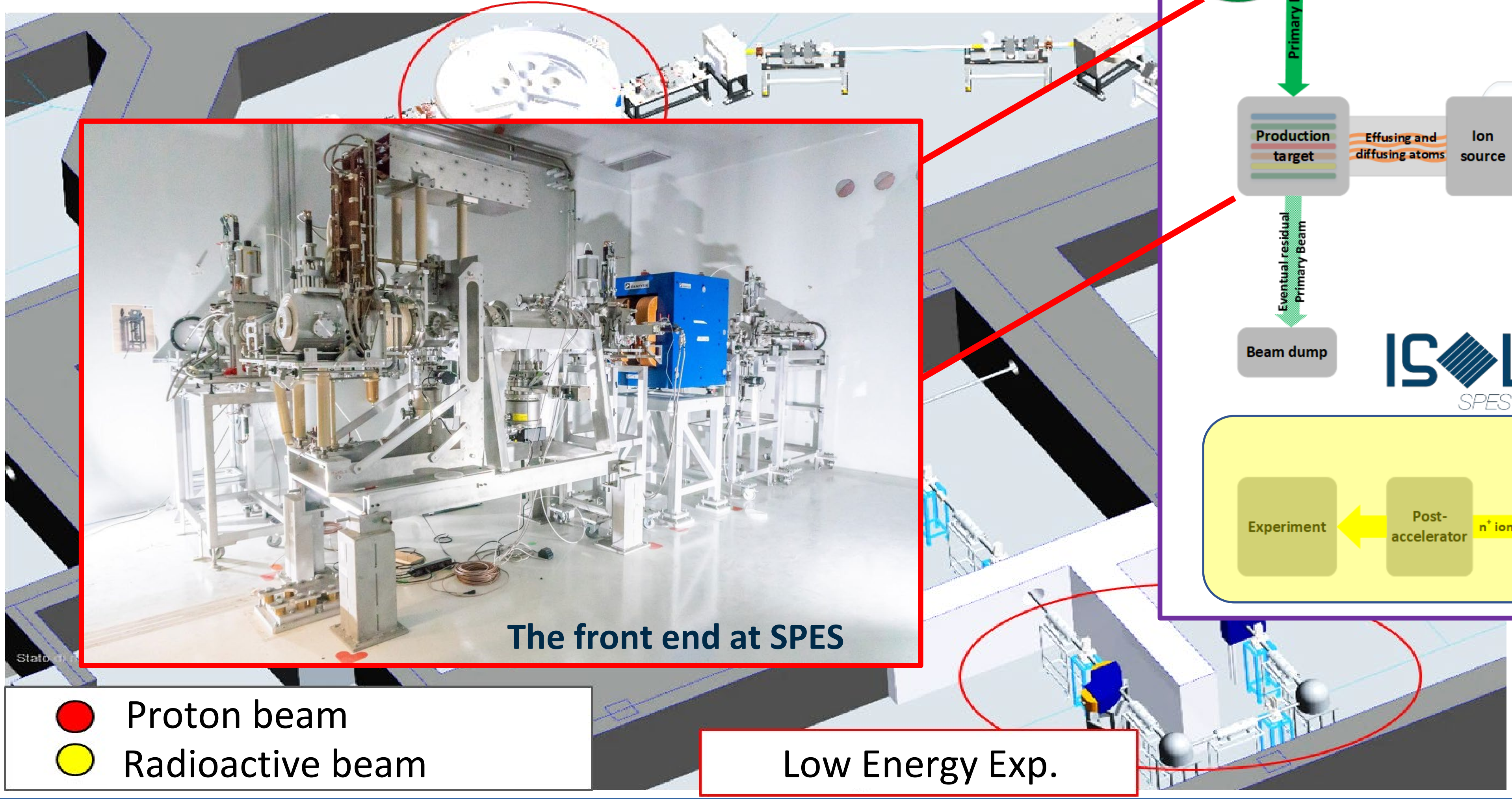
SPECT
Single Photon Emission Computed Tomography



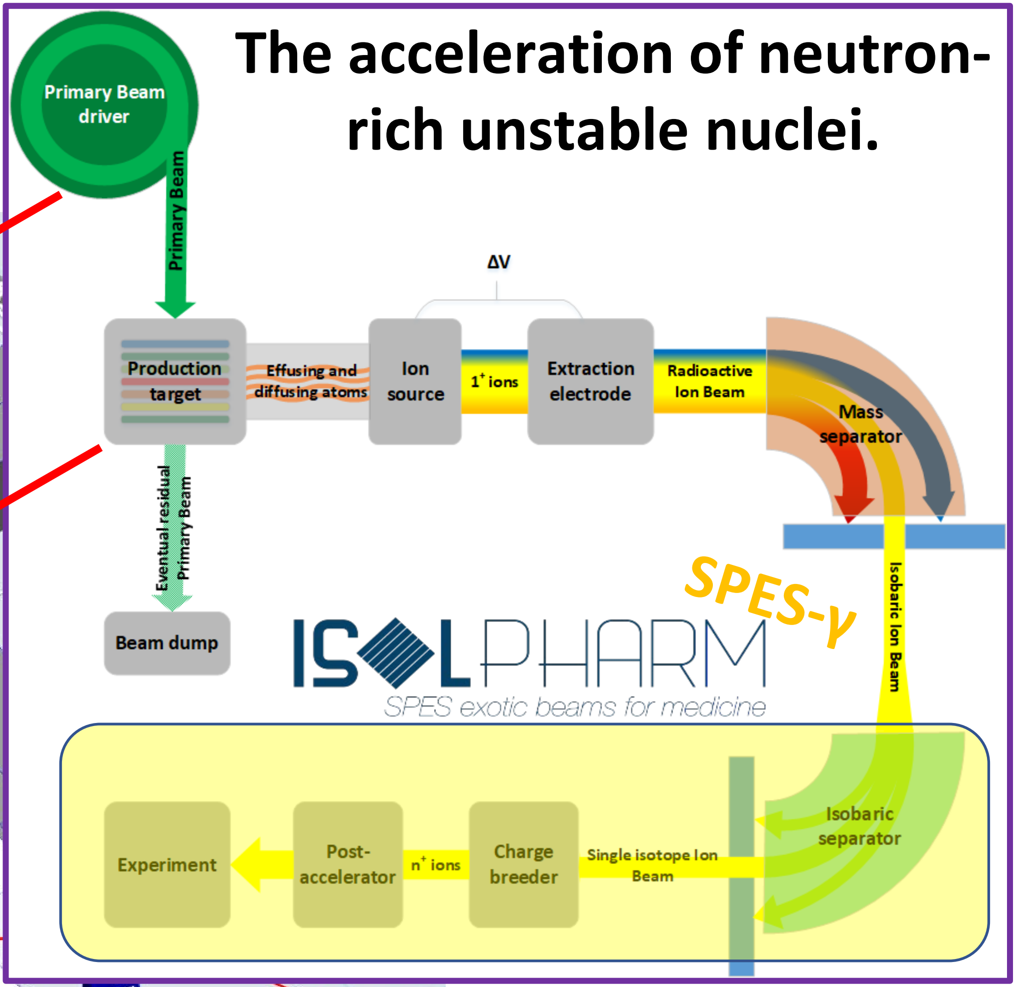
The ISOL facility

SPES-β

ISOL: Isotope Separation On Line
from Cyclotron through Target to Experiment



The acceleration of neutron-rich unstable nuclei.



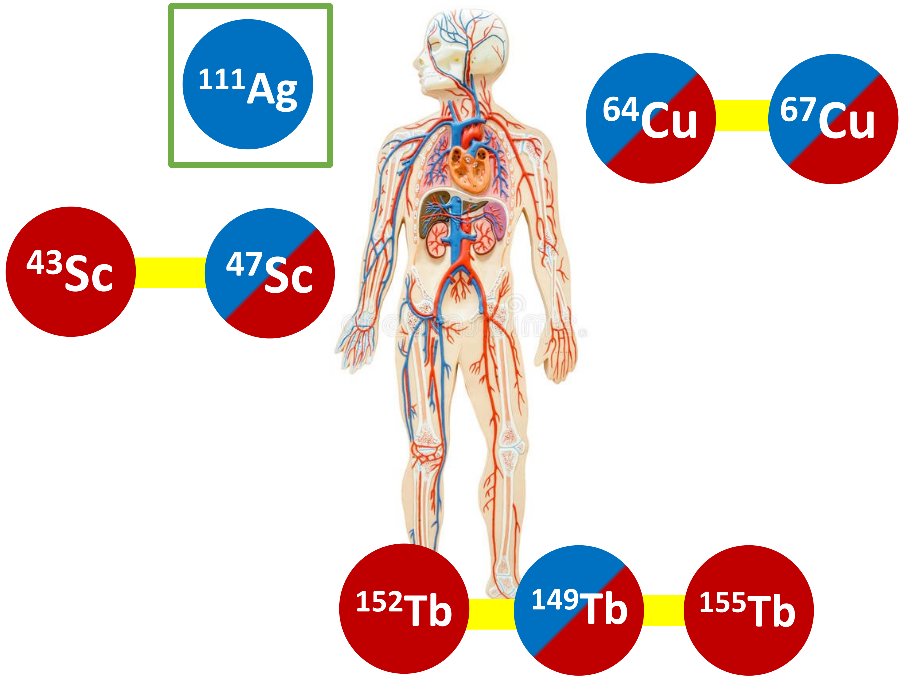
ISOLPHARM

SPES exotic beams for medicine

The ISOLPHARM method radiopharmaceuticals production is an INFN PATENT

The ISOLPHARM **ion collection target**

ISOLPHARM allows to produce unconventional medical radionuclides with high specific activity & RNP



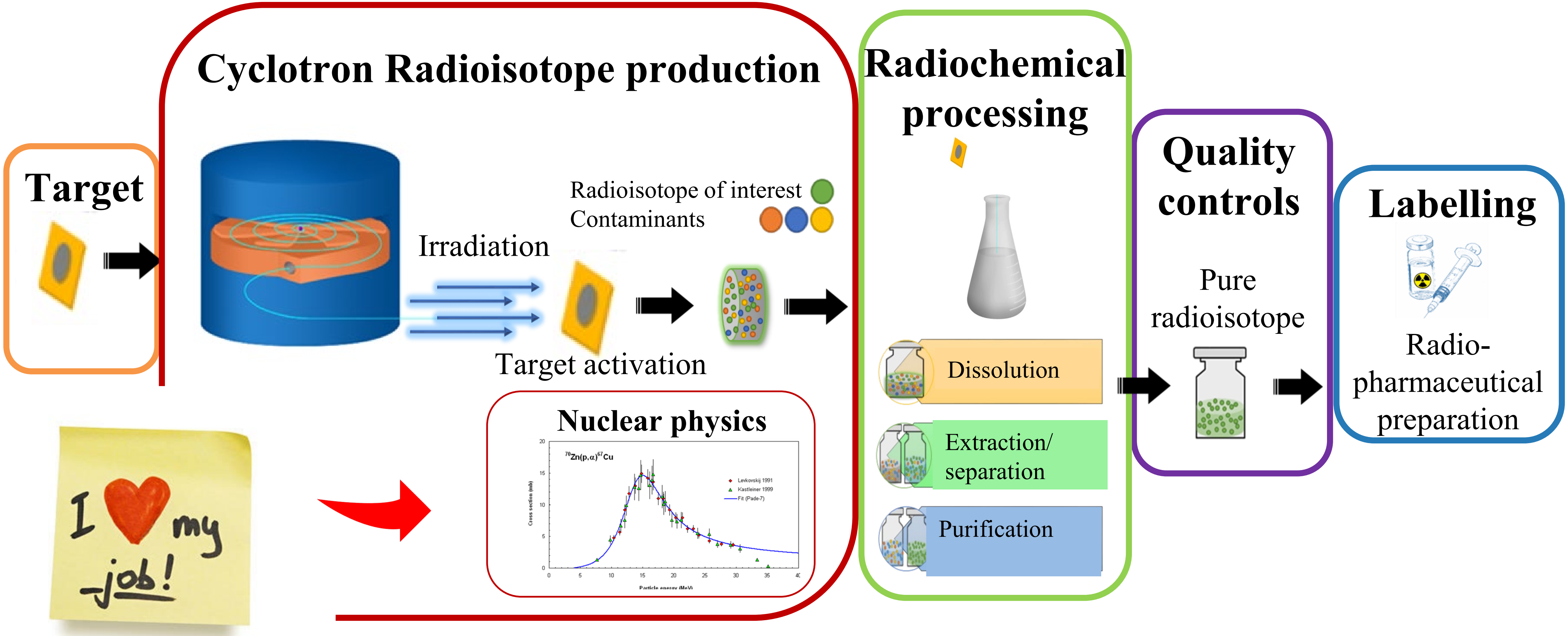
therapy   diagnostics   theranostics pairs

^{111}**Ag** production is investigated with two INFN-csn5 projects

ISOLPHARM_Ag (2018-2019)

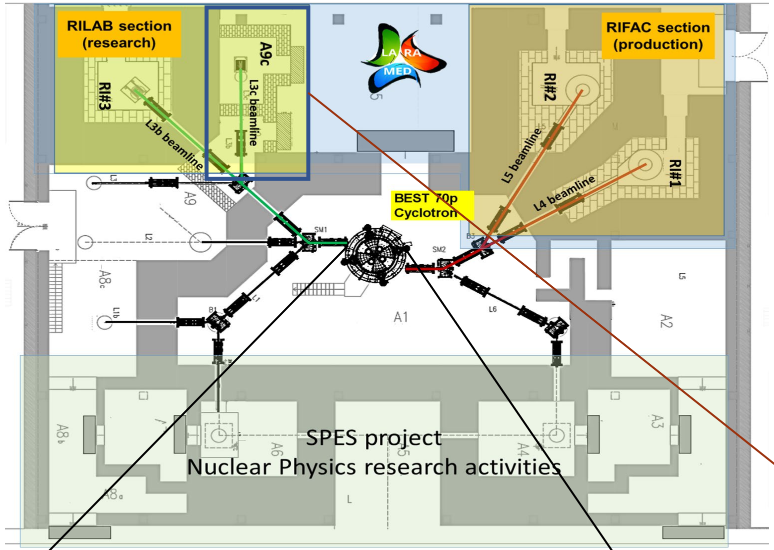
ISOLPHARM_EIRA (2020-2022)

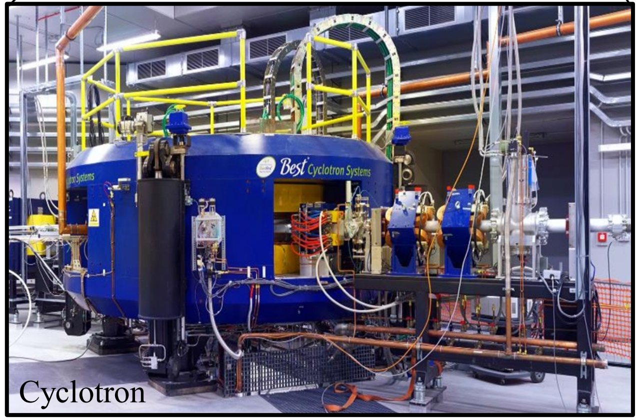
Cyclotron radiopharmaceutical production

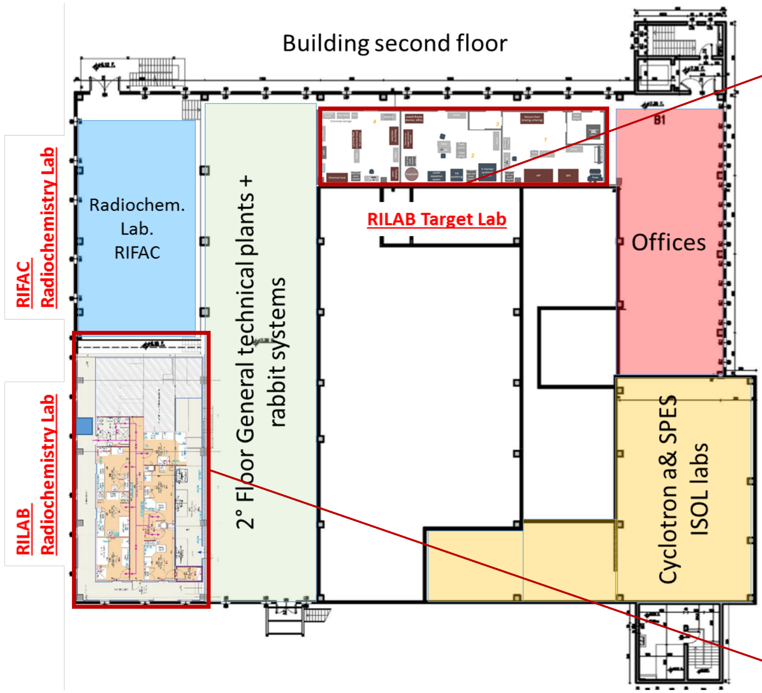


LARAMED facility @ LNL

Radioisotopes research area
(LARAMED)





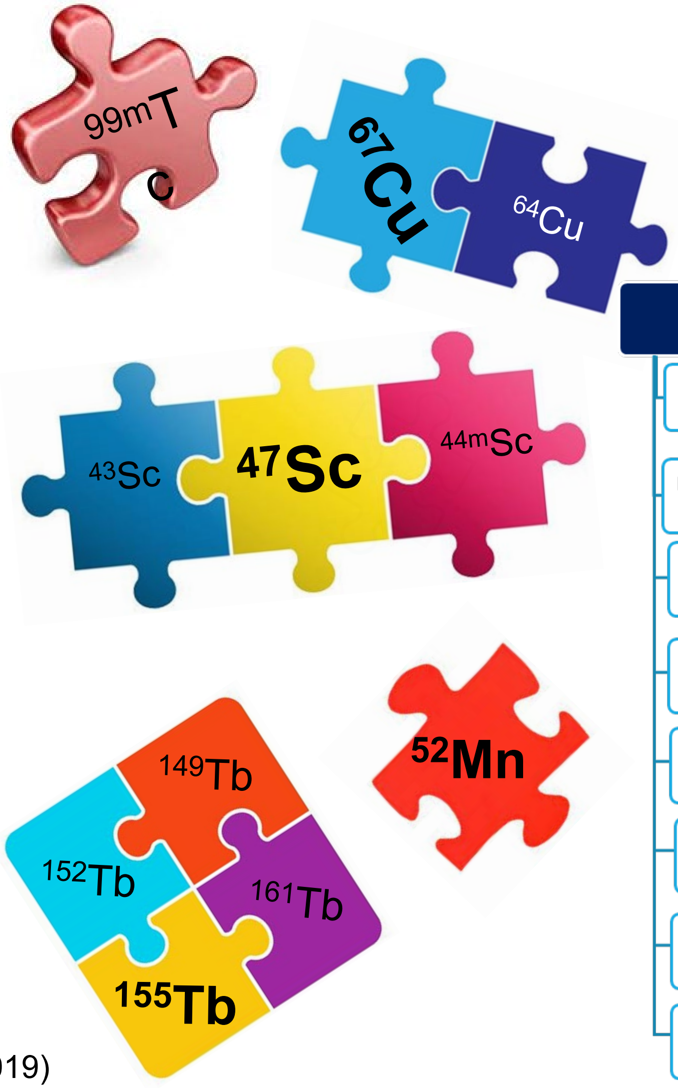


J. Esposito et al., LARAMED: a LAboratory for Radioisotopes of MEDical interest, (2019) Molecules 24(1) 20

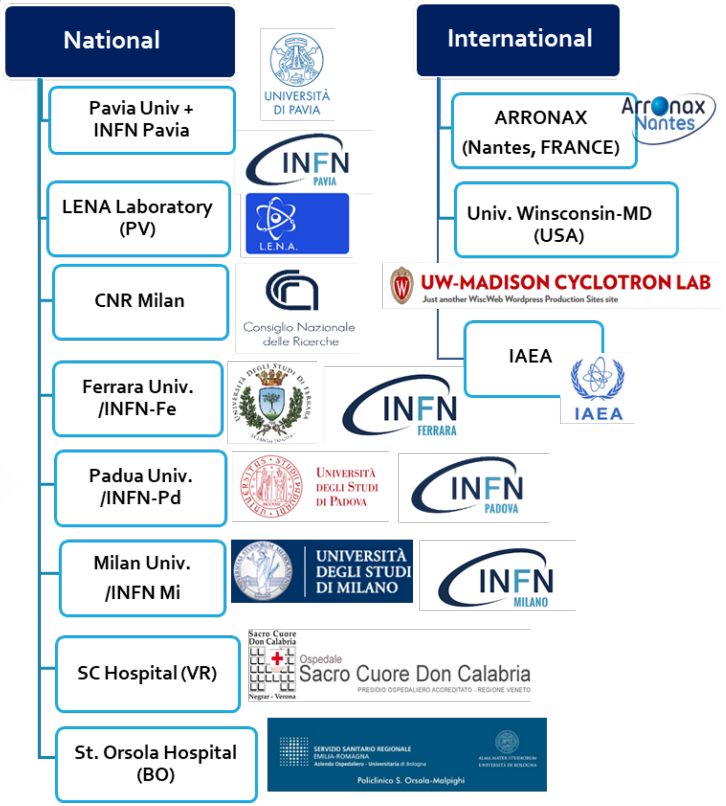
LARAMED research activities & network

Research lines and international projects	Years
Accelerator ^{99m}**Tc** direct production route through hospital cyclotrons	**APOTEMA (2012-2014)** **TECHNOSP (2015-2017)**
"Alternative, non HEU-based, ^{99m}**Tc**/^{99}**Mo** supply" IAEA	**IAEA CRP (2011-2015)**
COpper MEasurement: ^{70}**Zn(p,x)**^{67}**Cu**	**COME (2016)**
Production with Accelerator of ^{47}**Sc** for Theranostic Applications	**PASTA (2017-2018)**
"Radiopharmaceuticals Labelled with New Emerging Radionuclides (^{67}**Cu**, ^{186}**Re**, ^{47}**Sc**)" IAEA	**IAEA CRP (2016-2019)**
High Power Target concepts R&D	**TERABIO (2016-2019)**
High intensity vibrational powder plating (HIVIPP)	**E_PLATE (2018-2019)**
Multimodal pET/mRi Imaging with Cyclotron-produced $^{52/51}$**Mn** and stable paramagnetic Mn iSotopes	**METRICS (2018-2021)**
Research on Emerging Medical radIonuclides from the X-sections: ^{47}**Sc e** ^{149}**Tb**, ^{152}**Tb e** ^{155}**Tb (and therapeutic** ^{161}**Tb)**	**REMIX (2021-2023)**
TOTEM (magneTron sputtering cyclotrOn TargEt Manufacturing)	**TOTEM (2021-2022)**

J. Esposito et al, Molecules 24(1), 20 DOI:10.3390/molecules24010020 (2019)



27 EU PRISMAP Medical Radionuclides

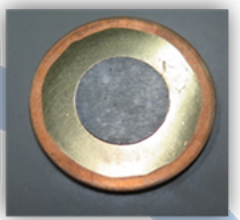


^{99m}Tc direct production cycle

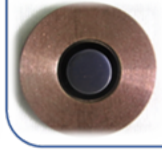
Closed-loop technology developed at LNL: recovery of costly target material

^{99m}Tc is il «gold standard» for SPECT procedures worldwide. Currently obtained by ^{99}Mo/^{99m}Tc generator systems

Target production



INFN International Patent no. PCT/IB2018/056826



Sputtering on chemically inert baseplate

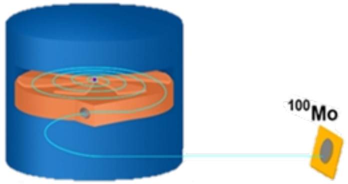
APOTEMA
TECHN-OSP
projects
INFN-CSN5
2012-2017

H. Skliarova et al., Instruments, 2019, 3, 17

^{100}Mo recovery technique

^{100}Mo(p,2n)^{99m}Tc

Cyclotron Irradiation



J. Esposito, Sci Tech of Nuc Inst 2013 ID:972381
S. Manenti, Appl. Rad. Isotop. 2014 94C

Radiopharmaceuticals, QC, imaging

P. Martini et al. Appl. Rad. Isotop. 2018, 135

Radiochemistry Process. (extraction/separation/ purification)

P. Martini et al. Appl. Rad. Isotop. 2016, 118

IAEA
CRP on ^{99}Mo/^{99m}Tc suppy (2011/2015)

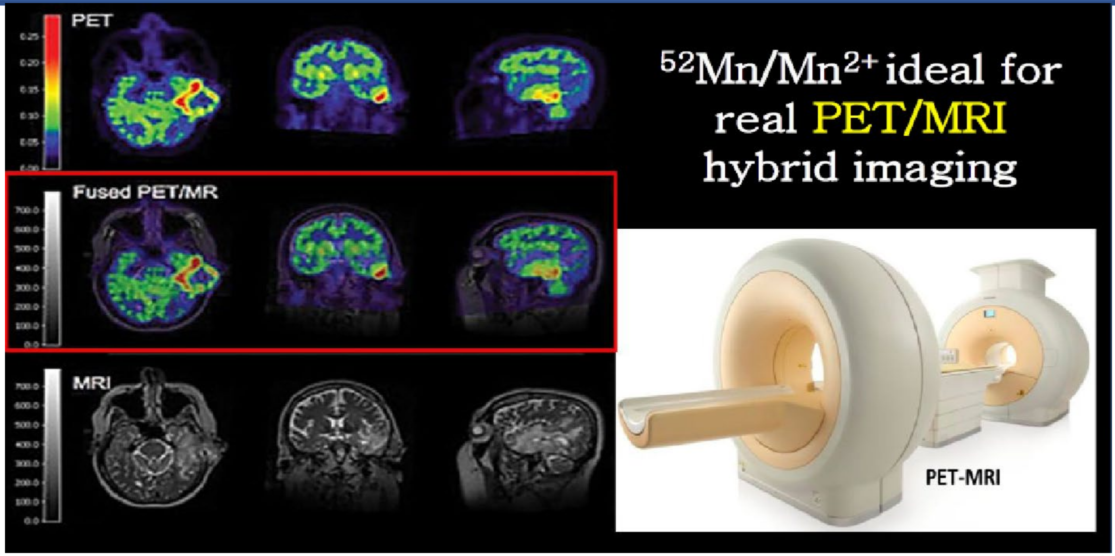
^{52}Mn and the METRICS project

In Multi Modal Imaging (MMI) a mismatch occurs because the contrast and radioactive agents used are chemically different.....

GOAL : to achieve a **genuine fusion between PET and MRI**, the contrast and radioactive agents should be chemically identical

Multi Modality Imaging MMI	
PET/SPECT	**CT/MR**
functional imaging	anatomical imaging
radiolabeled tracer	**contrast agent**
e.g. ^{18}F-FDG for PET	**e.g. Ba and I for CT**
or ^{99m}Tc-HMPAO for SPECT	**or Gd-OMNISCAN for MRI**

^{52}Mn	$E_{\beta+ (avg)}$ 250 keV	PET
^{51}Mn	$E_{\beta+ (avg)}$ 960 keV	
Mn^{2+}	Paramgnetic properties	MRI contrast agent

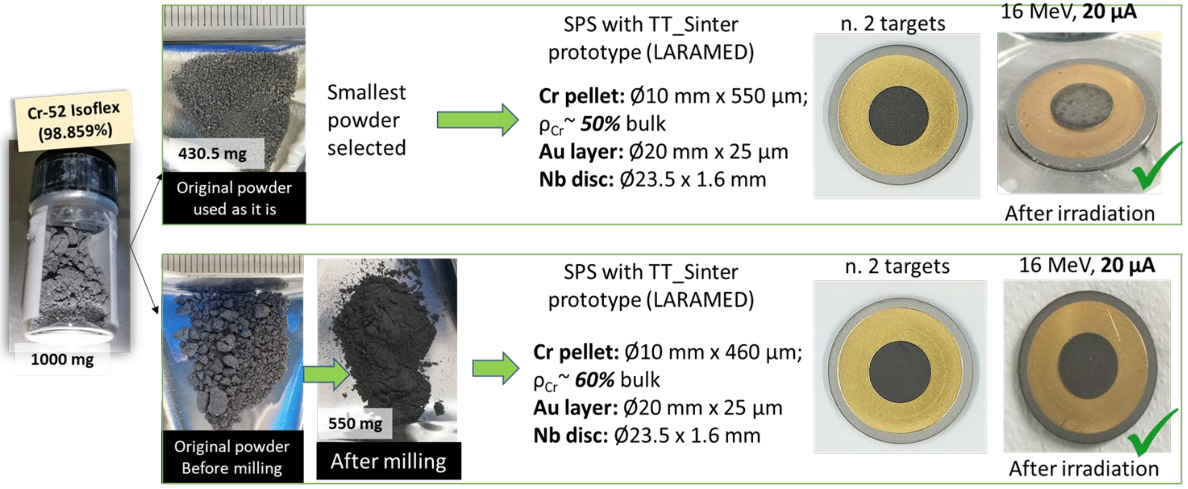


GOAL of METRICS project

- To Develop/optimize the ^{52}Mn cyclotron production and separation/purification method
- To establish stable Mn(II)/^{52}Mn-complexes

^{52}Mn

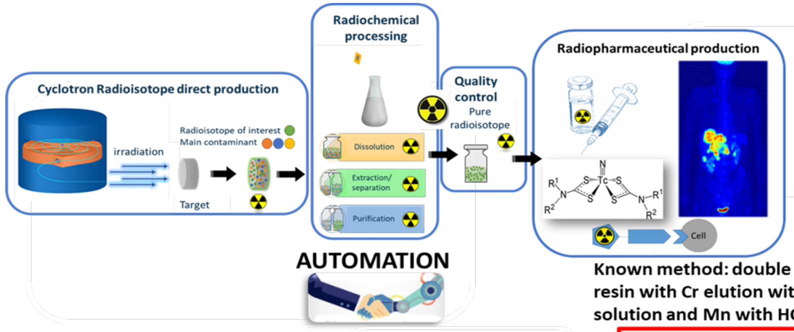
^{52}Mn and the METRICS project

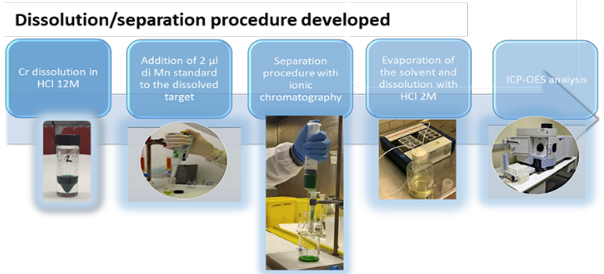


Irradiation at 16 MeV energy for pure ^{52}Mn production

^{52}Cr target manufacturing technology developed by SPS technique

Development of Efficient Separation Procedures of Cyclotron Produced $^{52/51}$Mn





Known method: double anion exchange resin with Cr elution with a hydroalcoholic solution and Mn with HCl 0.1M

Original approach used: a first anion and a second cation exchange resins arranged in series

Ag1X-8 + Ag1X-8 coupling

Sample	Cr (mg)	Mn (µg)
WASTE 1	200.2	< LDR
WASH 1	1.9	< LDR
WASTE 2	0.9	< LDR
WASH 2	0.03	< LDR
PRODUCT 2A	< LDR	2.1
PRODUCT 2B	< LDR	0.6

LDR: Cr= 11.9 ppb; Mn=5.30 ppb

Ag1X-8 + AG50W-X4 coupling

Sample	Cr (mg)	Mn (µg)
WASTE 1	188.8	< LDR
WASH 1	2.1	< LDR
WASTE 2	0.4	< LDR
WASH 2A (10 ml di HCl 0.1 M)	0.2	< LDR
WASH 2B (2 ml di HCl 0.3 M)	0.02	0.2
WASH 2C (2 ml di HCl 0.5 M)	0.06	0.6
PRODUCT 2A(1 mL HCl 1.5 M)	0.06	1.8
PRODUCT 2B 1 mL HCl 1.5 M)	0.02	0.8
PRODUCT 2C (1 mL HCl 2 M)	0.004	0.3
PRODUCT 2D (1 mL HCl 2M)	< LDR	0.07

6

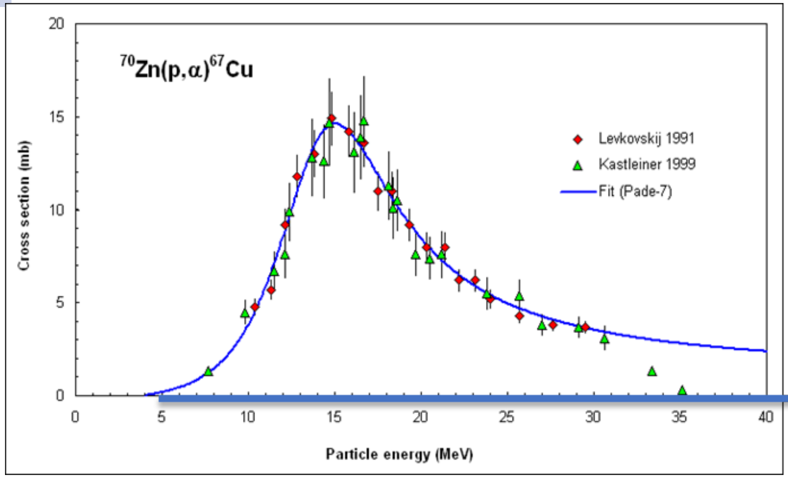
^{67}Cu as theranostic agent

Cu-67 61.83 h	γ-ray [keV]	γ-ray [%]	β energy [keV]	β int [%]	Auger [keV]	Auger [%]
	SPECT		THERAPY			
β^- : 100 %	184.6	48.7	51.0	1.11	0.99	19.14
(Zn-67)	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

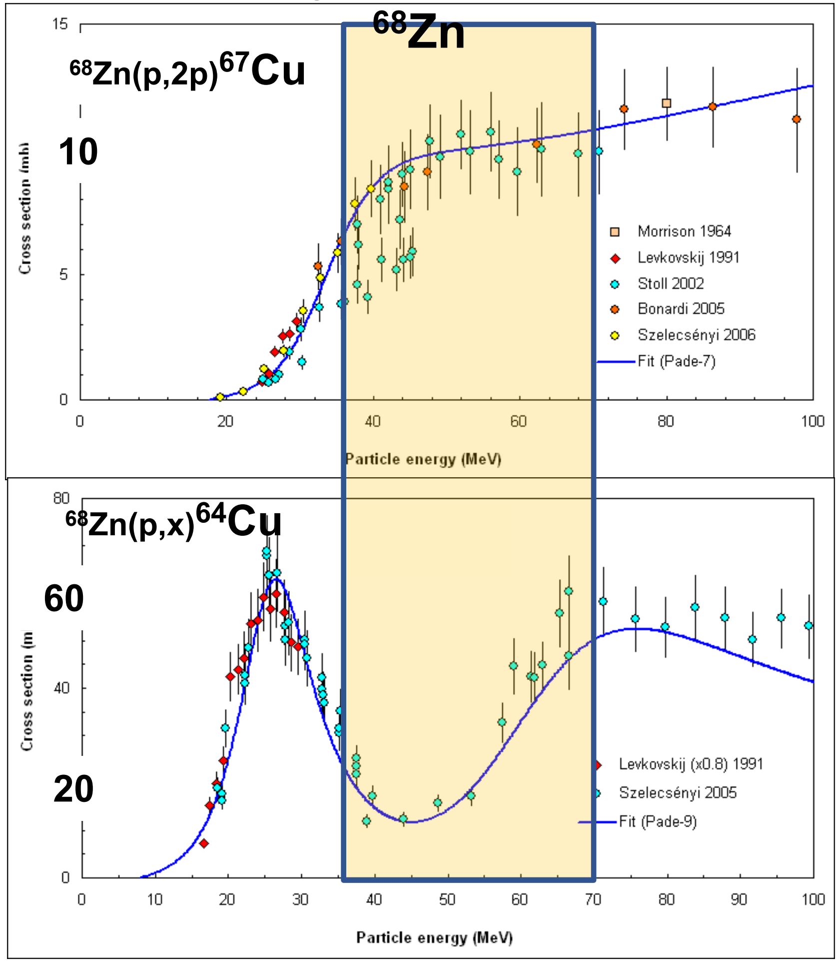
IAEA

CRP on ^{67}Cu, ^{47}Sc, ^{186}Re (2016/2020)



COME project
INFN-CSN3 2016

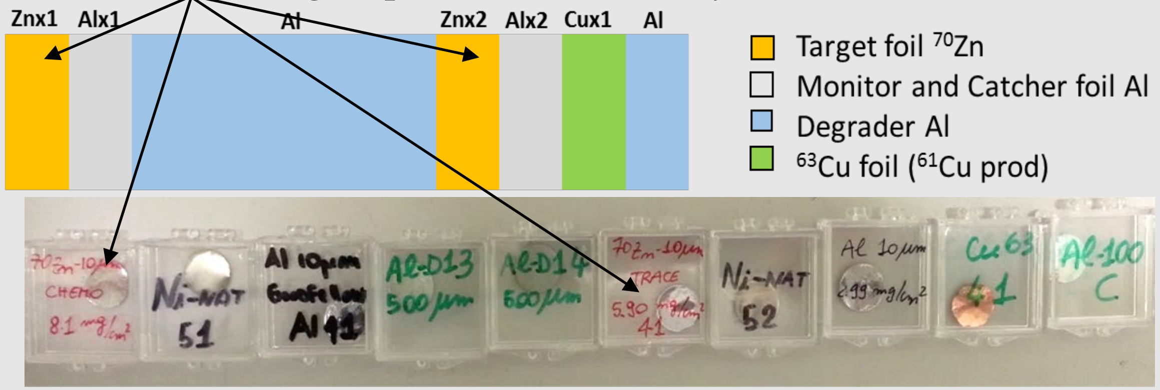
Most used targets for ^{67}Cu production:



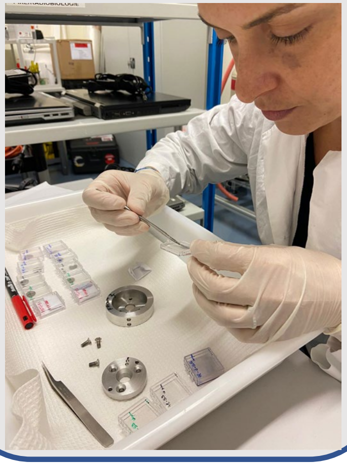
^{67}Cu as theranostic agent

Scheme of a typical stacked-foils target

Enriched ^{70}Zn targets produced at LNL by lamination

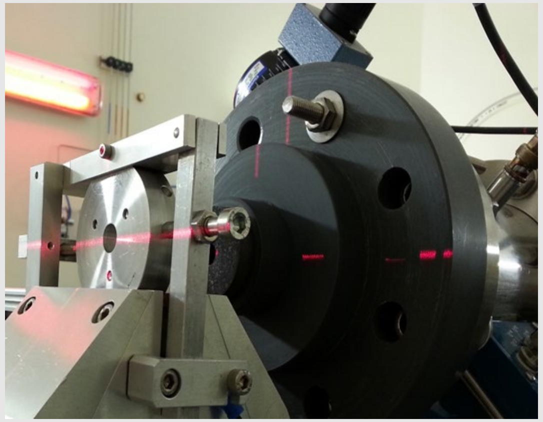


Stacked-foils target assembly

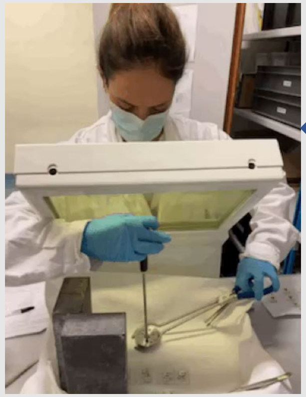


Beam setting with alumina

Irradiation runs on the AX3 beam-line

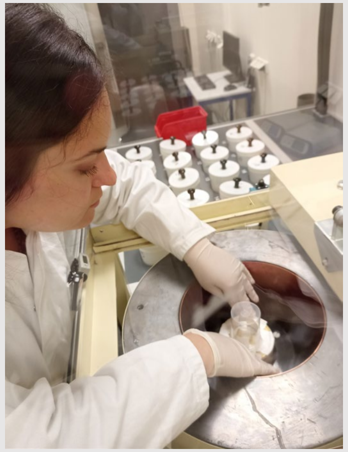


Target disassembly

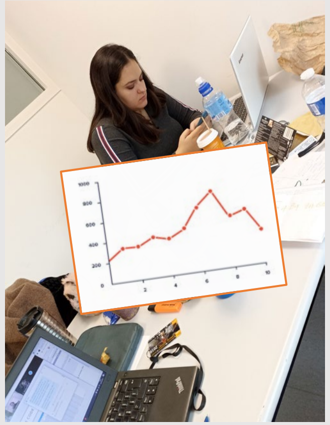


Radiochemistry

γ-spectrometry



Data analysis



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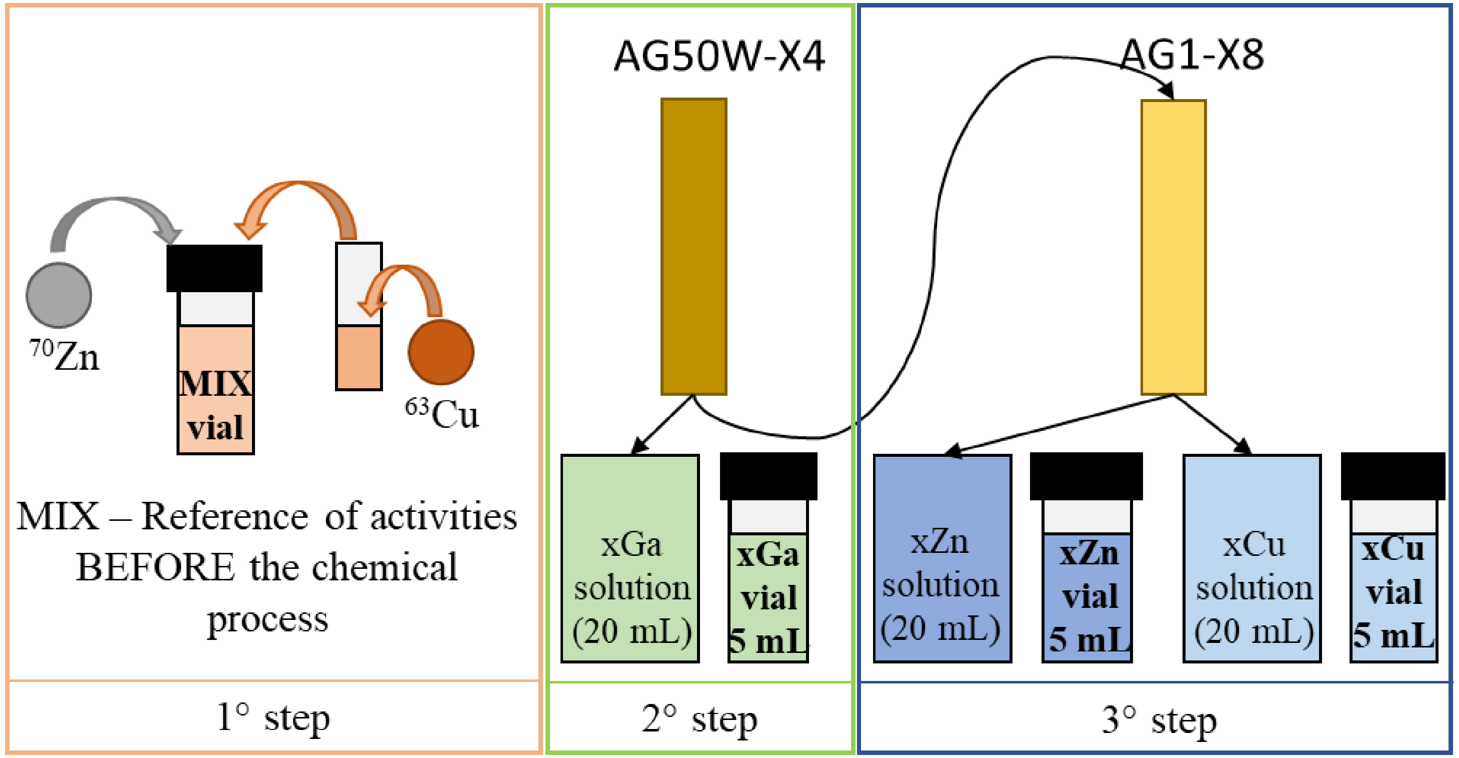
Cu/Ga separation process from Zn

Energy [keV]	Cu-67 Int. [%] $t_{1/2}$ = 61.83 h	Ga-67 Int. [%] $t_{1/2}$ = 78.24 h
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*

POLICLINICO DI SANT'ORSOLA

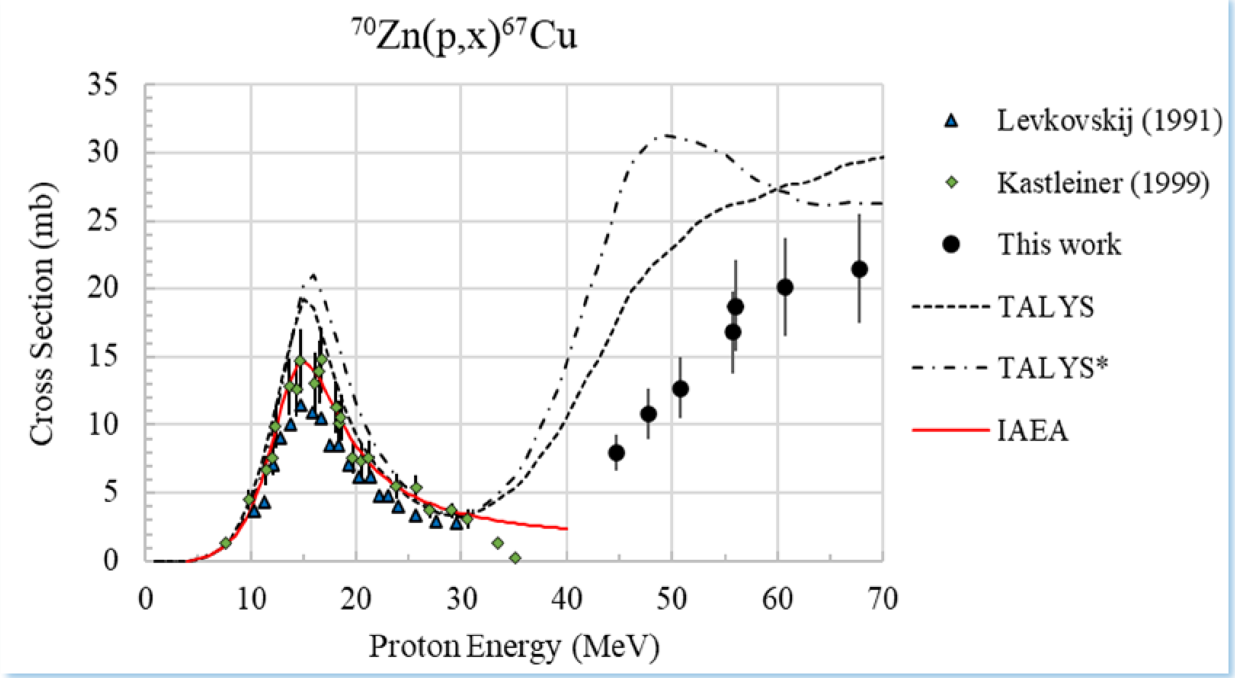
Università degli Studi di Ferrara

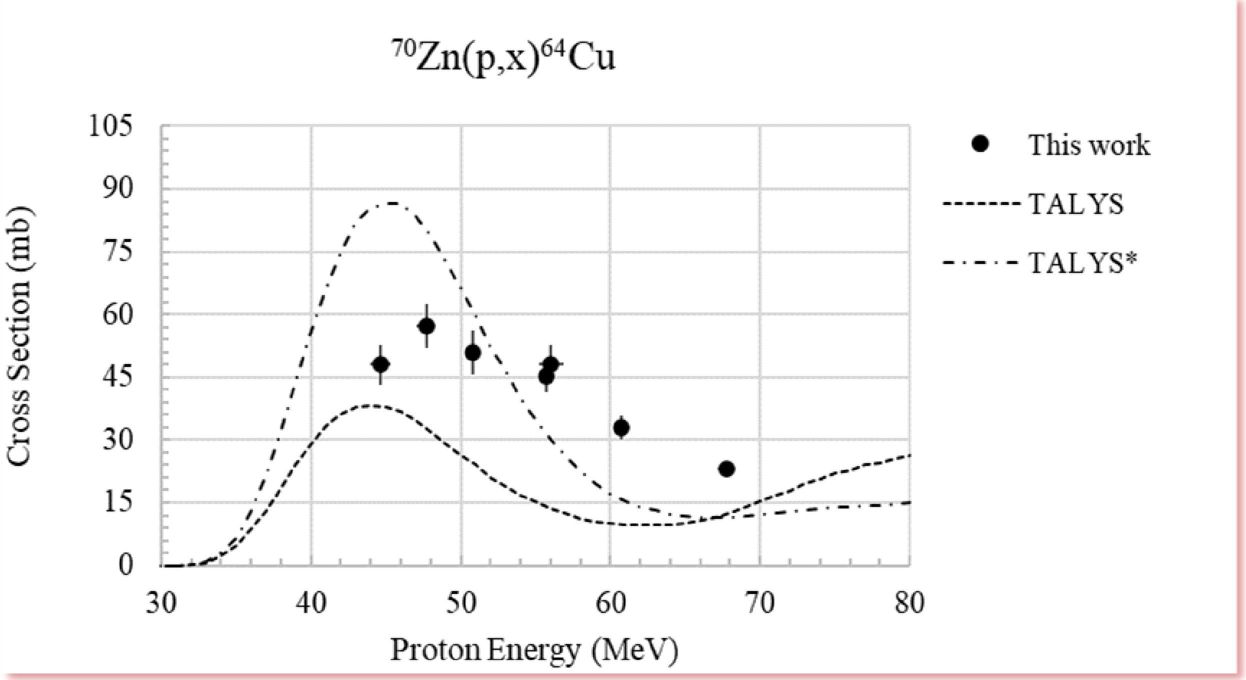


%	Gallium Sol	Copper sol	Zinc sol
Ga-66	79 ± 11	2 ± 1	ND
Cu-61	ND	95 ± 2	ND
Zn-69	ND	ND	84 ± 2

G. Pupillo, L. Mou, **P. Martini**, et al. *Radiochimica Acta*, 2020, 108(8), pp. 593–602

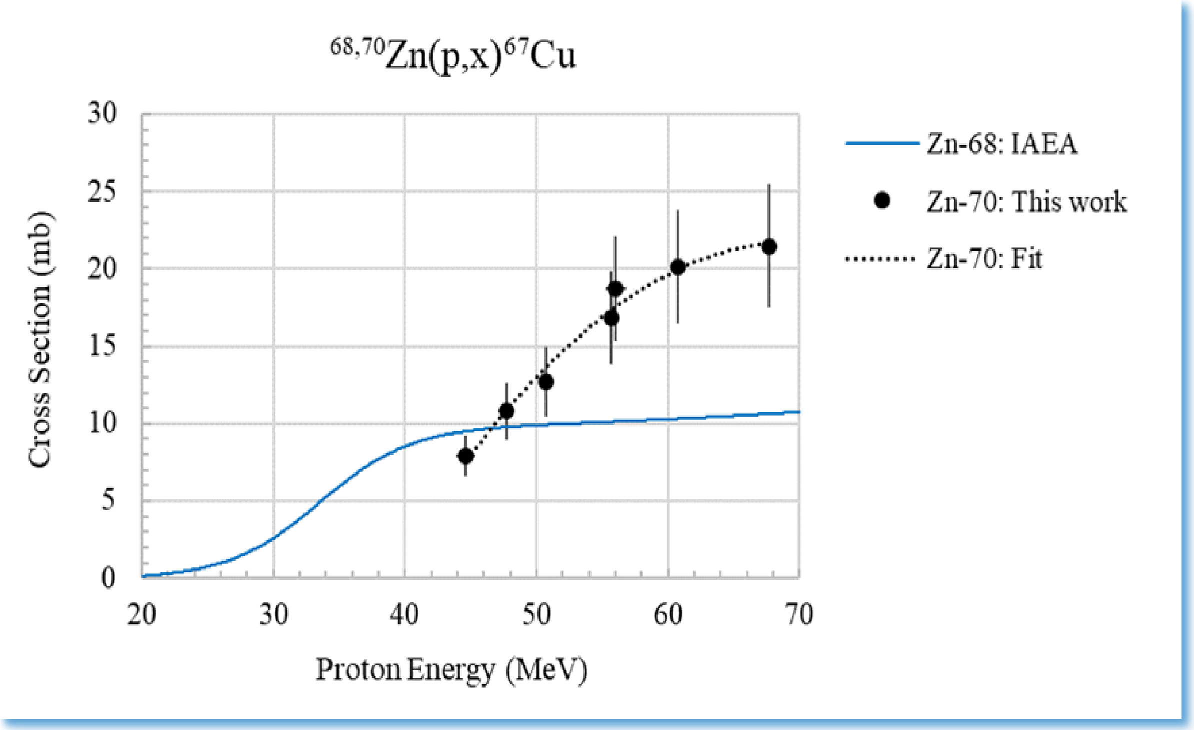
The $^{70}Zn(p,x)^{67}Cu$,^{64}Cu cross sections

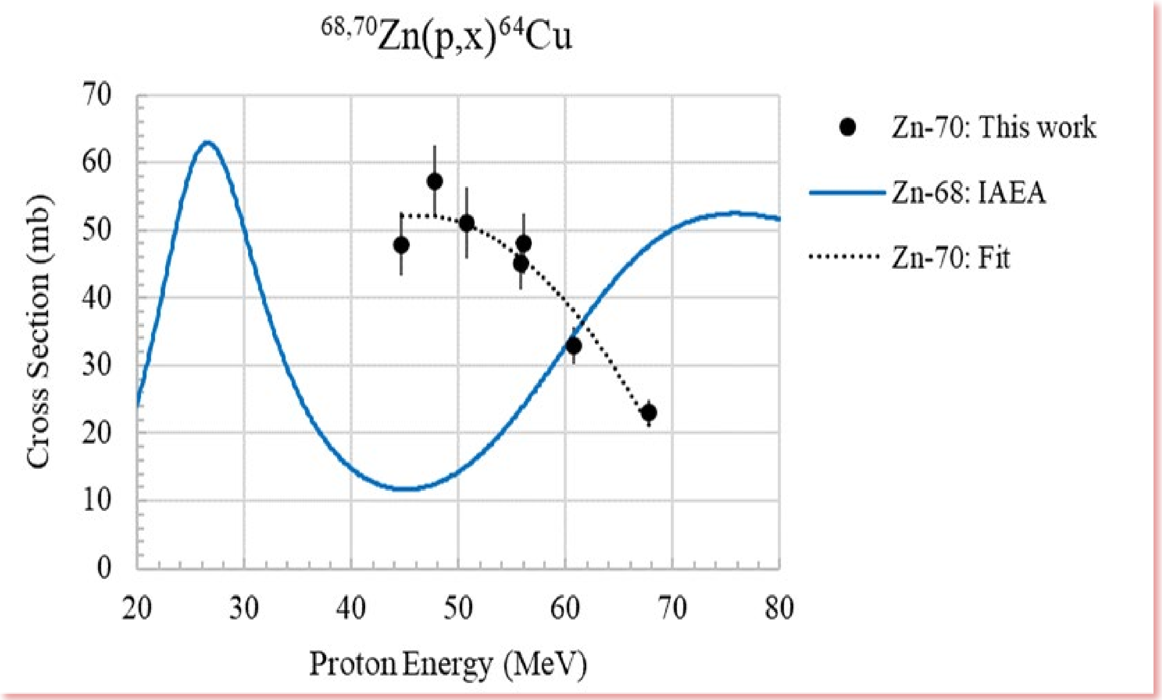




G. Pupillo, L. Mou *et al.*, *Production of ^{67}Cu by enriched ^{70}Zn targets…*, Radiochim. Acta 108 (8) 2020

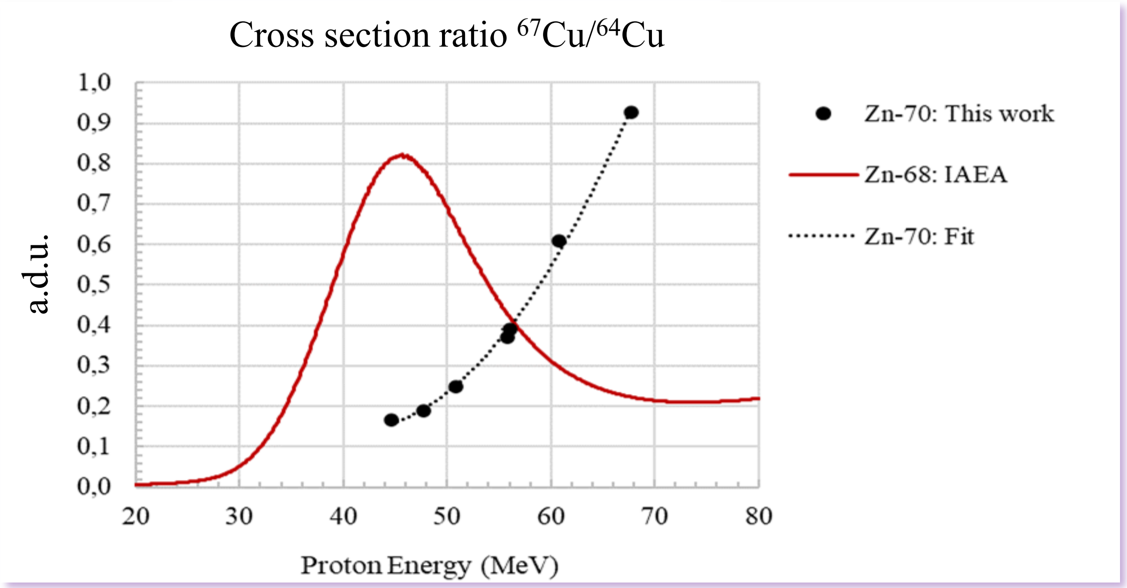
Comparison of the ^{70}Zn and ^{68}Zn targets

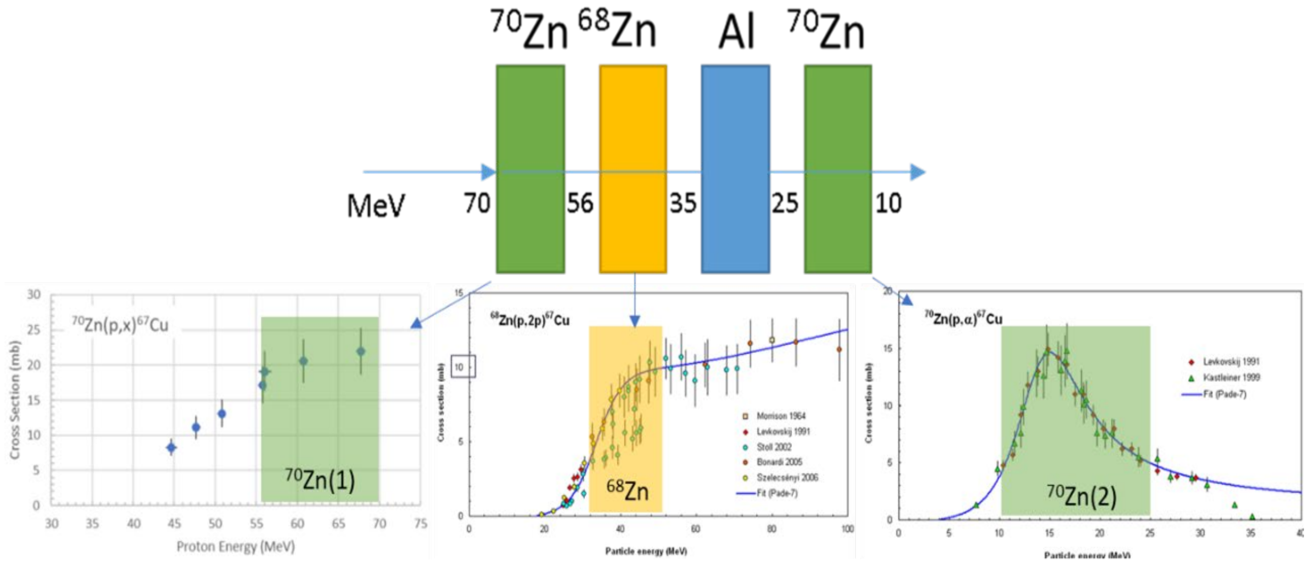




G. Pupillo, L. Mou *et al.*, *Production of ^{67}Cu by enriched ^{70}Zn targets…*, Radiochim. Acta 108 (8) 2020

A multi-layer target to optimize ^{67}Cu production: an INFN patent





⇩

^{67}Cu/^{64}Cu ratio favourable from ^{70}Zn target above 56 MeV

"A method and a target for the production of ^{67}Cu"

Mou, Pupillo, Martini, Pasquali

International Patent
n° WO 2019/220224 A1

November 2019

INFN Istituto Nazionale di Fisica Nucleare

CUPRUM_TTD proposal

INFN

INFN-CSN5 2023-2025

LARAMED

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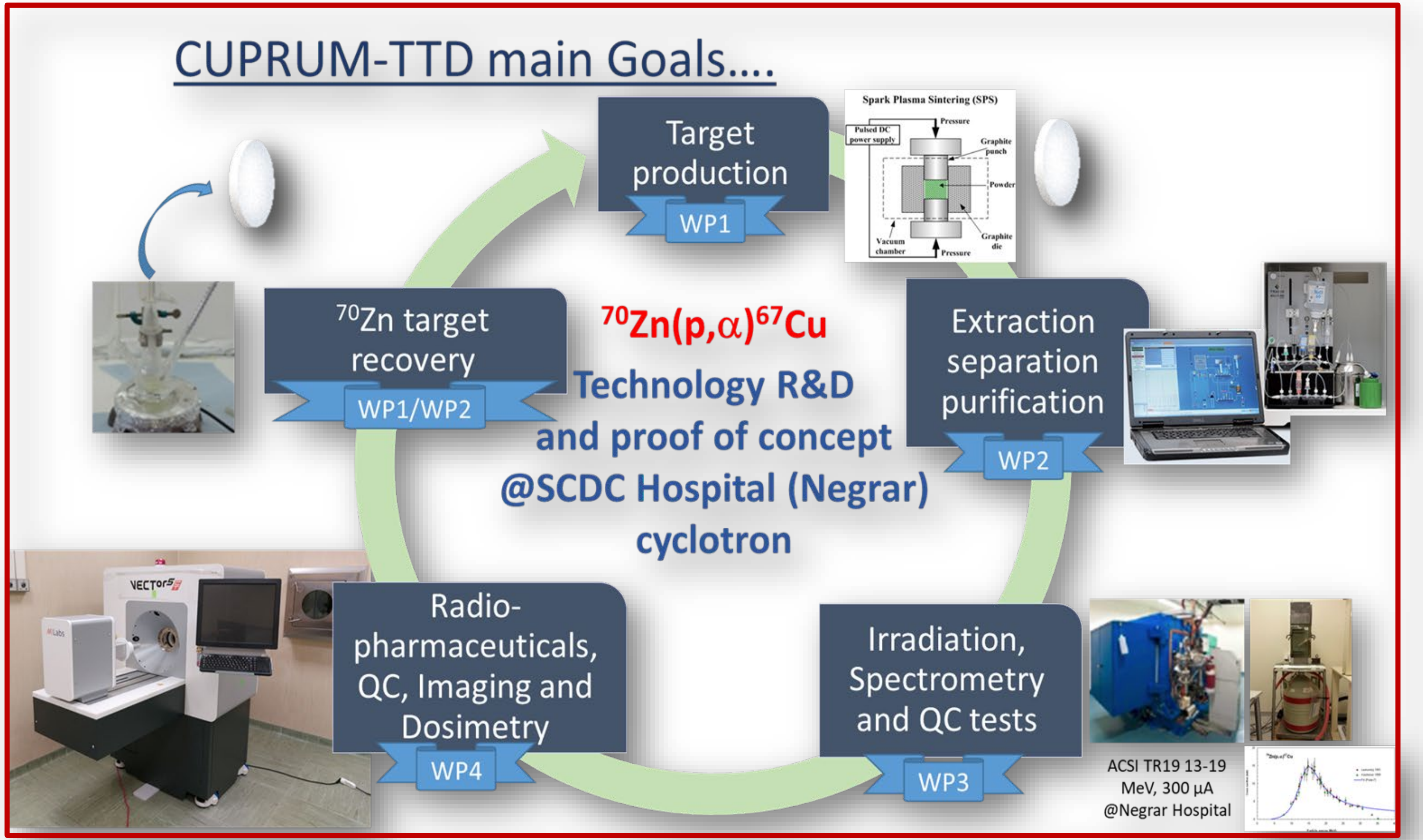


^{47}Sc as theranostic agent

	SPECT		THERAPY			
^{47}Sc 3.35 d	γ-ray [keV] SPECT	γ-ray [%]	β^- energy [keV]	β^- int [%]	Auger β^- [keV]	Auger β^- [%]
β^- : 100 %	159.381	68.3	142.6	68.4	0.42	0.461
	SPECT		203.9	31.6	4.0	0.215
			Mean β^- : 162.0 keV		154.415	0.277

Nuclear Data Sheets 108, 923 (2007) - NNDC

IAEA

CRP on ^{67}Cu, ^{47}Sc, ^{186}Re (2016/2020)

The limiting factor for clinical and preclinical studies is the lack of ^{47}Sc availability

PASTA project
INFN-CSN5
2017-2018

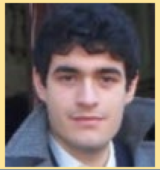
REMiX

REMIX project
INFN-CSN5
2021-2023

IN PROGRESS

REMiX

WP1. Production and target characterization
Sara Cisternino (INFN-LNL & UniPD)



WP7. Devices for INFN-LNL beam-line
Gabriele Sciacca (INFN-LNL & UniPD)

WP2. XS measurements with ^{49}Ti e ^{50}Ti
Liliana Mou (INFN-LNL)

WP6. ^{155}Tb TTY production @ The SCDC hospital
Petra Martini (UniFE & INFN-FE)

WP3. XS measurements with ^{nat}Dy, ^{159}Tb, ^{nat}Eu
Simone Manenti (UniMI & INFN-MI)

WP5. Dosimetric calculations
Laura De Nardo (UniPD & INFN-PD)
Laura Melendez-Alafort (IOV)

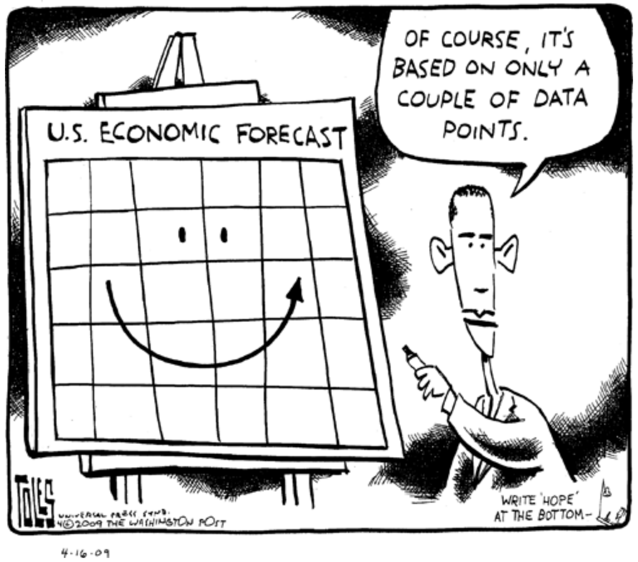
WP4. Nuclear codes (TALYS, EMPIRE, FLUKA)
Luciano Canton (INFN-PD)
Andrea Fontana (INFN-PV)

^{47}Sc production routes

Interesting targets for proton-induced reactions

47V 32.6 m ε = 100.00%	48V 15.9735 d ε = 100.00%	49V 330 d ε = 100.00%	50V > 2.1E+17 y 0.250% ε ≈ 92.90% β- < 7.10%	51V STABLE 99.75%	52V 3.743 m β- = 100.00%
46Ti STABLE 8.25%	47Ti STABLE 7.44%	48Ti STABLE 73.72%	49Ti STABLE 5.41%	50Ti STABLE 5.18%	51Ti 5.76 m β- = 100.00%
45Sc STABLE 100%	46Sc 83.79 d β- = 100.00%	47Sc 3.3492 d β- = 100.00%	48Sc 43.67 h β- = 100.00%	49Sc 57.18 m β- = 100.00%	50Sc 102.5 s β- = 100.00%
44Ca STABLE 2.09%	45Ca 162.61 d β- = 100.00%	46Ca 2.8E+16 [illegible] 0.004% 2β-	47Ca 4.536 d β- = 100.00%	48Ca 5.8E22 y 0.187% 2β- = [illegible]00%	49Ca 8.718 m β- = 100.00%

Only few literature data on enriched ^{xx}Ti..



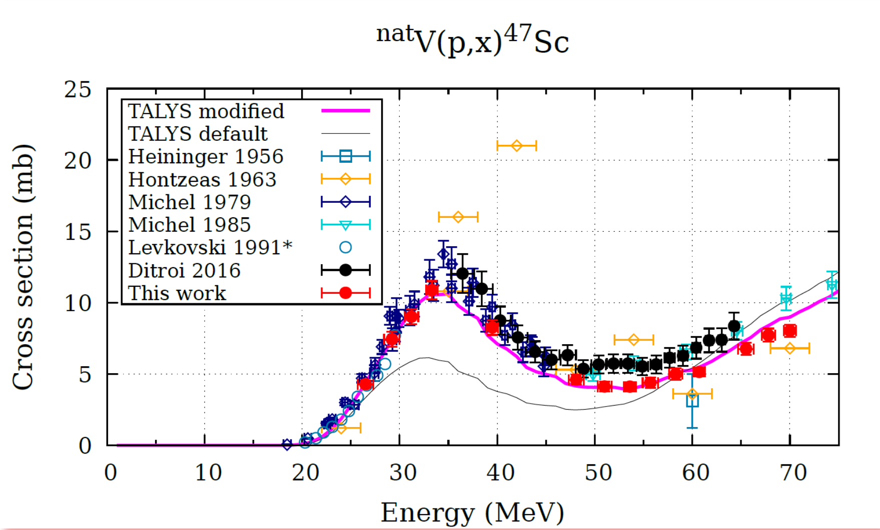
.. I am going to show you some cross section results obtained with **proton-beams** at Arronax Nantes

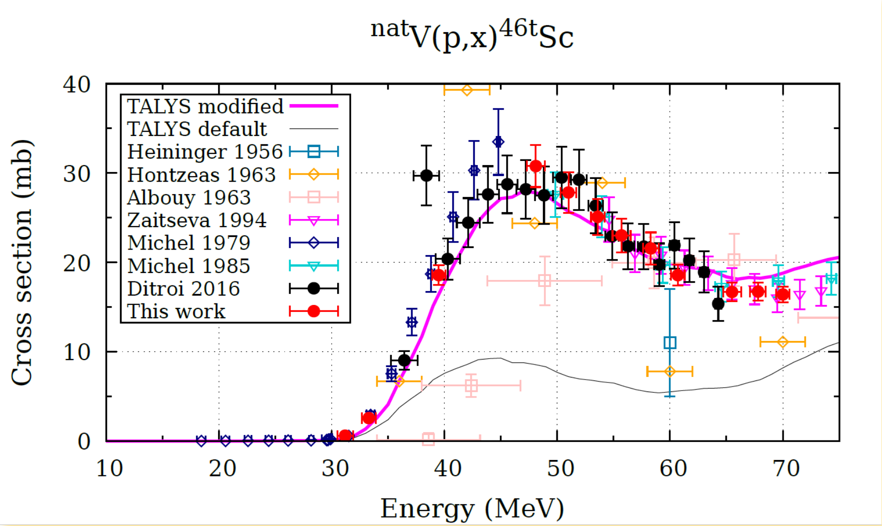
G. Pupillo et al., Journal of Radioanalytical and Nuclear Chemistry 297, 3 (2019) doi: 10.1007/s10967-019-06844-8 F. Barbaro et al., Physical Review C (2021) arXiv:2107.13773, doi: 10.1103/PhysRevC.104.044619

^{47}Sc production with ^{nat}V targets

G. Pupillo, L. Mou et al., *New results on the $^{nat}V(p,x)^{43}Sc$ cross section: Analysis of the discrepancy with previous data*, Nucl. Inst. and Methods B 464 (2020) 32-35

F. Barbaro et al., *New results on proton induced reactions on Vanadium for 47Sc production and the impact of level densities on theoretical cross sections*, http://arxiv.org/abs/2107.13773, Physical Review C 2021

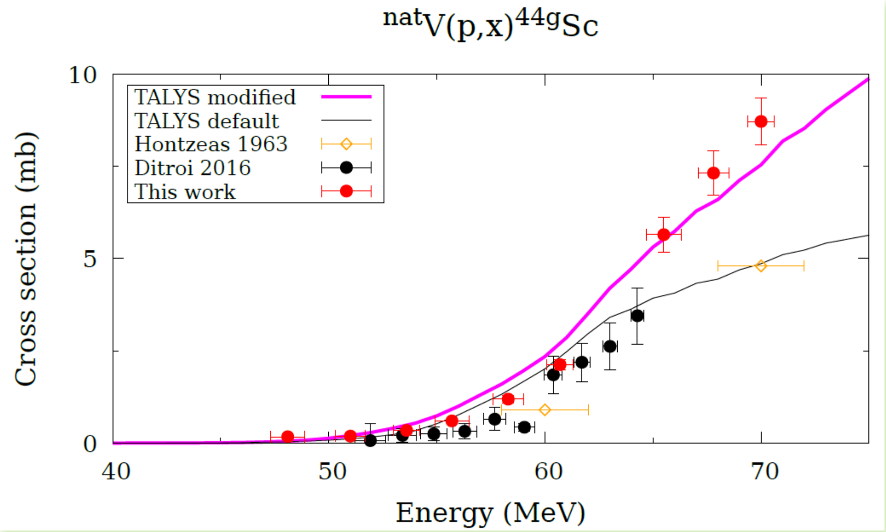


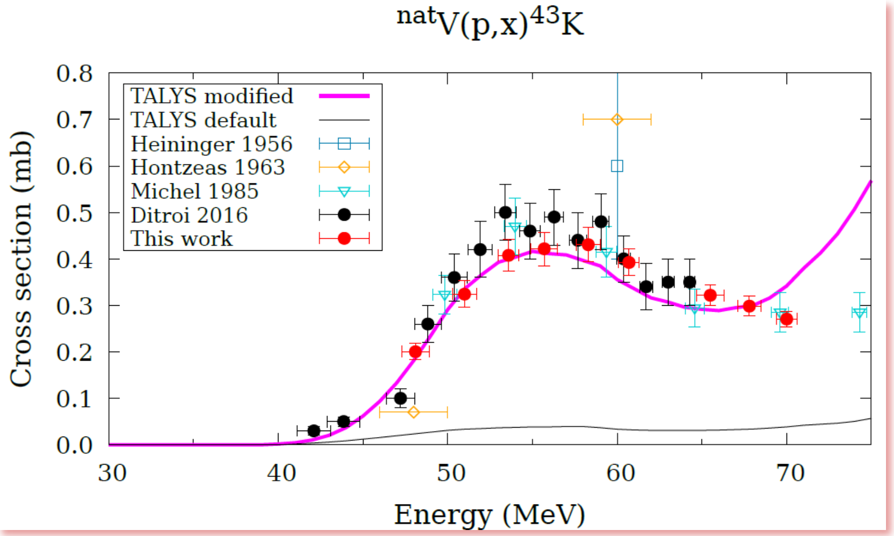


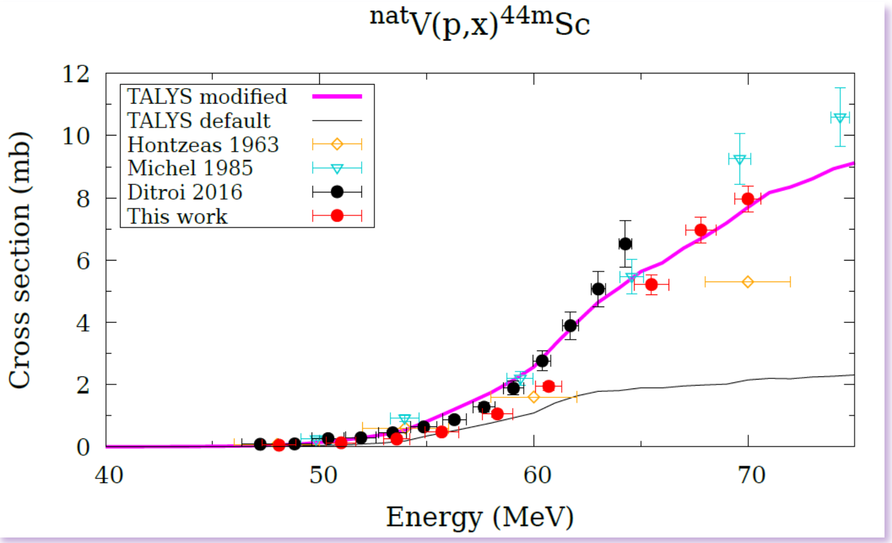
… but we measured the co-production of all the contaminant radionuclides!

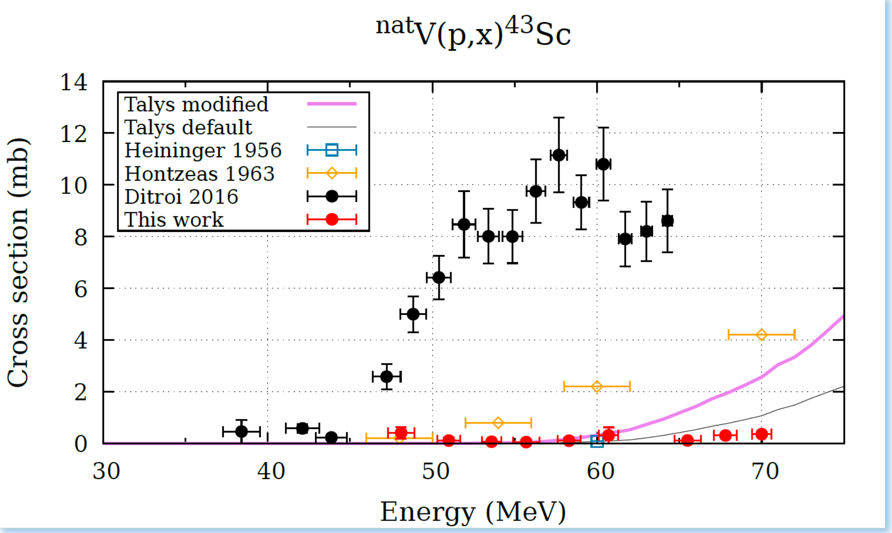
^{47}Sc production with ^{nat}V targets

F. Barbaro et al., *New results on proton induced reactions on Vanadium for 47Sc production and the impact of level densities on theoretical cross sections*, http://arxiv.org/abs/2107.13773, Physical Review C 2021

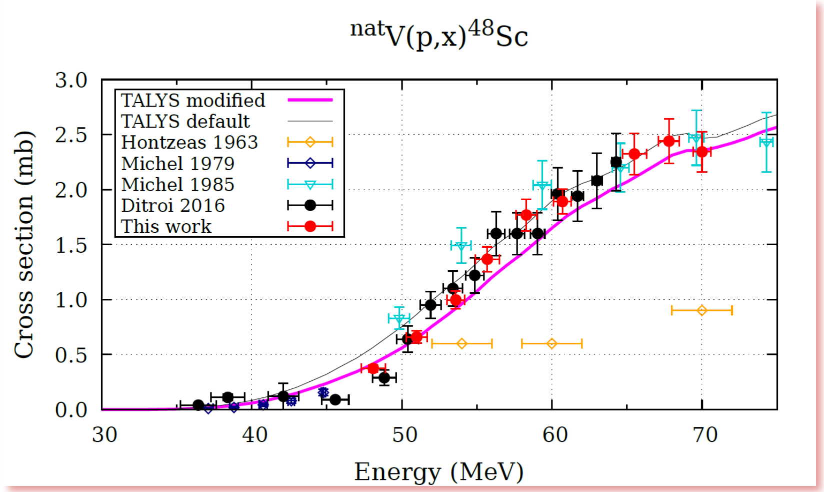


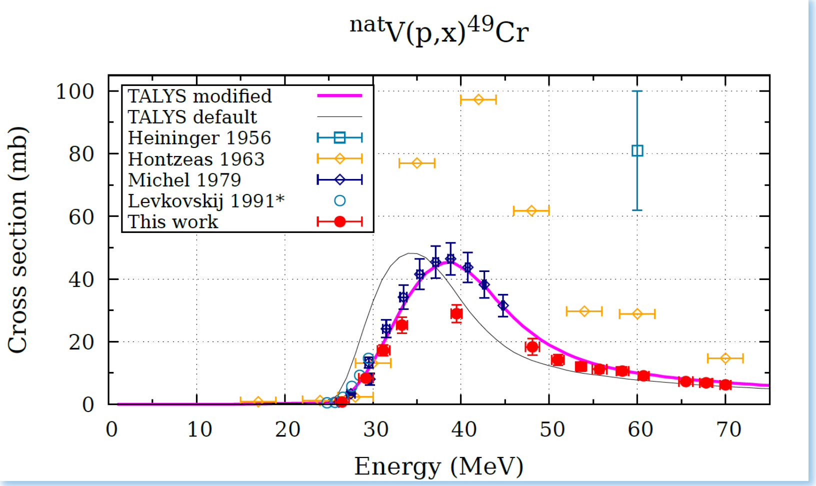


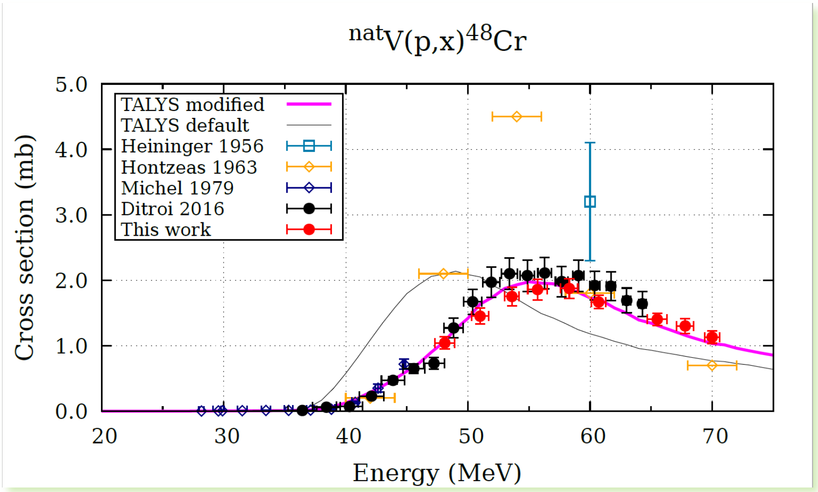


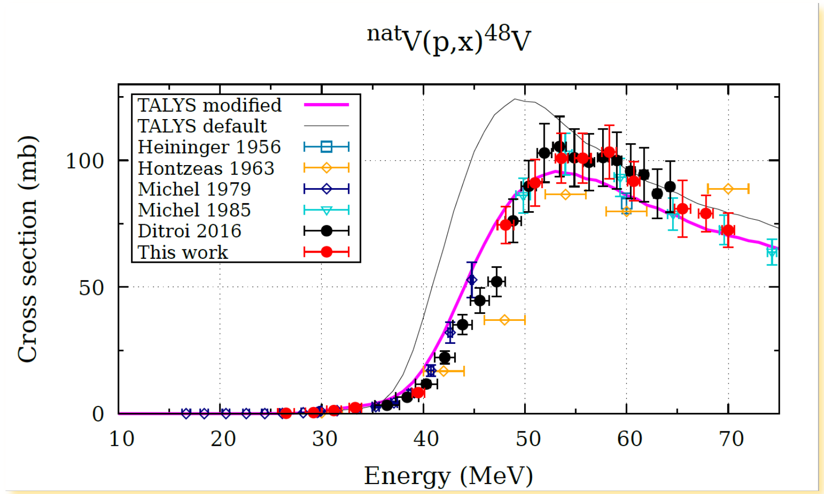


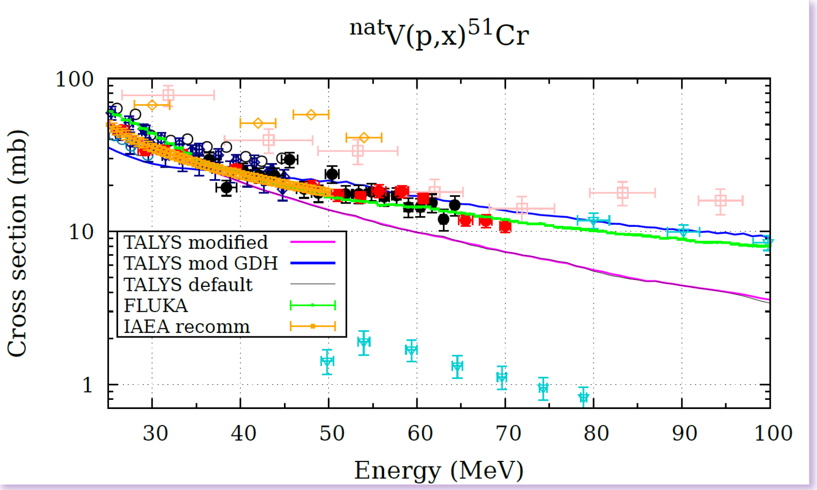
^{47}Sc production with ^{nat}V targets

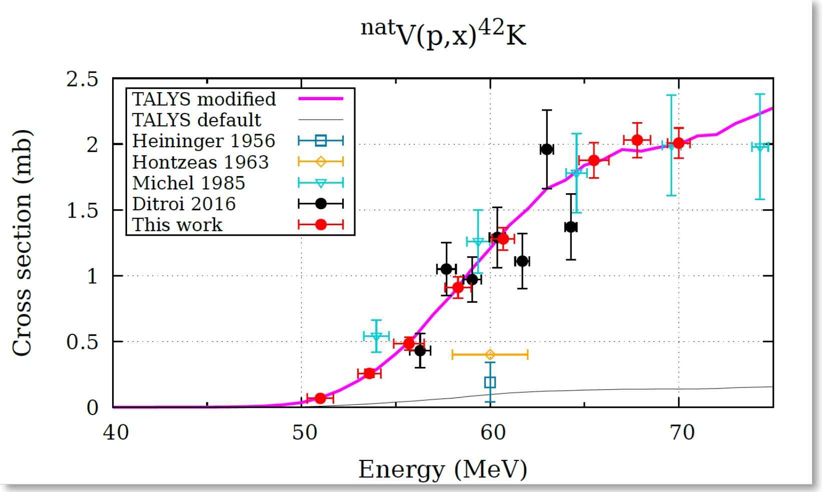








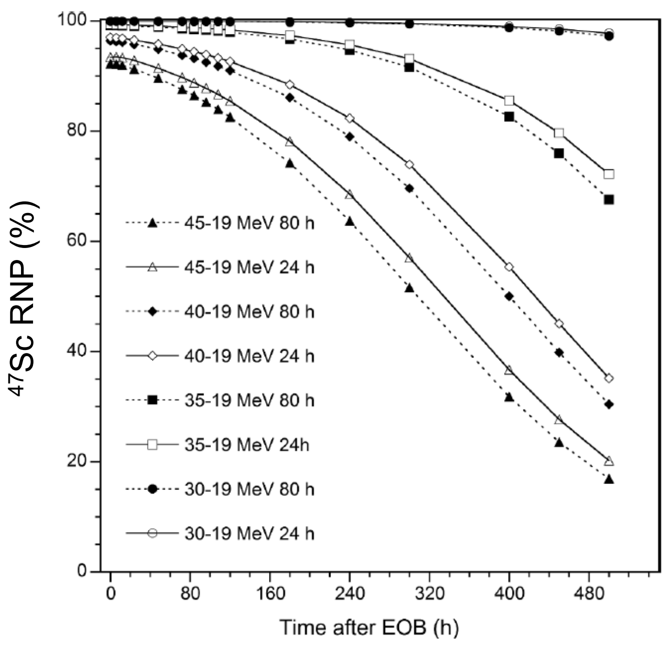


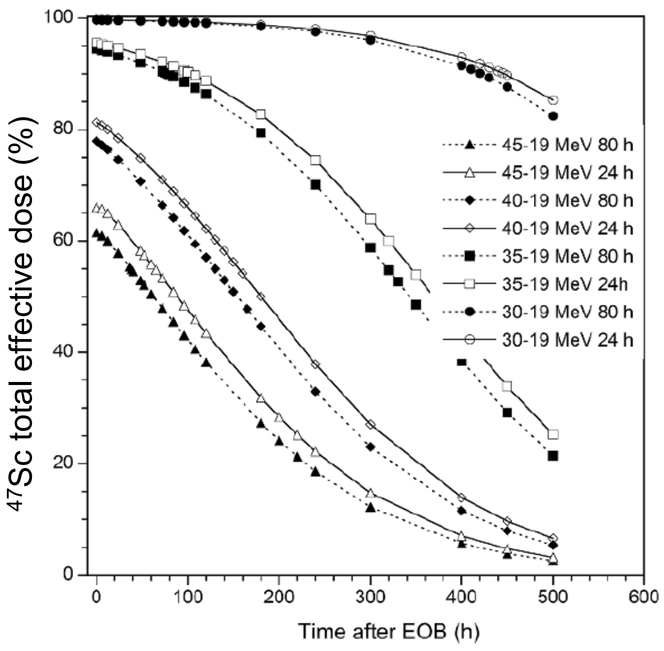


The $^{nat}V(p,x)^{47}Sc$ route

Low ^{46}Sc co-production for E_P > 30 MeV
but at E_P > 35 MeV also ^{48}Sc is co-produced!

✓ Dosimetric calculations (OLINDA code)



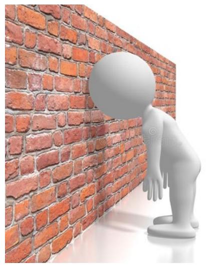


L. De Nardo et al., Physics in Medicine and Biology DOI:10.1088/1361-6560/abc811 (2021)

^{47}Sc can be produced with ^{nat}**V** (100 μA, 80 h):

E_P= 35-19 MeV ; t_{MAX} = 30 h ; ca. 28 GBq
E_P= 30-19 MeV ; t_{MAX} = 375 h ; ca. 11 GBq

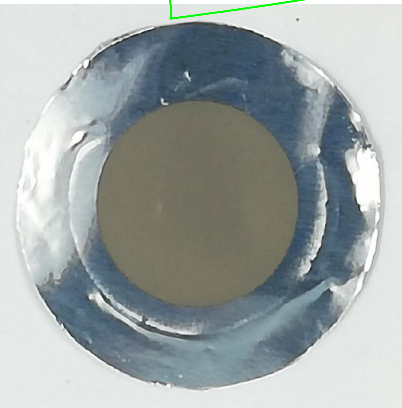
RNP > 99%



As expected, higher the ^{47}Sc purity lower the yield!

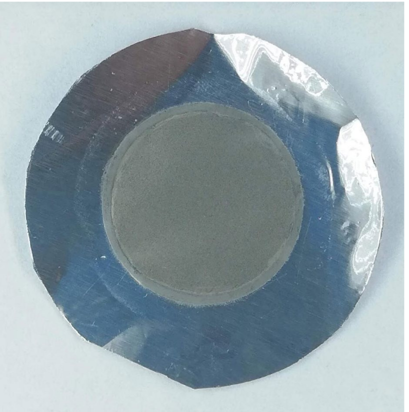
^{47}Sc production with ^{xx}Ti enriched targets

HIVIPP depositions



No. 20 ^{49}Ti targets

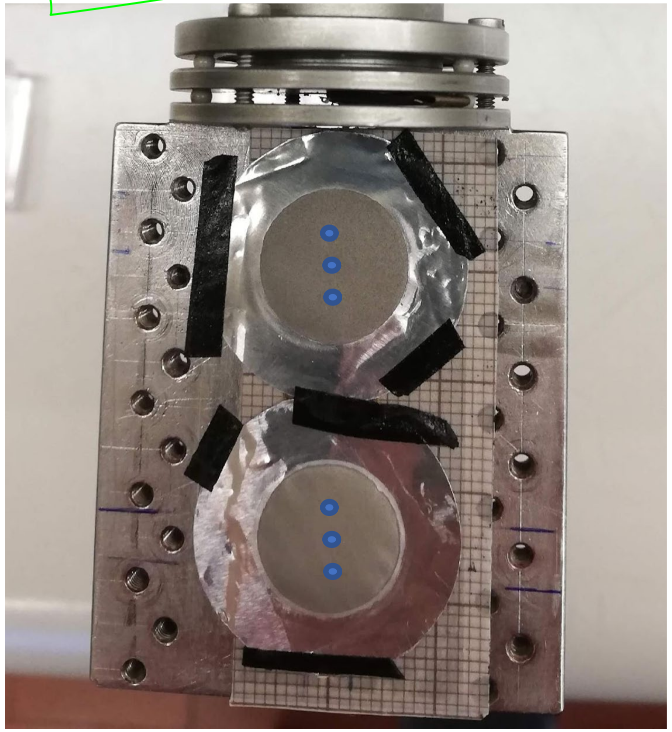
Mass thickness
measured by weigh
486±110 µg/cm²
(n=20)



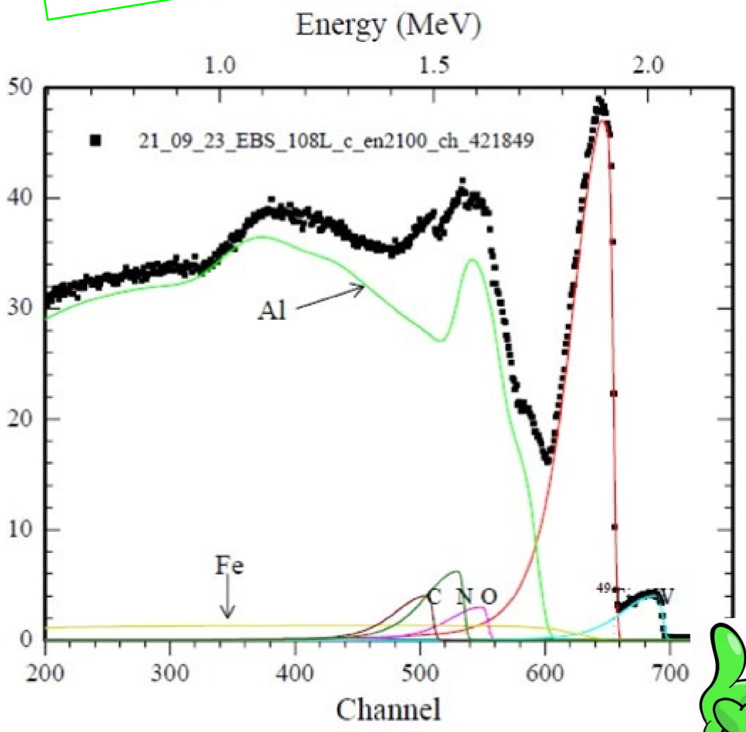
No. 20 ^{50}Ti targets

Mass thickness
measured by weigh
637±200 µg/cm²
(n=20)

Uniform thickness

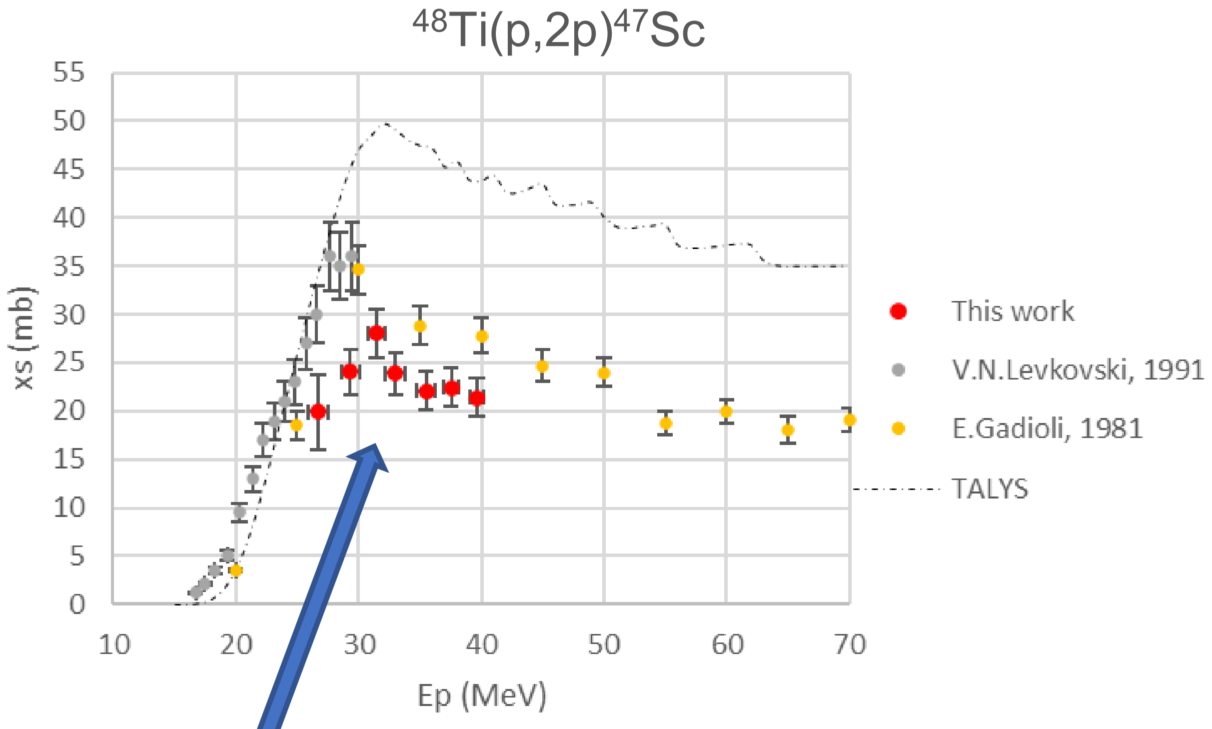


Low contamination traces (about 10s ppm)

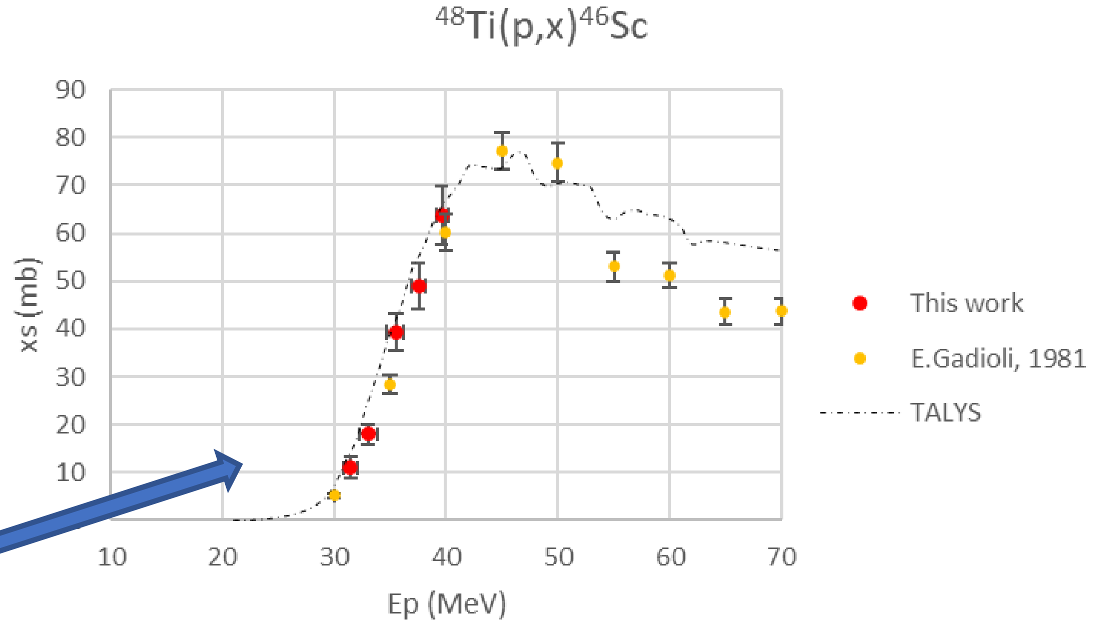


S. Cisternino et al., Upgrade of the HIVIPP deposition apparatus for nuclear physics thin targets manufacturing, Instruments (2022)

Proton-induced cross sections on ^{48}Ti targets



^{47}Sc half-life 3.3492 d
^{46}Sc half-life 83.79 d

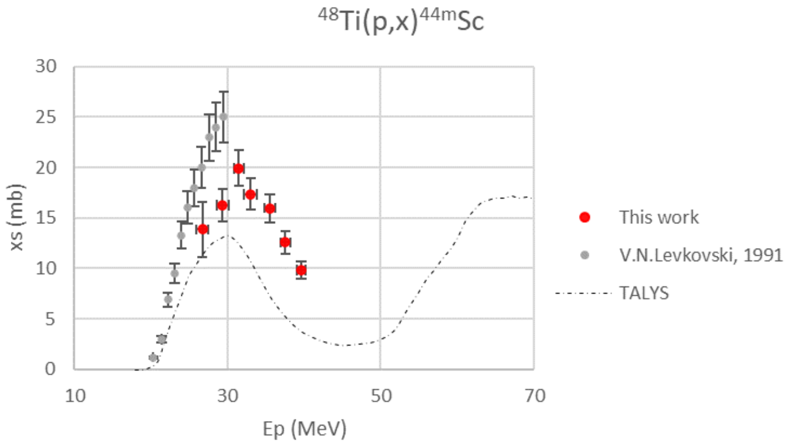


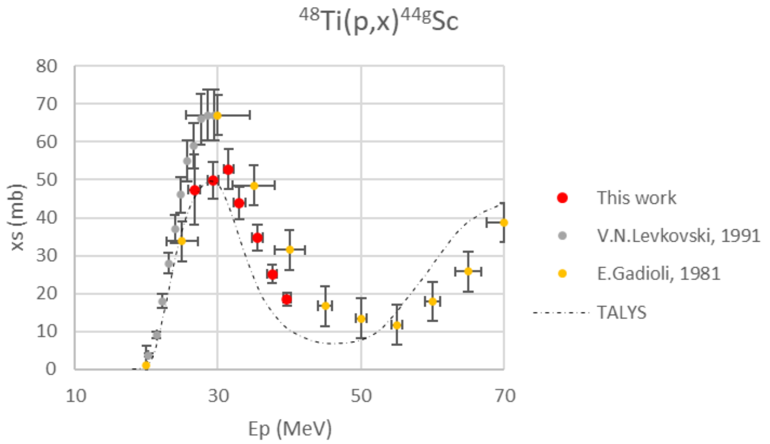
Up to 20% discrepancy with literature data

Good agreement

L. Mou et al., Nuclear cross sections of proton-induced reactions on enriched ^{48}Ti targets for the production of the theranostic ^{47}Sc radionuclide (..)(2022) Submitted

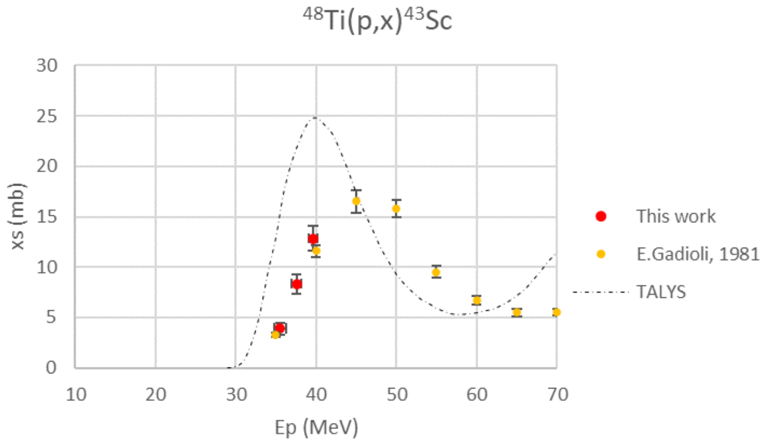
Proton-induced cross sections on ^{48}Ti targets

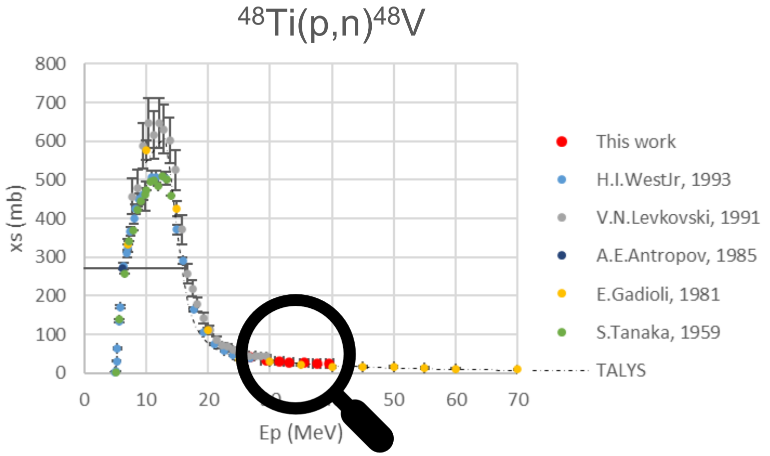


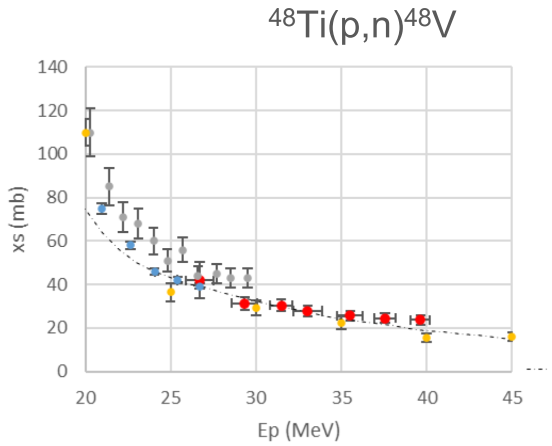


^{44m}Sc half-life 58.61 h
^{44}Sc half-life 3.97 h
^{43}Sc half-life 3.891 h

^{48}V half-life 15.974 d

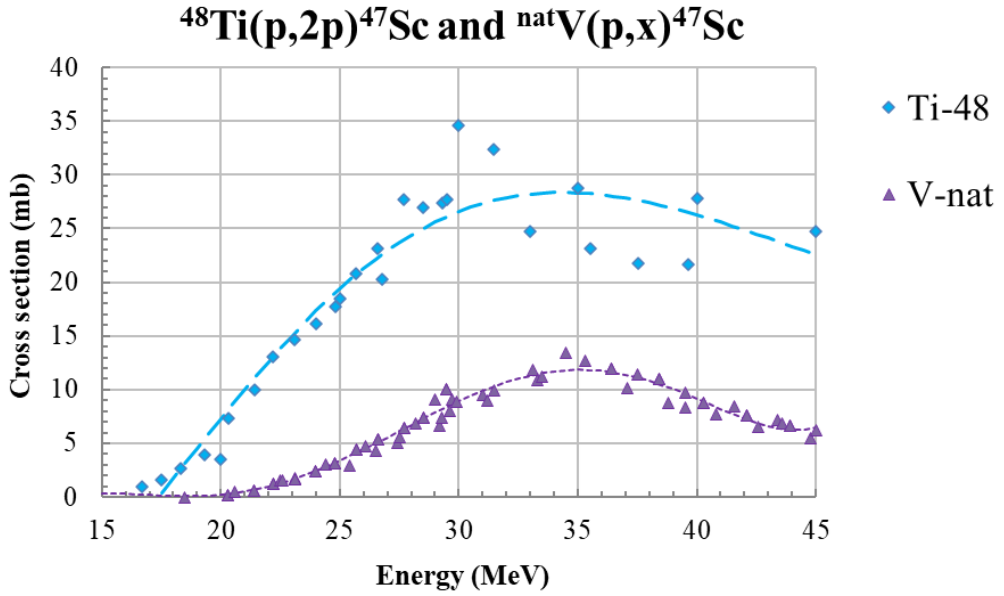






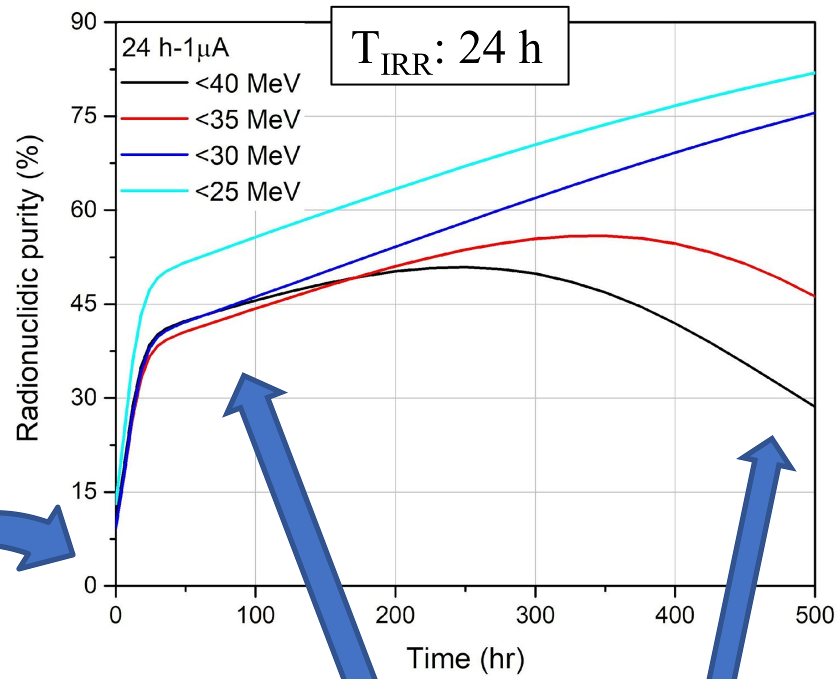
L. Mou et al., Nuclear cross sections of proton-induced reactions on enriched ^{48}Ti targets for the production of the theranostic ^{47}Sc radionuclide (..)(2022) Submitted

Comparison of ^{nat}V and ^{48}Ti targets



^{48}Ti targets are **not suitable** for a p-induced ^{47}Sc production!

The use of ^{48}Ti targets gives a larger ^{47}Sc yield in comparison to ^{nat}V, however..

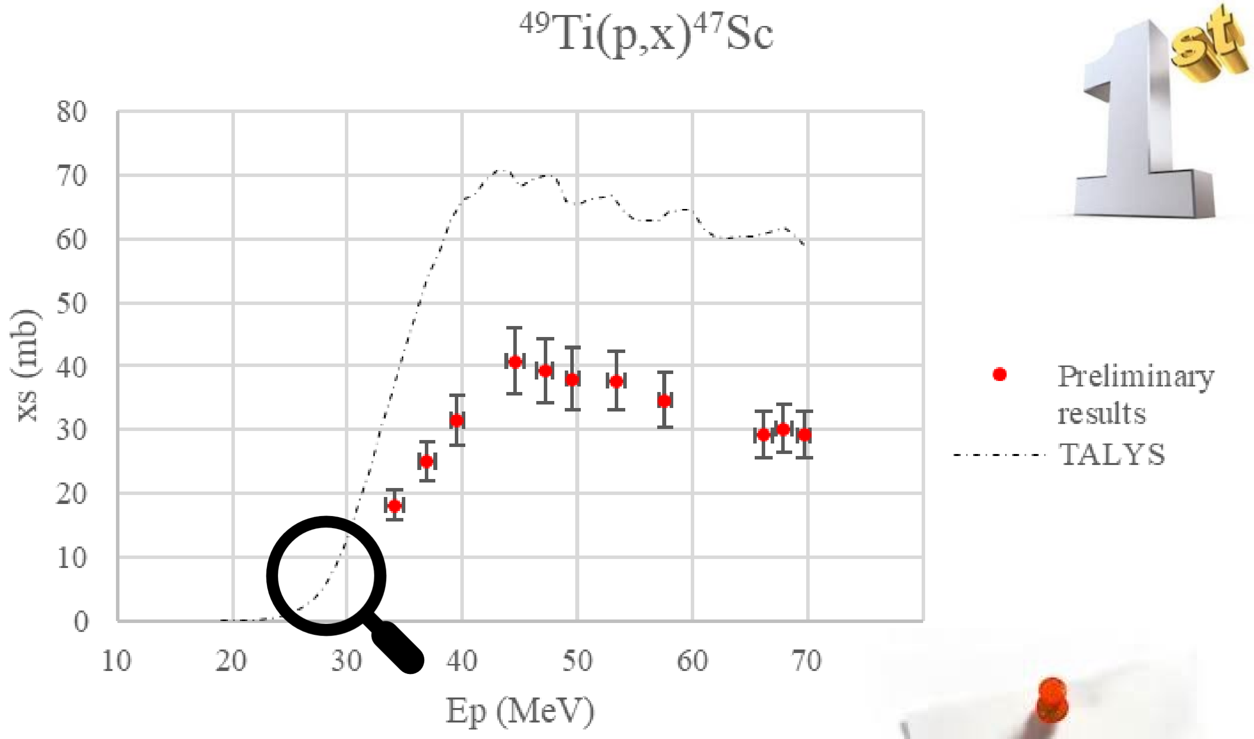


Decay of the short half-time impurities ^{43}Sc and ^{44g}Sc

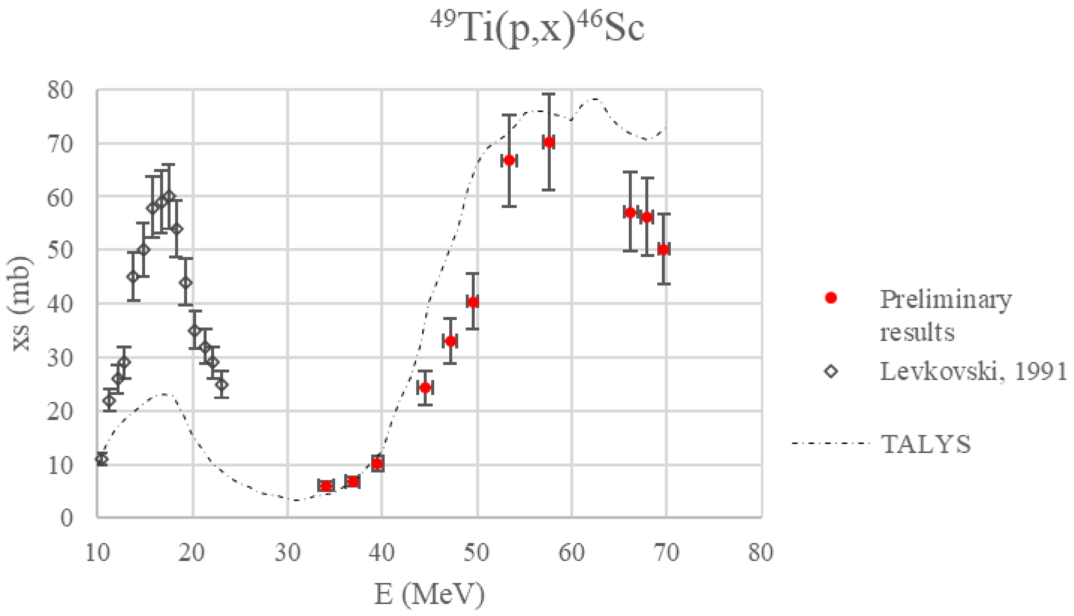
Decay of ^{44m}Sc

^{46}Sc activity

Proton-induced cross sections on ^{49}Ti targets

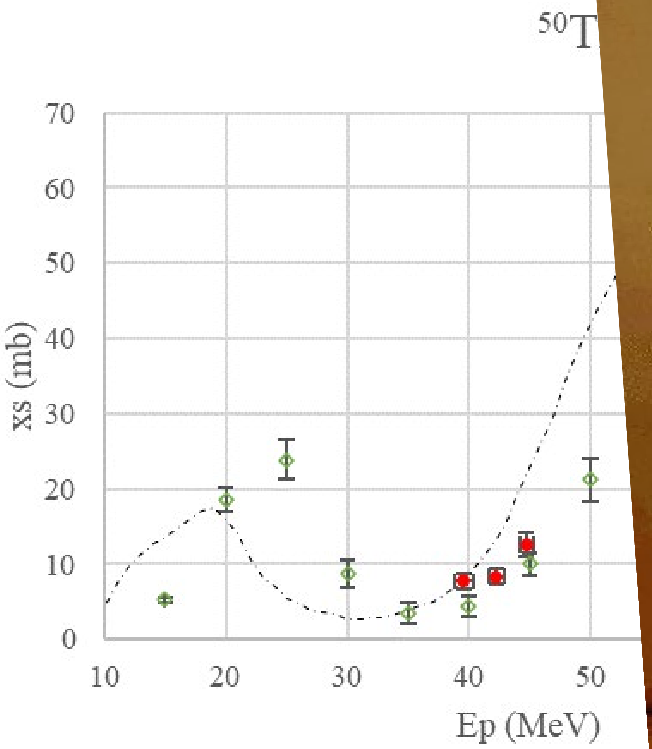


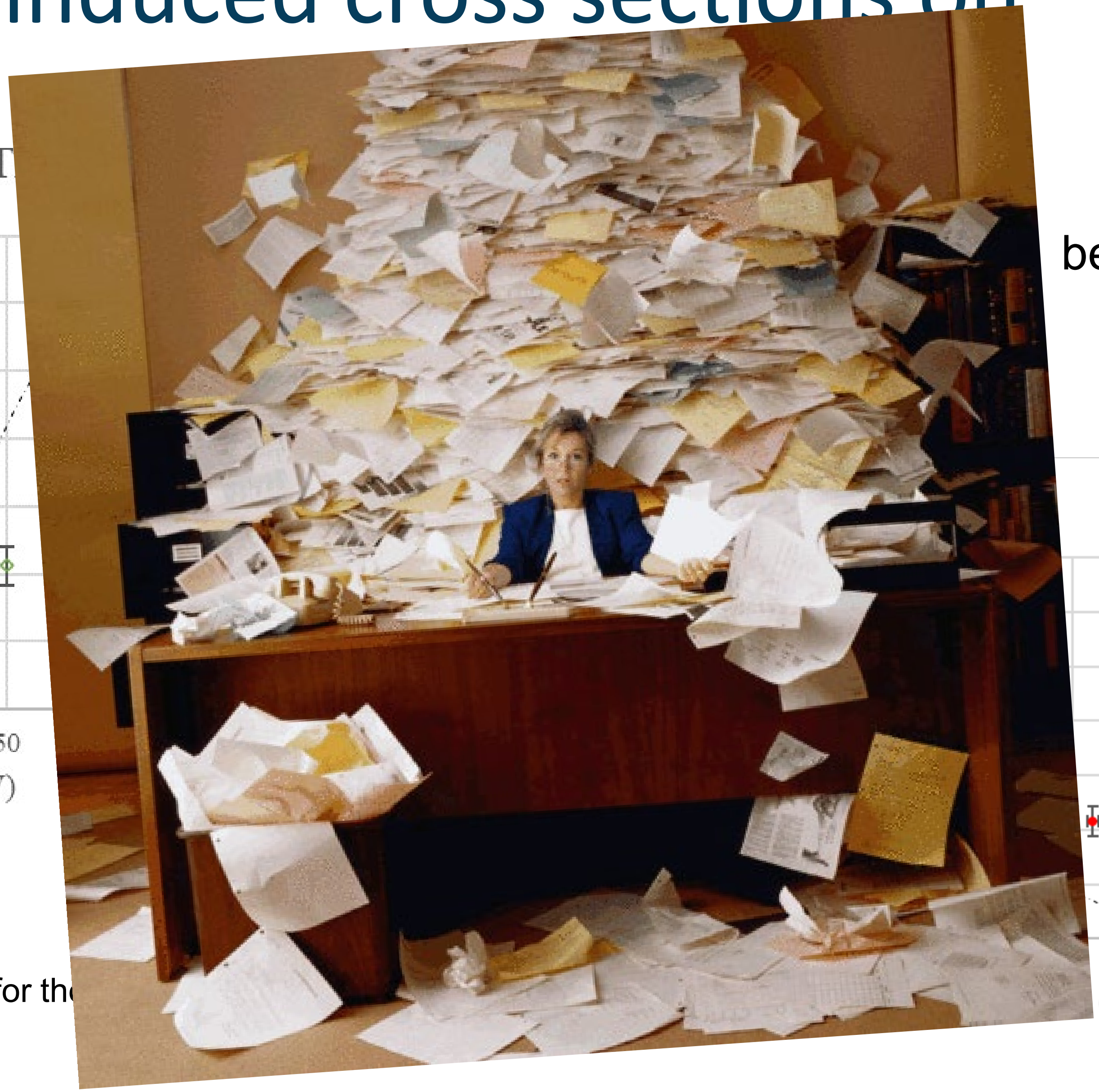
Preliminary data since we used the weighting values, but soon the **^{49}Ti EBS** values will be available!



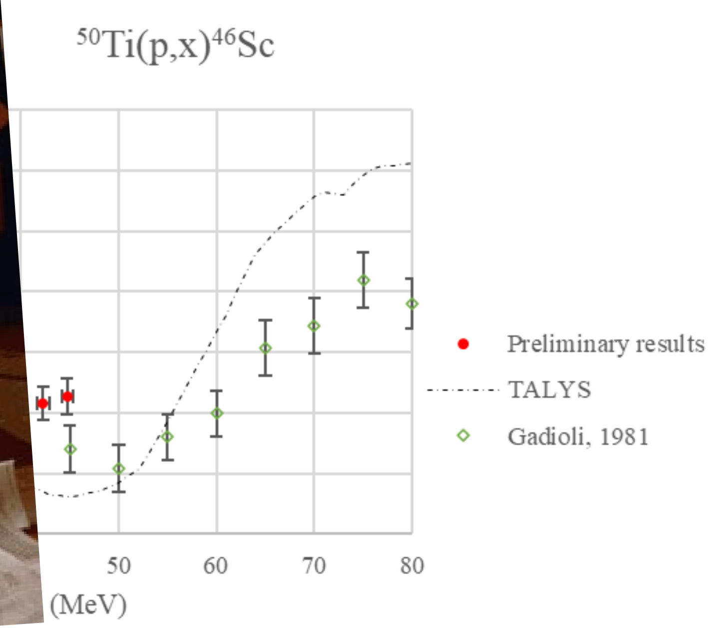
Work in progress

Proton-induced cross sections on ^{50}Ti targets





Extra preliminary data because the irradiation runs are ongoing!



Weighting values for th

➢ **Many medical radionuclides of interest!**

➢ **Young team of researchers with different expertise** (targetry, nuclear physics, engineering, radiochemistry, etc.)

➢ **Wide national & international network** of collaborations & PRISMAP Medical Radionuclides

➢ **High potential impact** with the possibility to exploit both ISOL and DIRECT production @ SPES