The LARAMED Project: Status and perspectives

J. Esposito, on behalf of LARAMED collaboration
III International SPES workshop LNL, October 11th, 2016
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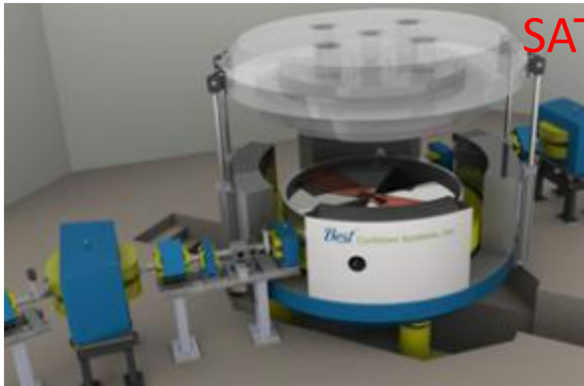
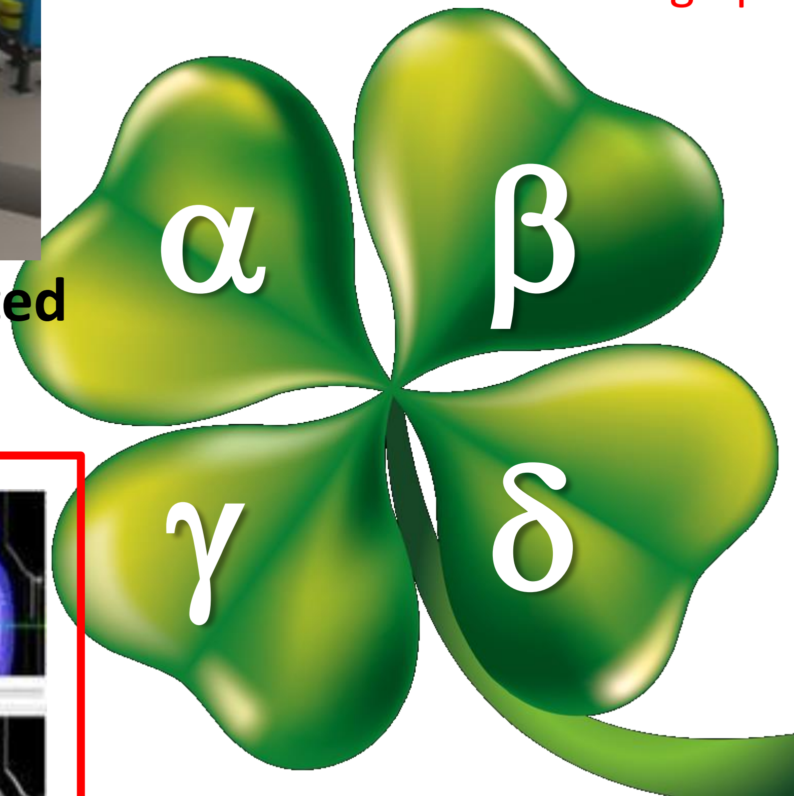
- **LARAMED facility infrastructure set-up**
- **LARAMED radionuclides of interest research ongoing program**
- **Emergency radionuclides of interest for theranostic applications**
- **^{64}Cu/ ^{67}Cu production with high-performance cyclotron**

The four stages of SPES project



SAT underway:

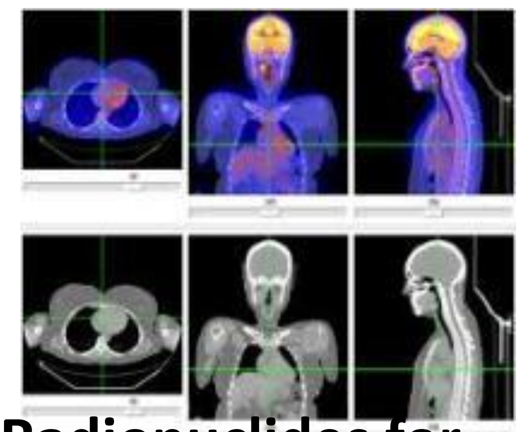
Cyclotron and related infrastructure



Infrastructure setting up

Radioactive Ion beam facility

LARAMED



Radionuclides for health and research

Infrastructure Setting up

Facility design study

AB neutron sources for applied physics and industry

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Why LARAMED

- **Share our facility** with different scientific and trade communities is a must nowadays (e.g. TRIUMF, JAEA, LANSCE etc. already do it
- Social recognition of the **nuclear physics role for human health** is an important bonus for INFN as a research institution
- **External funds** from radioisotopes research activities are a must for the future running of SPES/LARAMED facility
- **Interesting nuclear science & technology research center** dedicated both to nuclear medicine and applied physics R&D activities (e.g. INFN research projects)
- **The big Challenge**: is INFN ready for partnership with private enterprises?

How LARAMED Project is planned

LAboratory of **RA**dionuclides for **MED**icine, granted as "competitive project" at national level includes:

– **A research laboratory (RILAB),** owned jointly by INFN and CNR for:

- Nuclear cross section measurements (i.e. standard stack-foils activation technique)
- A proving ground for high power target tests
- Low-activity-production of experimental radioisotopes/radiopharmeceutical (^{99m}Tc, ^{64}Cu, ^{67}Cu, ^{89}Zr, ^{47}Sc...)

– **A production facility (RIFAC)**, operated by INFN and a private partner, to supply market demands for parent nuclides $^{82}Sr/^{82}Rb$ and $^{68}Ga/^{68}Ge$ generator systems

The new 70 MeV, 750µA proton driver

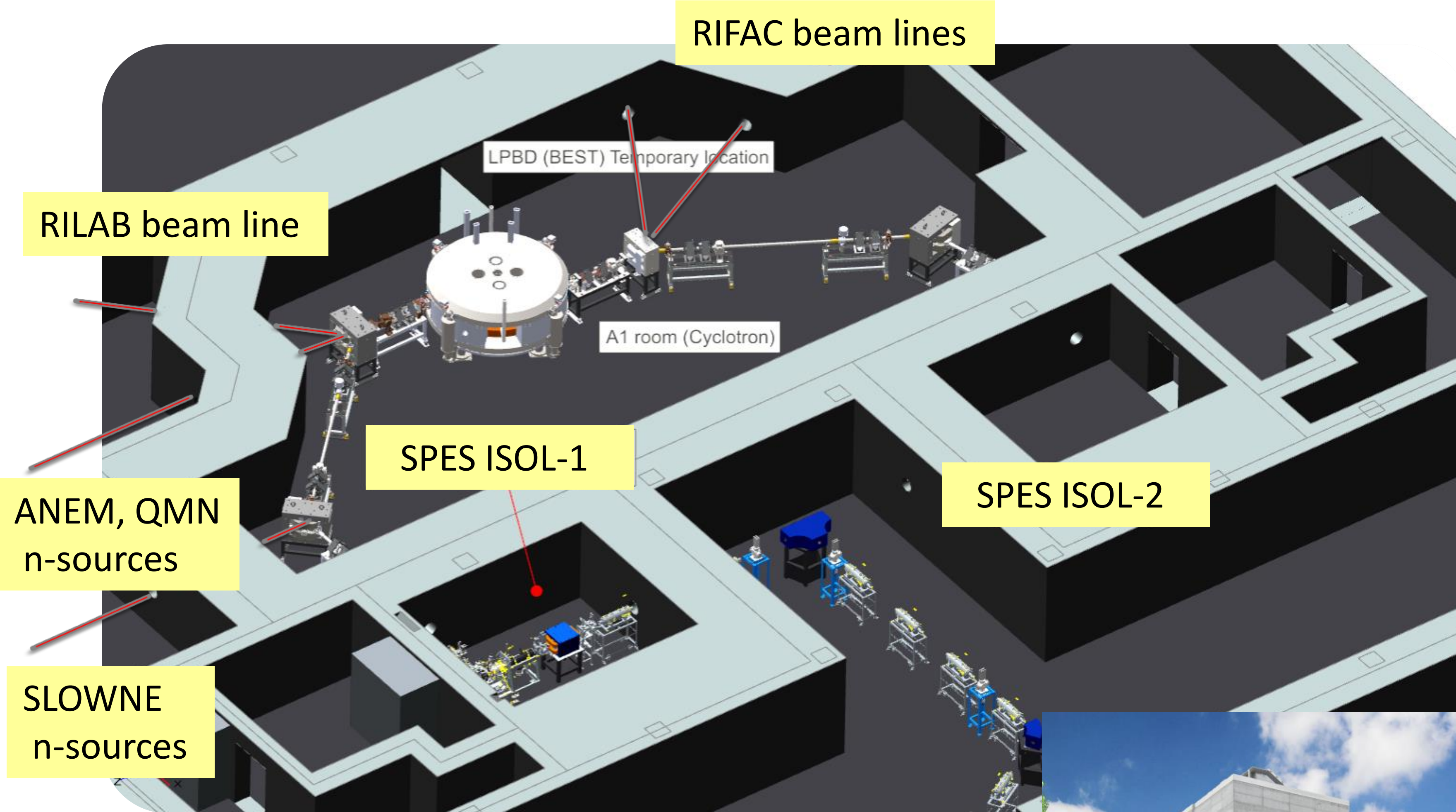
The brand new B70 cyclotron: Installed in May 2015, now under commissioning

Dual simultaneously beam extraction cyclotron (E_P = 35-70 MeV):

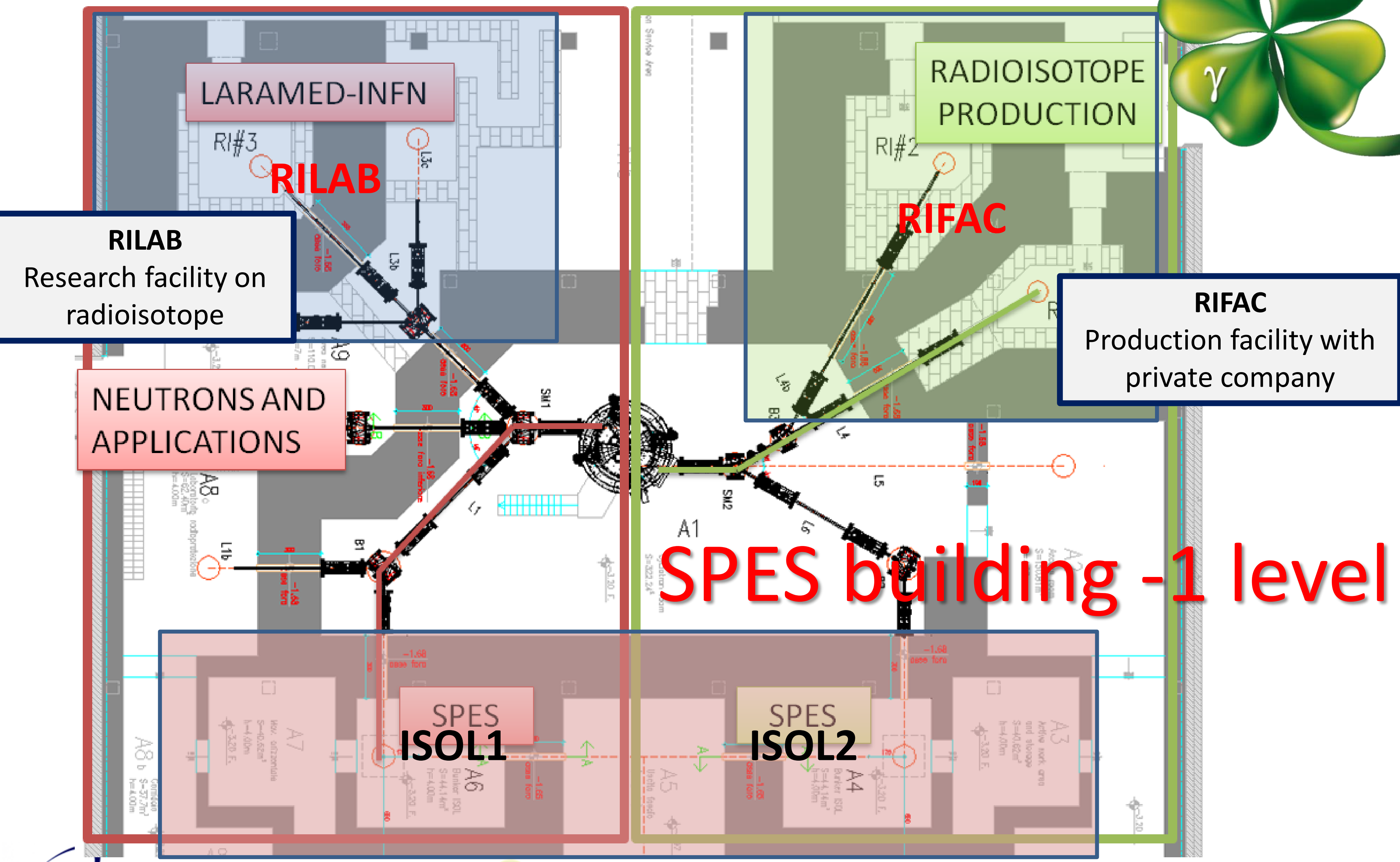
1° - nuclear physics research on RIBs **(SPES project)** : **E=40 MeV , I=200 µA** (and future upgrades)

2° - applied physics **(LARAMED project**, neutron source**)** : **E=35-70 MeV , I=300 µA** (upgrade 500µA)

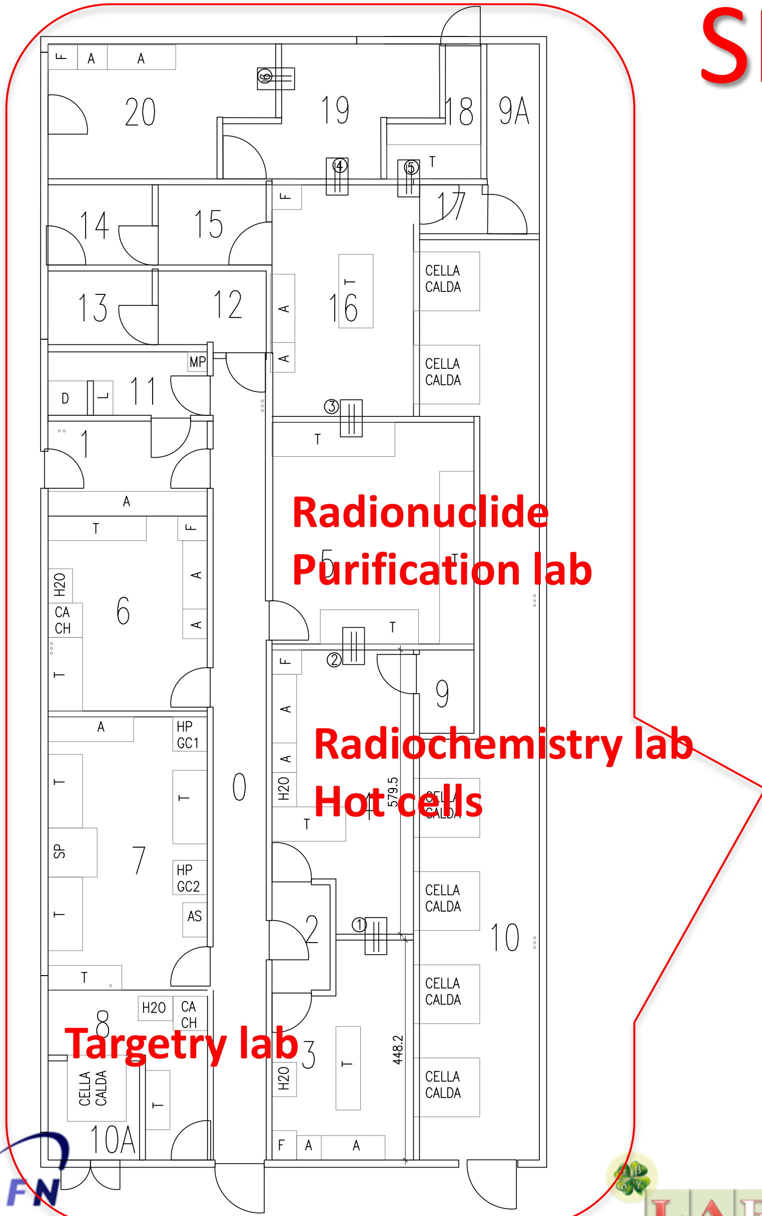
The SPES building (-1 floor): 3D layout



Final layout and cyclotron beams sharing foreseen

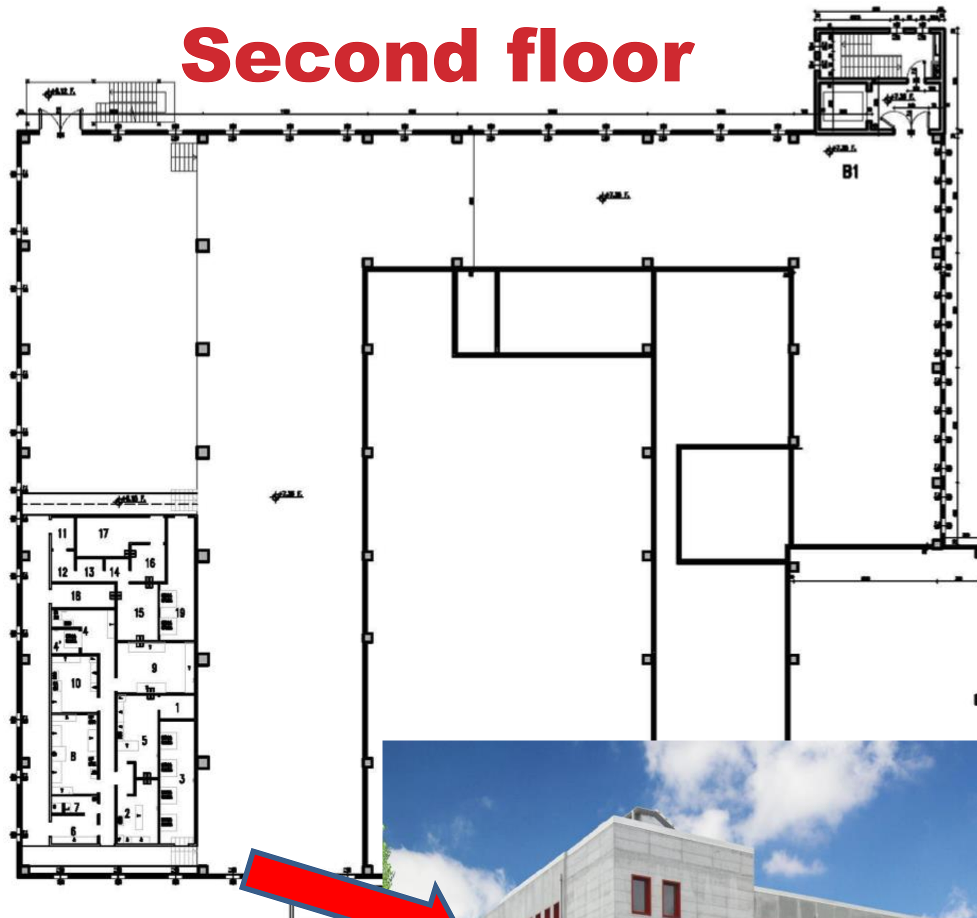


RILAB future laboratories layout



SPES building +2 level

Second floor



LARAMED External Collaboration Network

Waiting for a dedicated beam-line and available laboratories, we are collaborating with:

ARRONAX facility (Nantes, France)
70 MeV multi-particle cyclotron

St. Orsola Hospital (Bologna, Italy)
16 MeV cyclotron routinely used for 18FDG

University of Ferrara (Italy).
YAP-(S)PET-CT small-animal imaging system

National Research Council (CNR) in Milan (Italy).
Facility for cellular and pre-clinical studies

At LNL we already use γ-spectroscopy laboratory fully equipped with HPGe detectors and technologies for metal vapour deposition, brazing, surface treatment (Material Science lab.).

Running R&D activities within LARAMED framework

INFN already funded/running projects	Project name
Tc-99m/Mo-99 direct production routes using accelerators	APOTEMA (2012-2014) TECHN-OSP (2015-2017)
Participation to IAEA ' Coordinated Research Project ' (CRP) on"*Alternative, non HEU-based, Tc-99m/Mo99 supply*" (PI: J. Esposito)	CRP (F22062) (2011-2015)
Cu-67/Sc47 new (i.e. more efficient) production routes	COME (2016) PASTA (proposal)
Participation to IAEA ' Coordinated Research Project ' (CRP) on "*Radiopharmaceuticals Labelled with New Emerging Radionuclides Cu-67, Re-186, Sc-47*"	CRP (F22053) (2016-2019)
Sr-89 production with ISOL technique	SPES/ISOLPHARM
RILAB laboratory infrastructure set up	LARAMED comp. project (2013-2016)
High Power Target concepts R&D ($^{64/67}Cu$)	TERABIO comp. project (2016-2019)

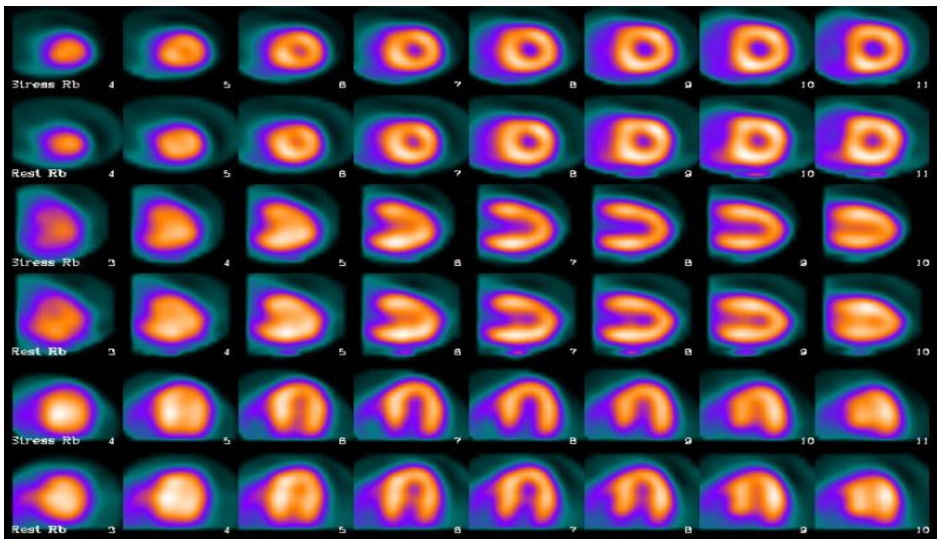
LARAMED first radionuclides list of interest

Radioisotope	Half-life
Sc47	3.35 d
Cu-64	12.7 h
Cu-67	2.58 d
Sr-82	25.4 d
Ge-68	270.8 d
Tc99m	6.01 h
Sr-89	50.5 d

Starting radionuclides of interest for nuclear medicine. They can be produced by means of the SPES cyclotron. Additional ones are under examination

$^{82}Sr/^{82}Rb$: heart function tracer

Isotope	Sr-82	Rb-82
$\tau_{1/2}$	25d ⇒	1.27m
EC	100% in Rb82	-
β+	-	100%
β-	-	-



- The ion Rb^+ is a biologic analog of K^+, fundamental in the heart cell operation.
- Once administered by intravenous injection, $^{82}Rb^+$ γ emitter radioisotope, **can be used as tracer to study the real-time heart functions**
- This radioisotope is actually produced in a limited amount in few accelerator facilities worldwide

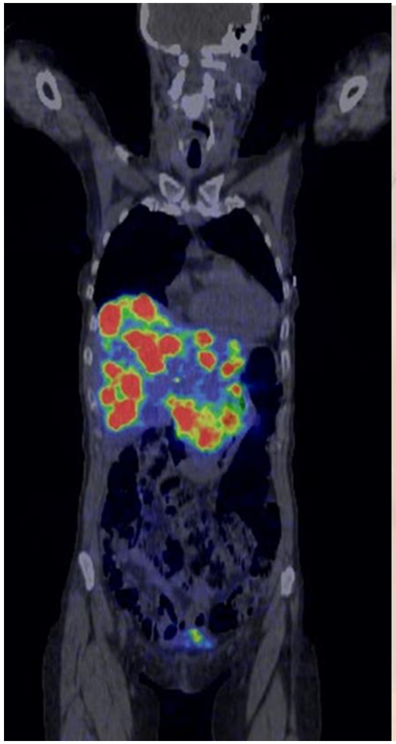
$^{68}Ge/^{68}Ga$: many pathologies tracer

- Together with F-18 e C-11, recently, the request of the β^+ emitter radionuclide ^{68}Ga has grown exponentially

- Ga-68 proved to be stably labelled to small peptidic biomolecules, used in the **diagnosys of many pathologies of peptide receptor tissues**

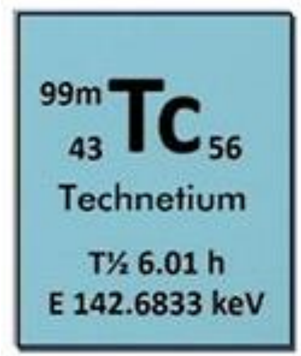
- The production, by means of medium-high energy cyclotrons, will provide an effective solution to the problem of availability of the generator nuclide ^{68}Ge, whose production, with the methods used nowadays, is not enough

Isotope	Ge-68 →	Ga-68
$\tau_{1/2}$	271d	68m
EC	-	-
β+	-	100%
β-	100% in Ga-68	-



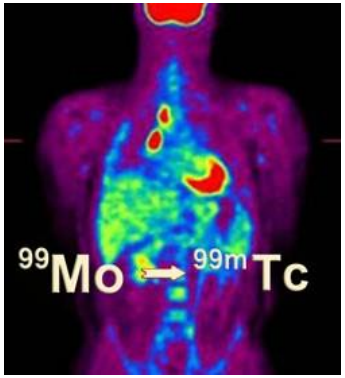
J. Esposito, October 11, 2016

Tc-99m: the workhorse of modern medical imaging



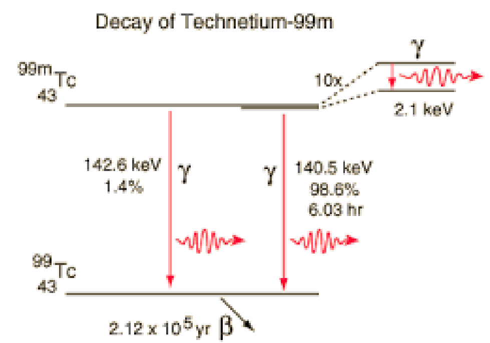
90% of all nuclear medicine (NM) studies involve diagnostic imaging;

- ^{99m}Tc use: ~80% (>30 million procedures per year)
- ^{18}F use: ~10%;
- rest others ***one study every second !!!!!***



Quasi-ideal radioisotope for imaging: main properties

- Suitable (soft 140.5 keV) γ energy → good image quality, low radiation dose to the patient
- Nearly pure gamma emitter
- Proper half-life → for medical examination
- versatile and well-known chemistry → label various molecules
- β$^-$ decay product of **^{99}Mo (66 h half-life)**



$$^{99}_{42}Mo \rightarrow {}^{99m}_{43}Tc + e^- + \bar{\nu}_e$$

Currently available on the market under the ***Mo-99/Tc-99m generators***

Tc99m supply World crisis: seeking for alternative routes

Published online **15 July 2009** | **Nature 460, 312-313 (2009)** | doi:10.1038/460312a

nature International weekly journal of science

nature news home | news archive | specials | opinion | features | news blog | nature journal

Published online 15 July 2009 | *Nature* **460**, 312-313 (2009) | doi:10.1038/460312a

News

Medical isotope shortage reaches crisis level

Robust solutions sought urgently to shore up fragile supply chain.

Paula Gould

The worldwide shortage of medical isotopes is about to

Related stories

- Accelerating production of medical isotopes 28 January 2009
- Europe's isotope shortage will continue into 2009 23 October 2008
- Isotope shortage could delay cancer treatments 29 August 2008
- Nuclear-reactor closure hits cancer tests 12 December 2007

Published online **23 October 2008** | Nature | doi:10.1038/news.2008.1186

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Published online 23 October 2008 | Nature | doi:10.1038/news.2008.1186

News

Europe's isotope shortage will continue into 2009

Hospitals forced to use substitute procedures for medical scans.

Paula Gould

A Europe-wide shortage of medical isotopes will continue for at least three months while a Dutch

Related stories

- Isotope shortage could delay cancer treatments 29 August 2008
- Nuclear-reactor closure hits cancer tests 12 December 2007

Published online **12 February 2010** | Nature | doi:10.1038/news.2010.70

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Published online 12 February 2010 | Nature | doi:10.1038/news.2010.70

News

Medical isotope supplies dwindle

Nuclear-reactor shutdowns will cripple global isotope production next month.

of the five reactors that currently supply hospitals will be making the isotope.

Molybdenum-99 decays to yield the short-lived isotope technetium-99m (^{99m}Tc), which is used in about 70,000 medical imaging procedures every day, including bone and heart scans.

Supplies of ^{99}Mo have already been badly affected by the unplanned nine-month shutdown of the Canadian National Research Universal (NRU) reactor in Chalk River, Ontario, following a heavy-water leak in May 2009. The situation will get much worse on 19 February when the High Flux Reactor (HFR) in Petten, the Netherlands, is taken out of service so that corroded pipework can be repaired.

Together, these facilities normally produce two-thirds

Related stories

- Medical isotope shortage reaches crisis level 15 July 2009
- Accelerating production of medical isotopes 28 January 2009

Published online **12 December 2013** | Nature doi:10.1038/504202a

nature International weekly journal of science

NATURE | NEWS FEATURE

Radioisotopes: The medical testing crisis

With a serious shortage of medical isotopes looming, innovative companies are exploring ways to make them without nuclear reactors.

Richard Van Noorden

11 December 2013

Published online **12 September 2016** | Nature ! doi:10.1038/nature.2016.20577

nature International weekly journal of science

NATURE | NEWS

Reactor shutdown threatens world's medical-isotope supply

Canada's Chalk River reactor, which makes large amounts of technetium-99m, ceases production next month.

Jeff Tollefson

12 September 2016

INFN Istituto Nazionale di Fisica Nucleare

APOTEMA/TECHNOSP exp.: INFN contribution (2012-2017)

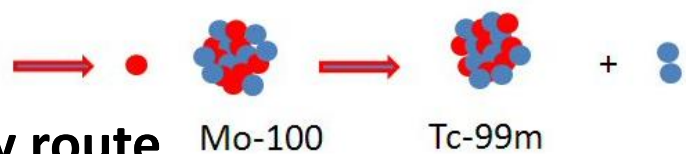
J. Esposito, Sci Tech of Nuc Inst, vol. 2013, Article ID 972381, 14 pages, 2013. doi:10.1155/2013/972381

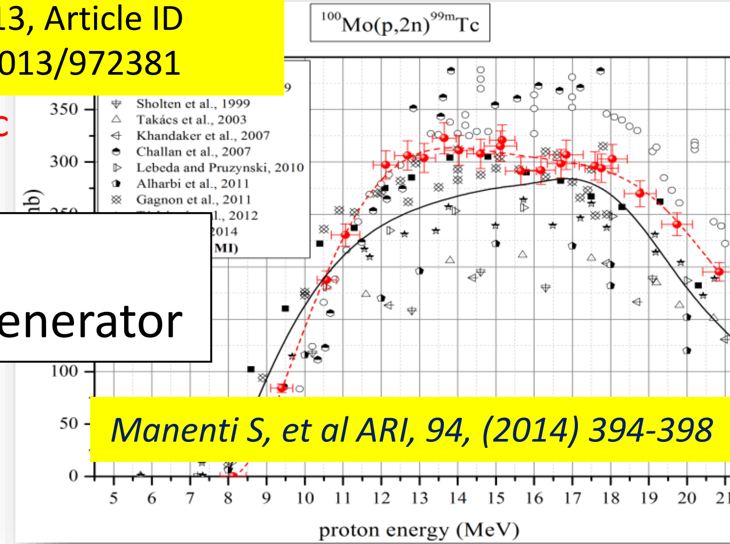
Main project goal

Assessment of accelerator-driven alternative production of ^{99m}Tc exploting the SPES proton cyclotron at LNL

Alternative Tc-99m production route

- $^{100}Mo(p,2n)^{99m}Tc$ (direct route)
- $^{100}Mo(p,x)^{99}Mo$ → $^{99}Mo/^{99m}Tc$ generator





Manenti S, et al ARI, 94, (2014) 394-398

Current supply route

^{99}**Mo parent production** in a few nuclear reactor sites in the world, as fission fragment product in high-enriched U235 «weapon grade» fissile material

Optimal production (direct route):

1. Ep ~ 18-20 MeV max
2. ^{100}Mo(>99%) enriched moly targets
3. Irr. Times not longer than $T_{1/2}$ (better within ½ $T_{1/2}$)

By using high-performance cutting edge technology cyclotrons (i.e. 300-500 µA current intensity (eg. SPES to LNL) and energies of up to 20 MeV) the **daily needs of the entire Veneto region (273 GBq/day = ~ 7 Ci/day)** may be supplied if necessary

P. Martini, et al. ARI, 118, (2016) 302-307

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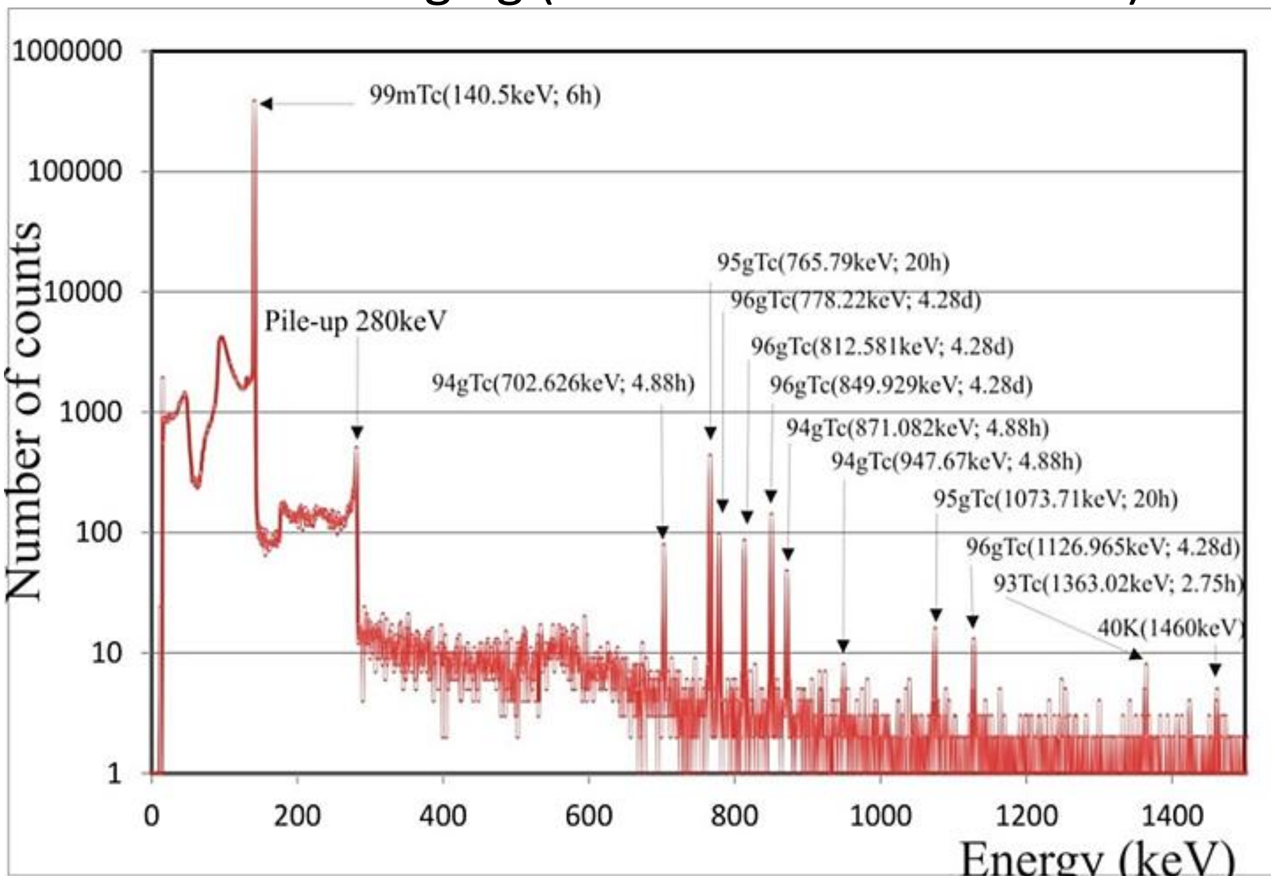
^{99m}Tc radionuclidic purity

- Radionuclidic purity of the ^{99m}Tc-eluate was performed with γ-spectrometry (HPGe detector)
- Total activity of ^{9x}Tc-isotopes < 1%
- ^{99m}Tc activity at the time of SPECT imaging (about 7 hours after EOB)

RNP ^{99m}Tc > 99%

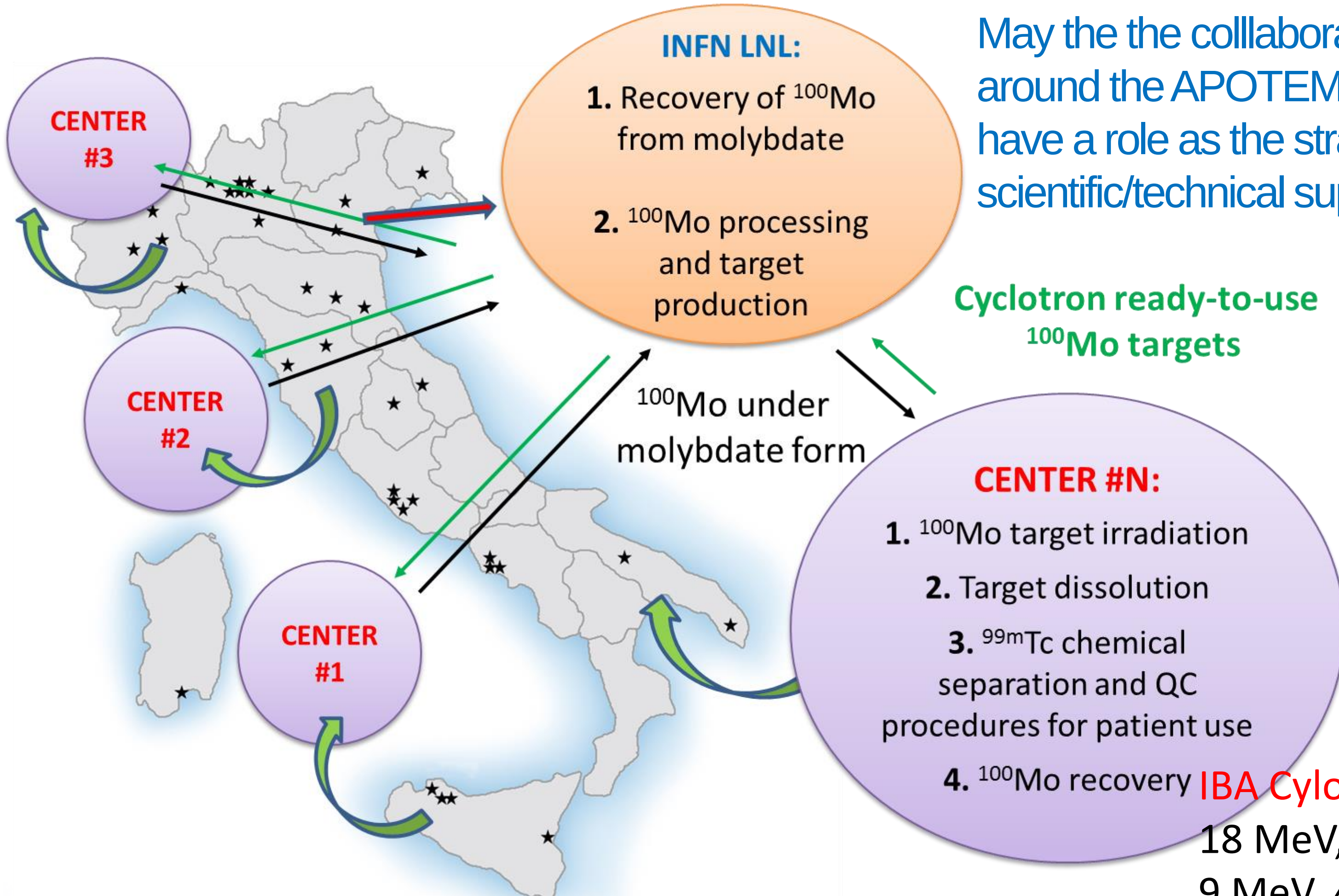
Isotope	Half-life
Tc-99m	**6.0067 h**
Tc-93g	2.75 h
Tc-94g	4.88 h
Tc-95g	20.0 h
Tc-96g	4.28 d

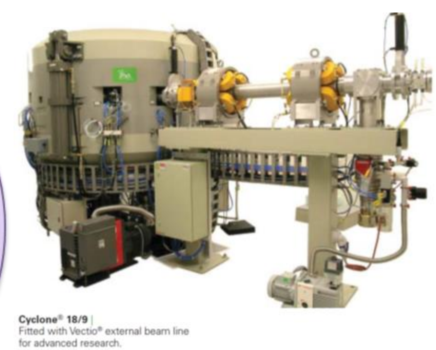


TECHN_OSP project (2015-2017): A hub and spoke approach

R&D activities aimed at an industrially-based technology for future homeland accelerator-^{99m}Tc production based on a selected cyclotrons' network in Italy:

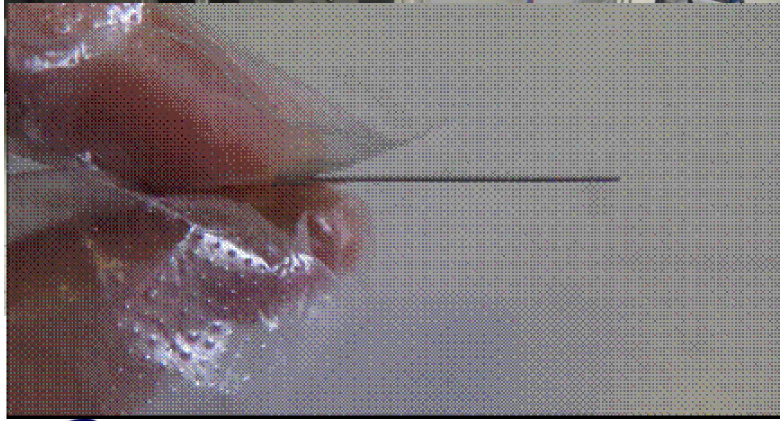
May the the colllaboration network gathered around the APOTEMA research project have a role as the strategic center for the scientific/technical support?

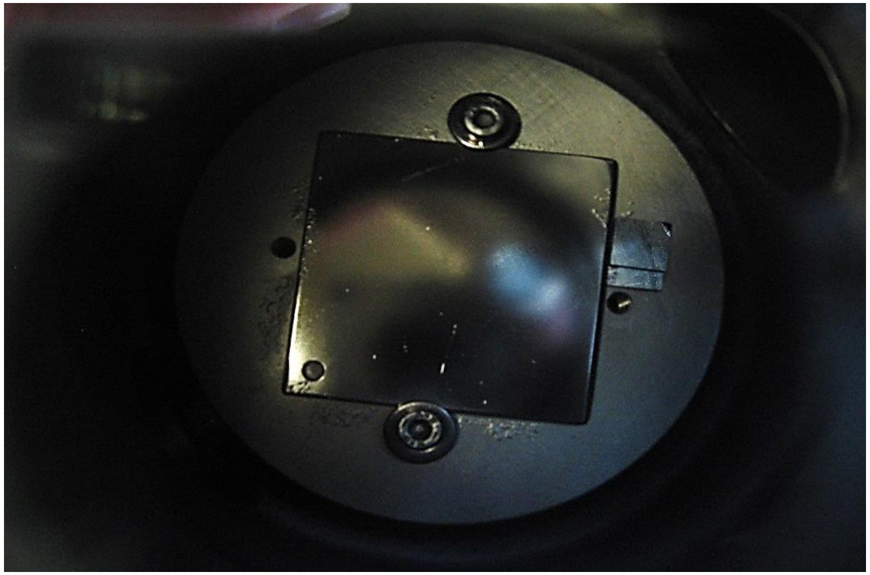




IBA Cylone 18/9 protons
18 MeV, up to 100 μA (1.8 kW)
9 MeV, 40 μA deuterons

~1kW/cm^2 new target concepts: successful tests at LNL STS lab of molybdenum layer deposition on backing material





First successful test **to deposit multiple layers (0.5 μm each) up to ~300 μm on a copper backing** using the **Physical Vapor Deposition (PVD) technique under UHV**.

No stress at micro-structure level has been observed.

The system has been fully automated

Further tests are underway to **fully optimize the production process able to produce good quality layers**

Irradiation tests at S. Orsola Hospital

110 µm Mo-nat directly sputtered onto **Cu backing (first time ever)**

70µA, 15.6 MeV -> ~1.1 kW/cm^2 achieved!!

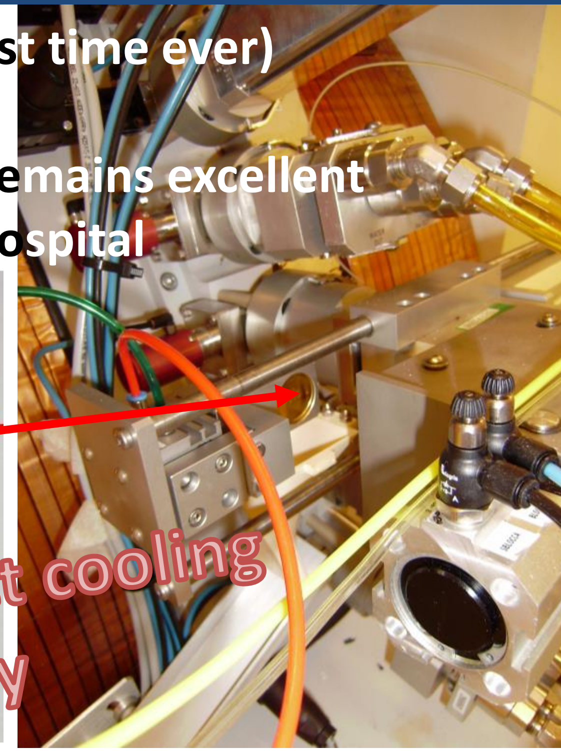
Contact between sputtered **Mo film, and Cu-backing remains excellent**

Double 3hrs irr/day -> ~1.5 Ci daily needs S. Orsola Hospital

GE PetTRACE -16

Protons: 16 MeV, up to 75 µA (1.2 kW)

Deuterons:8.4 MeV, 50 µA deuterons

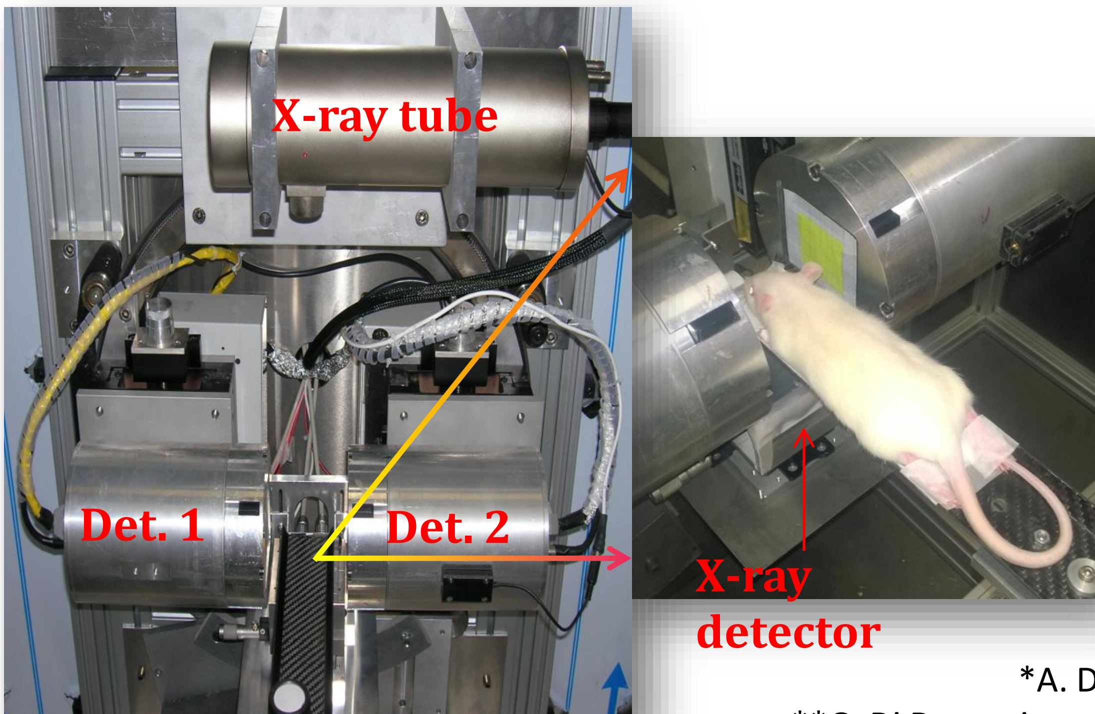


Additional ~1.5 kW/cm^2, no-direct cooling target concept under study

Standard production with **metallic** targets : <25 µA

Accelerator-^{99m}Tc: imaging studies

- Anesthetized WIST rats were injected into the jugular vein
- Whole-body SPECT-CT biodistribution studies were carried out with the hybrid YAP(S)PET-CT small-animal scanner at Ferrara Univ.
- Depending on rats' dimensions, n. 4-5 scans have been taken



SPECT modality *

Field of view: 4 x 4 x cm^2

Yap(Ce): 4 x 4 x 3 cm^3

Energy Res.: 26% (140 keV)

Spatial Res.: 3.5 mm

Sensitivity: 15 cps/MBq

CT **

Active area: 49.2 x 49.3 mm^2

GOS on dual CMOS array

(1024x1024 photodiodes)

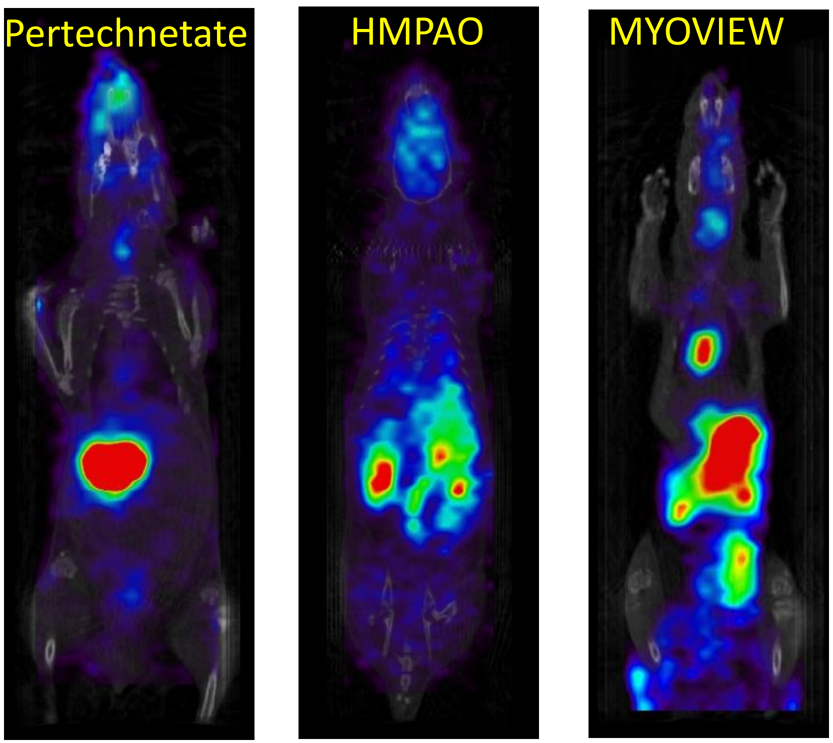
*A. Del Guerra et al., *IEEE Trans.Nucl.Science* (2004)

**G. Di Domenico et al., *Nucl Instrum Meth A* (2007) 571 :110–113

APOTEMA: First *in-vivo* SPECT-CT images

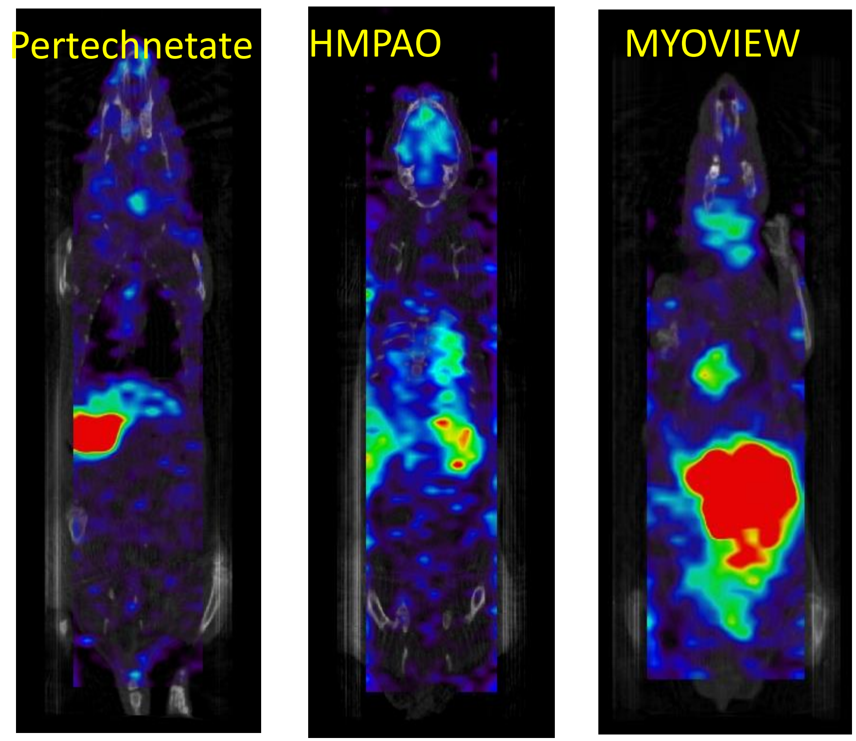
Generator-produced ^{99m}Tc

correction for injection time and activity



Accelerator-produced ^{99m}Tc

correction for inj. Time, activity and scatter



→ Preliminary SPECT-CT imaging study confirmed comparable biodistribution of radiopharmaceuticals labelled with ^{99m}Tc (generator- or cyclotron-produced)

→ The effect of scattered high-energy γ-rays strongly depends on the imaging system

^{67}Cu and ^{64}Cu: new emerging radionuclides

SPECT / THERAPY

Cu-67	γ-ray [keV]	γ-ray [%]	β energy [keV]	β int [%]	Auger [keV]	Auger [%]
61.83 h						
β- : 100 %	184.6	48.7	51	1.1	0.99	19.14
(Zn-67)	209.0	0.115	121	57	7.53	6.87
	300.2	0.797	154	22.0	83.65	12.09
	393.5	0.220	189	20.0	Mean β- : 141 keV	

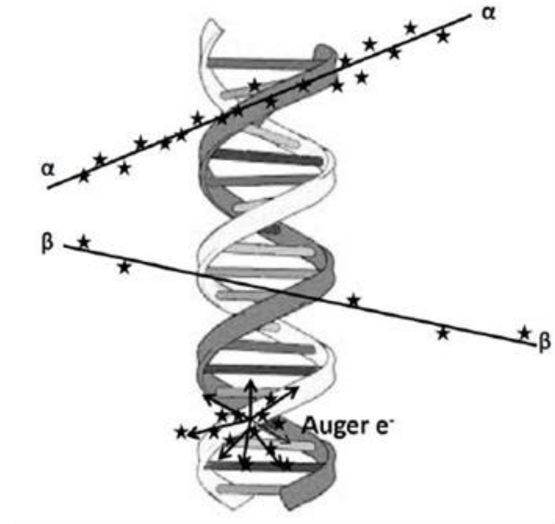
PET / THERAPY

Cu-64	γ-ray [keV]	γ-ray [%]	β+ energy [keV]	β+ int [%]	Auger [keV]	Auger [%]
12.701 h						
ε : 61.5 %	1345.77	0.475	278.21	17.60	0.84	57.7
(Ni-64)					6.54	22.51

THERAPY

Cu-64	β energy [keV]	β int [%]
β- : 38.5 %		
(Zn-64)	190.70	38.5

NuDat 2.6 database (2013) - NNDC



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

Cu-67 very attractive because of physical-chemical properties ($T_{1/2}$ 2.58 d). Suitable for **Theranostic (Therapy + Diagnostic) applications,** as single isotope, or in pair with ^{64}Cu (β-emitter, half-life 12.7 h).

Potential of **theranostic** is the selection of patients prior therapy and the use of maximum tolerated dose (MTD)*, based on previous SPECT/CT (^{67}Cu) or PET/CT (^{64}Cu) diag. proc.

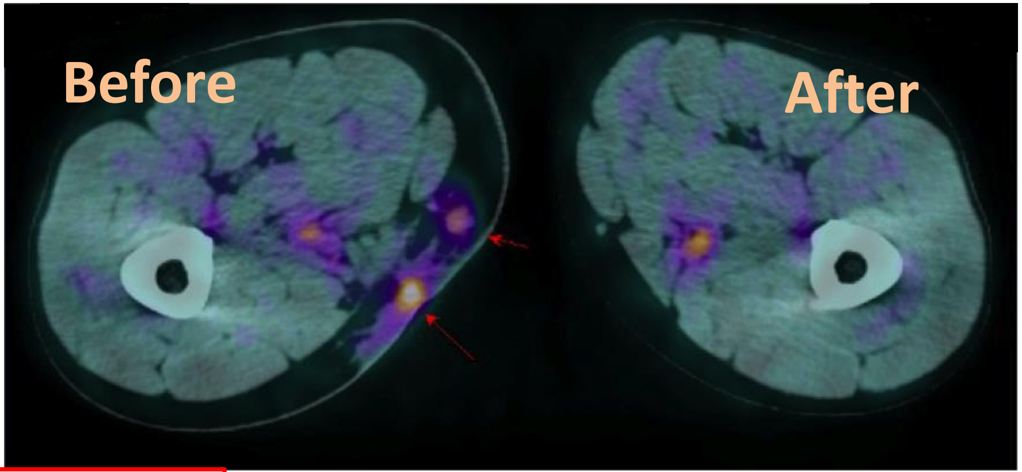
* Srivastava SC, . *J Postgrad Med Edu Res* 47 (2013) 1:31-46

Applications of ^{67}Cu and ^{64}Cu in nuclear medicine

Human Copper transporter 1 (hCtr1) plays a major role in the cellular uptake of copper in humans and it is overexpressed in a variety of cancers

- **^{64}Cu** is ALREADY used in nuclear medicine for PET (diagnostic proc.)
- **^{64}Cu** seems to provide excellent results also in THERAPY (under simple **^{64}Cu**Cl_2)

Malignant melanoma images (left leg) before and after **100 mCi** **^{64}Cu**Cl_2 injection



What will it happen by using **^{67}Cu** ?

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

Worldwide Production per month : only 1 patient dose (100 mCi ≈ 3.7 GBq)

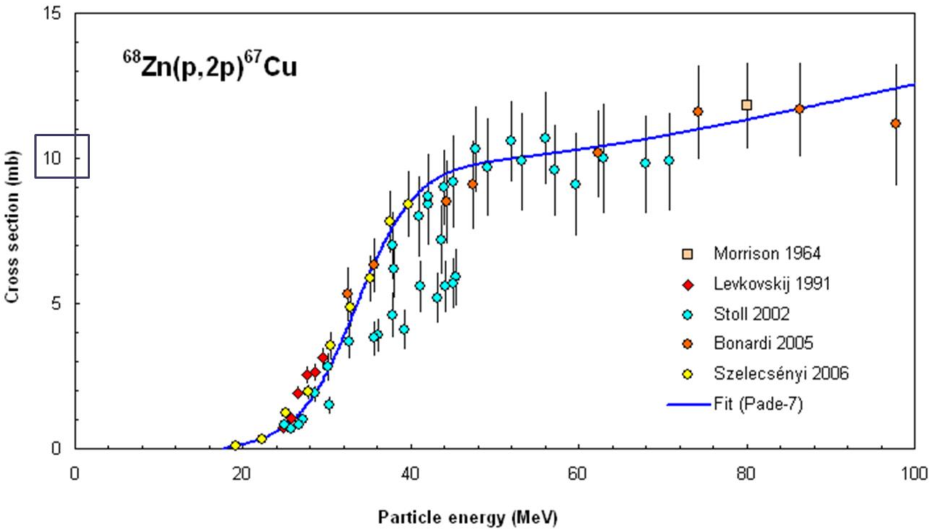
→ **^{67}Cu** production: Goal for both LARAMED and ARRONAX !

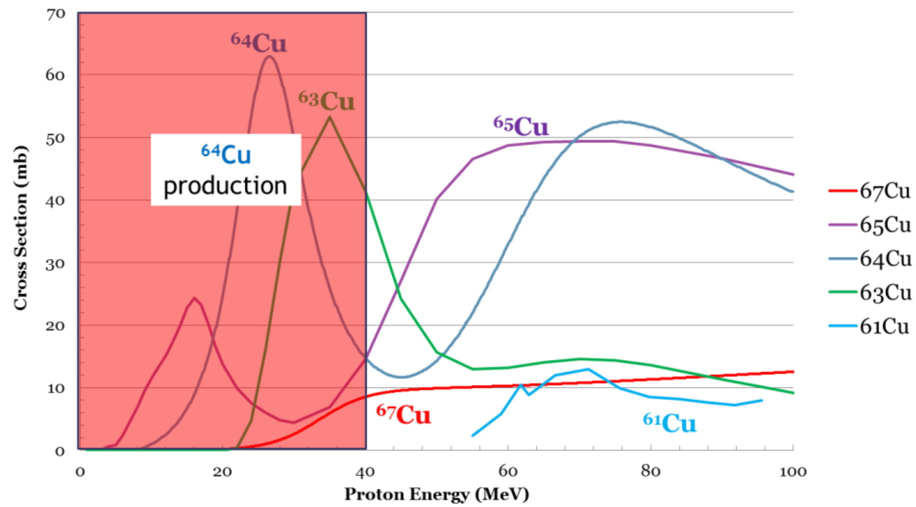
*Peng F et al., *J Nucl Med* (2006)47:1649-1652 ; **H Cai et al. , *J Nucl Med* (2014) 55:622-628.

^{67}Cu current production route

^{68}Zn(p,2p) reaction, already used but…not efficient

IAEA *Technical Report Series No. 473* (2011)





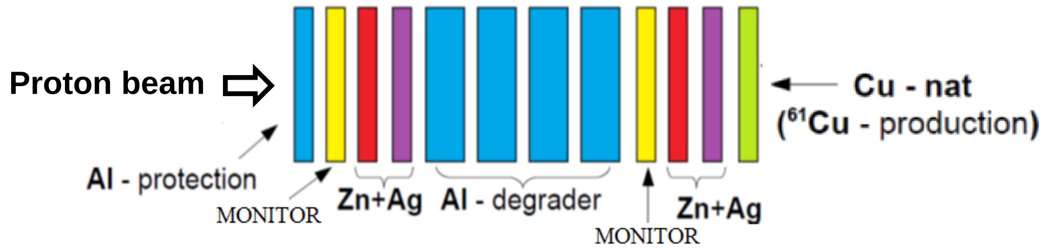
^{67}Cu monthly production:
100 mCi (@ BNL)
→Only ONE therapeutic dose !

In order to have a *pure* ^{67}Cu (RNP>99%) it is necessary to wait that ^{64}Cu decays
→ lose ≈ 80% of ^{67}Cu activity

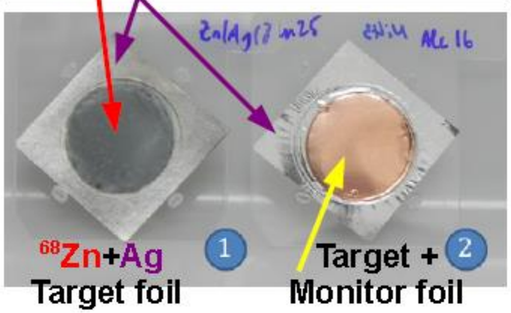
Assessment of current ^{68}Zn(p,2p)^{67}Cu xs data

New ^{68}Zn(p,2p)^{67}Cu xs measurements at ARRONAX

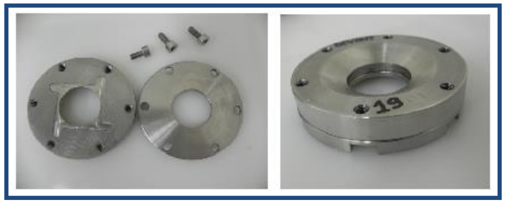
Stacked-foil target structure



Target foil(s):
^{68}Zn Elettrodeposition (~10μm)
Ag Support (~25μm)

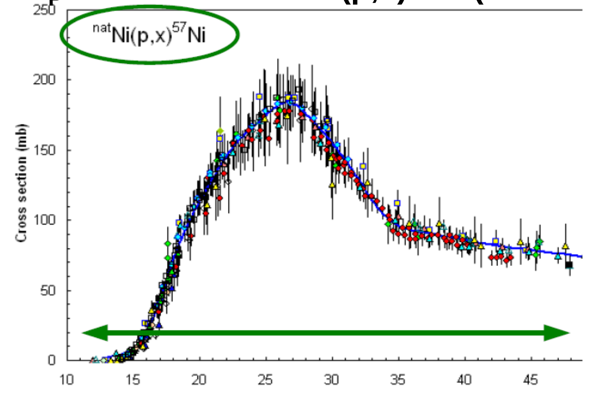


Stacked-foil Target holder

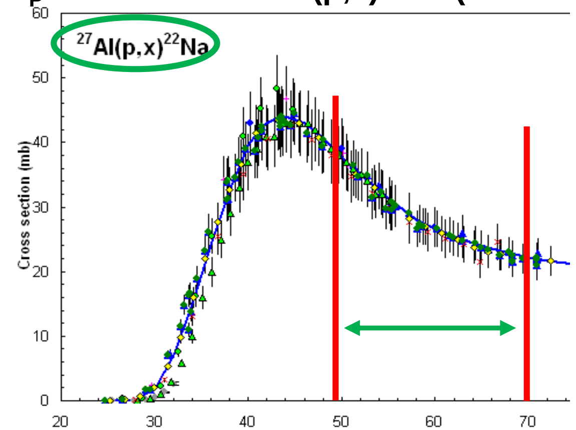


Monitor reactions*:

E_P < 50 MeV → ^{nat}Ni(p,x)^{57}Ni (^{nat}Ni ~ 20 μm)



E_P > 50 MeV → ^{27}Al(p,x)^{22}Na (^{27}Al ~ 20 μm)



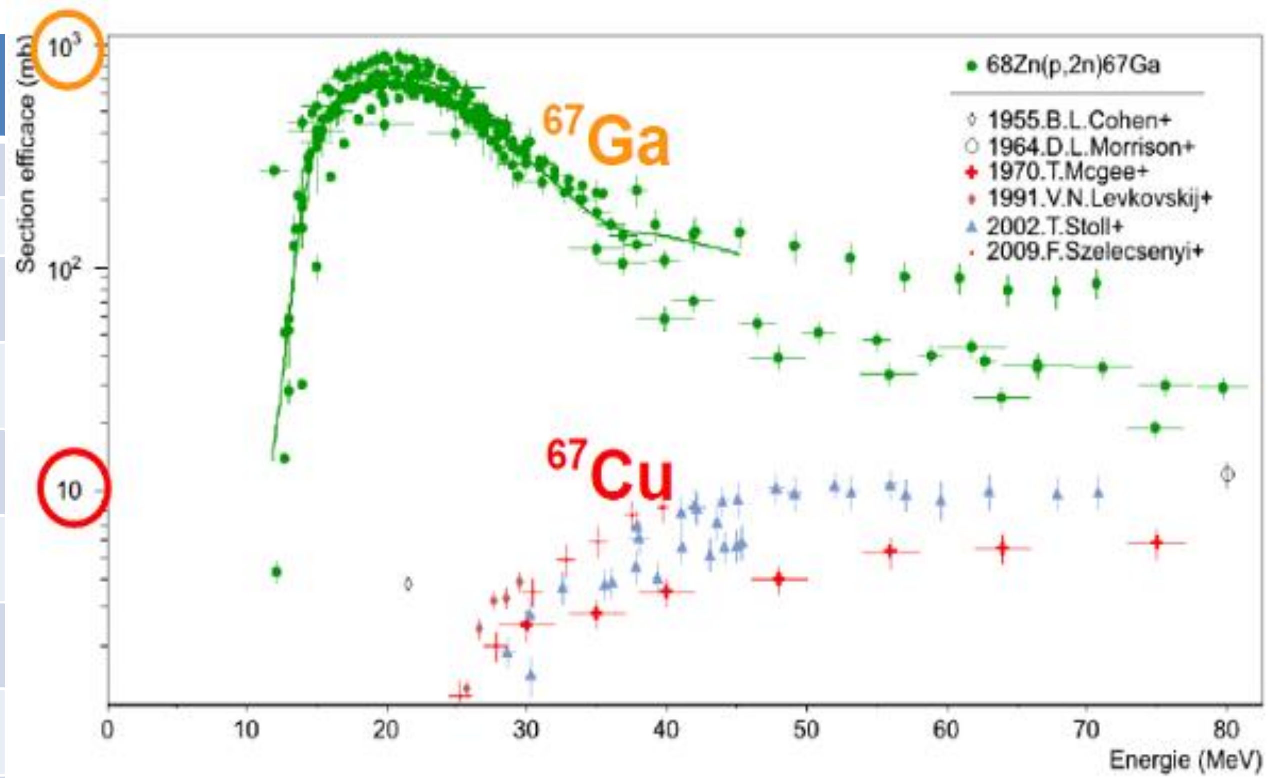
* International Atomic Energy Agency (IAEA)
http://www-nds.iaea.org/medical/monitor_reactions.html

Target foils prepared at the LNL targetry lab

^{67}Ga interfering radionuclide

^{68}Zn(p,x)reactions*: co-production of ^{67}Cu and ^{67}Ga

Energy [keV]	Cu-67 Intensity	Ga-67 Intensity
91.266 5	7.0 1	3.11 4
93.311 5	16.1 2	38.81 3
184.577 10	**48.7 3**	**21.41 1**
208.951 10	0.115 5	2.46 1
300.219 10	**0.797 11**	**16.64 12**
393.529 10	0.220 8	4.56 24
494.166 15		0.0684 14
703.106 15		0.0105 9
794.381 15		0.0540 18
887.688 15		0.148 3

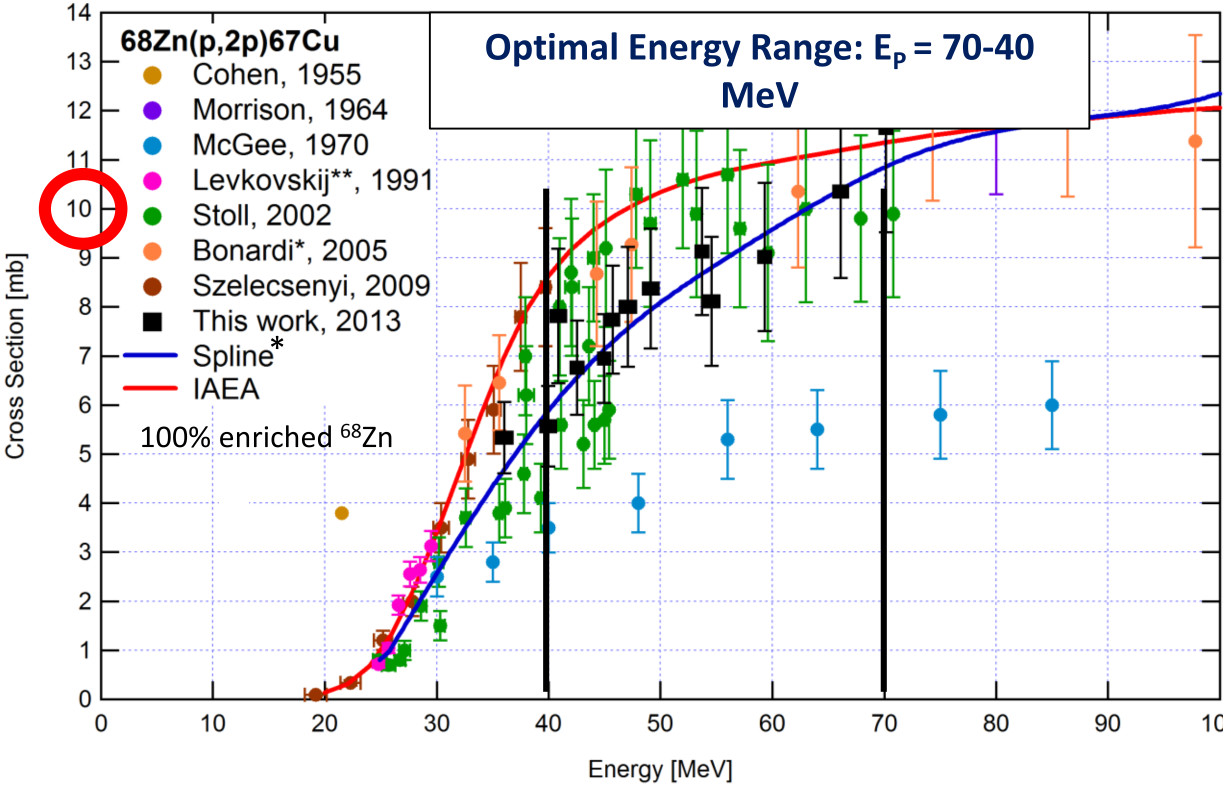


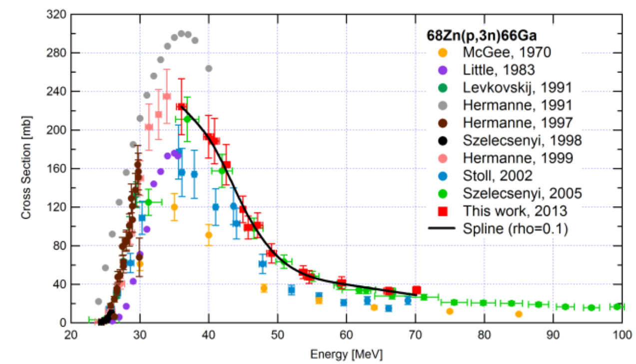
^{67}Cu ($t_{1/2}$ 61.83 h) ^{67}Ga ($t_{1/2}$ 78.24 h)

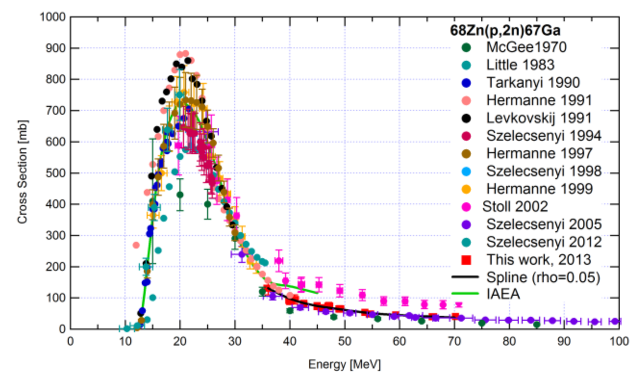
Chemical separation Cu/Ga is mandatory !!
Tracer: **Cu-61** and **Ga-66**

Xs measurements at 35-70 MeV

The $^{68}Zn(p,2p)^{67}Cu$ cross section at ARRONAX





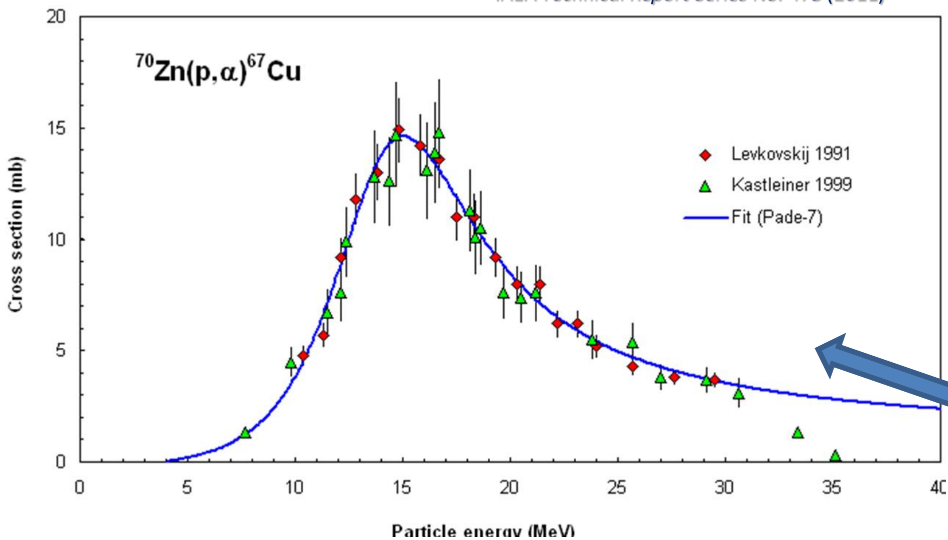


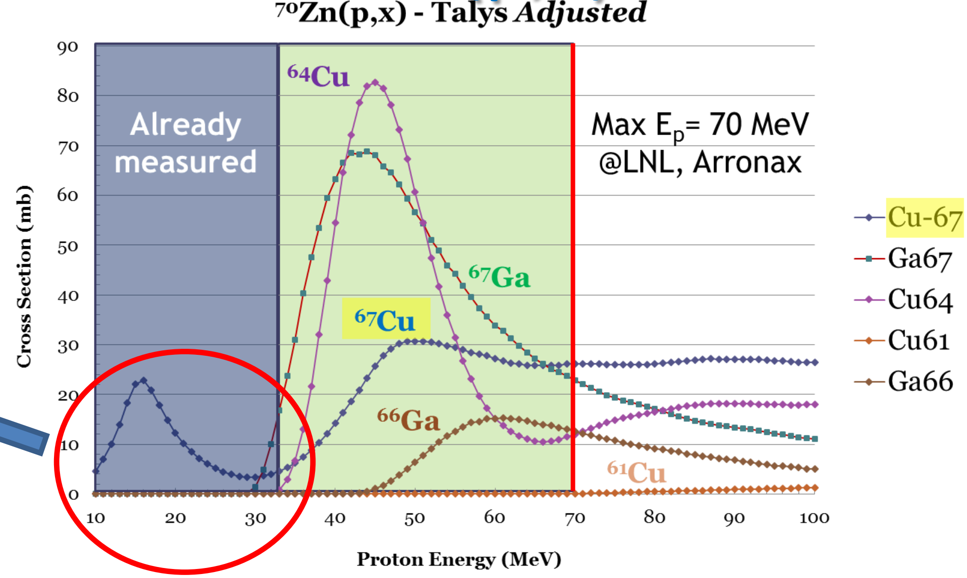
Results next to be issued

COME (COpper MEasurement) exp.: INFN funded (2016)

A new reaction route under exam.: $^{70}Zn(p,x)^{67}Cu$

IAEA *Technical Report Series No. 473* (2011)





No experimental data are available for $E_P > 35$ MeV

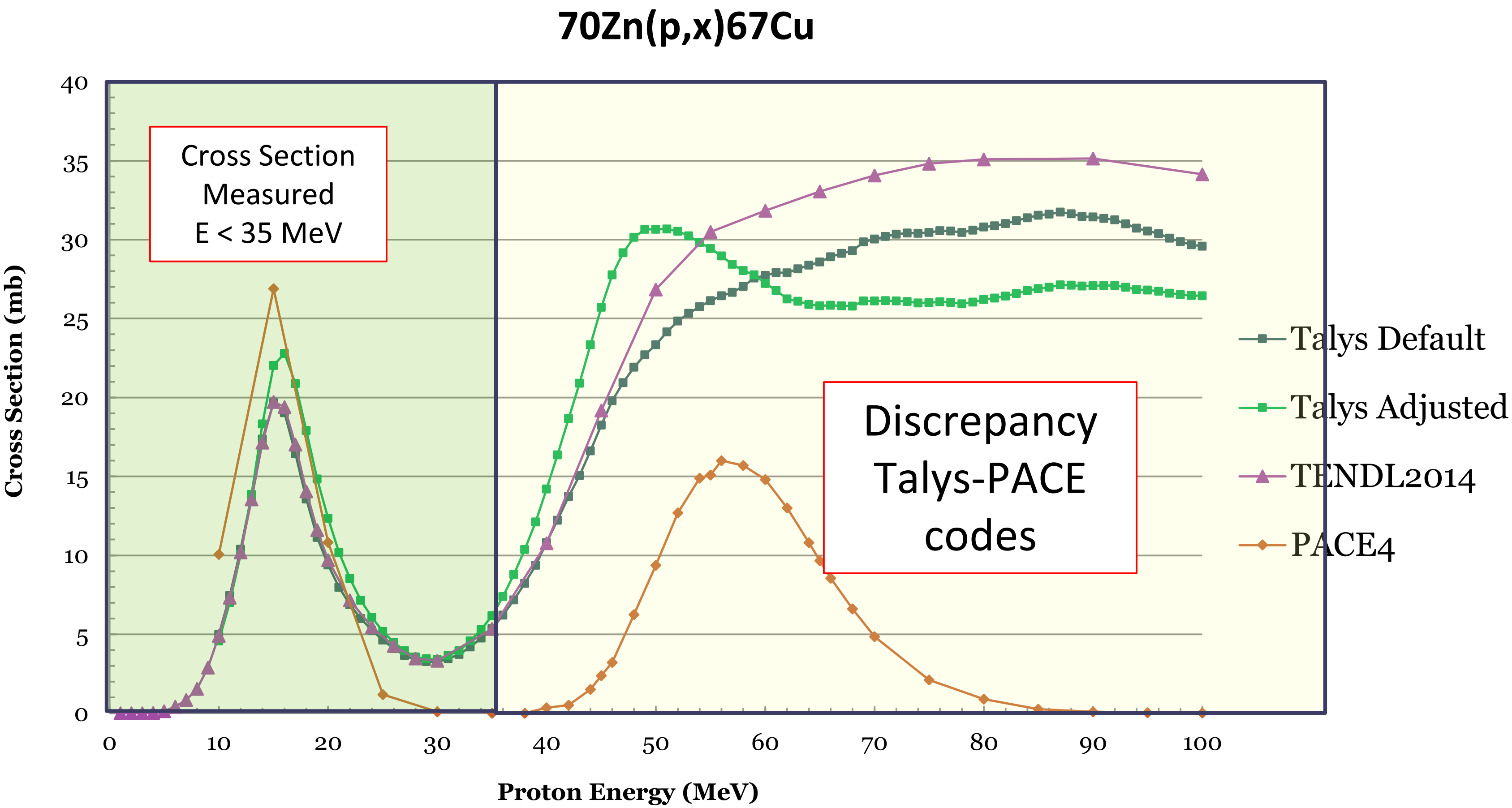
CoMe project:
$^{70}Zn(p,x)^{67}Cu, ^{64}Cu$
xs measurements

Estimations based on Talys code
Best energy range: 50-70 MeV
Exp data are needed !

5 Irradiation runs @ Arronax done during 2016 : data analysis in progress !

$^{70}Zn(p,x)^{67}Cu$ nuclear models diagreement

The $^{70}Zn(p,x)^{67}Cu$ cross section ESTIMATION



We need the support of nuclear physics community to explain this disagreement !

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THANK YOU

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J. Esposito, October 11, 2016