IAEA-CN301-73

Research activities on the cyclotron-based production of innovative radionuclides: The experience at the Legnaro National Laboratories of INFN

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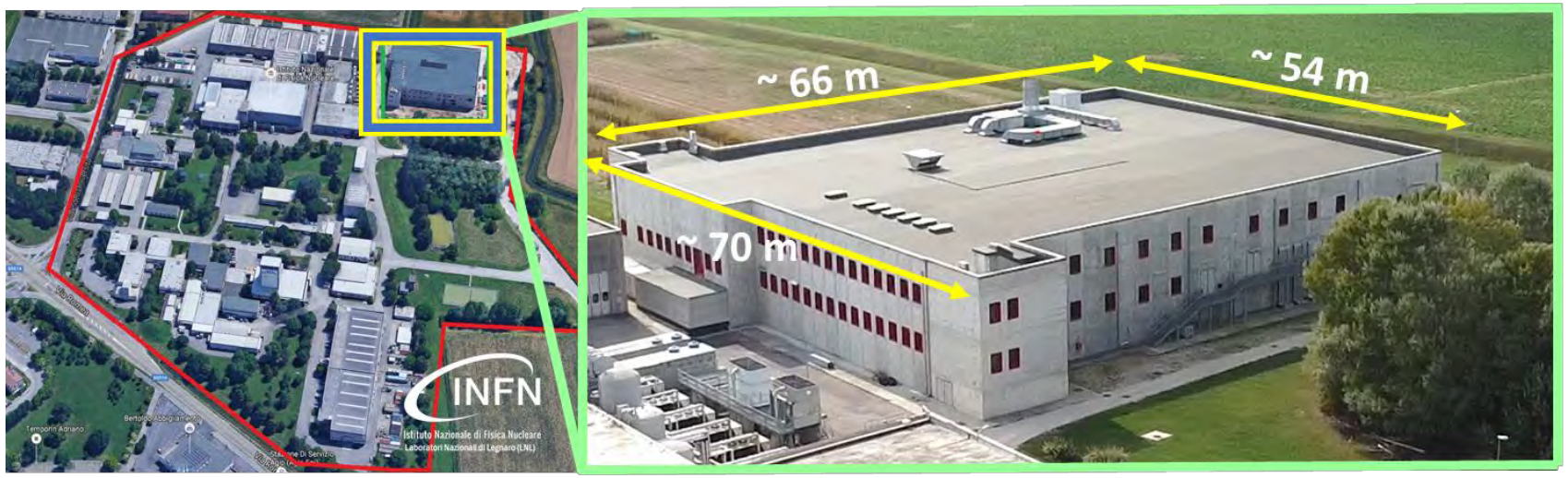
INFN-LNL are close to Padova and Venice



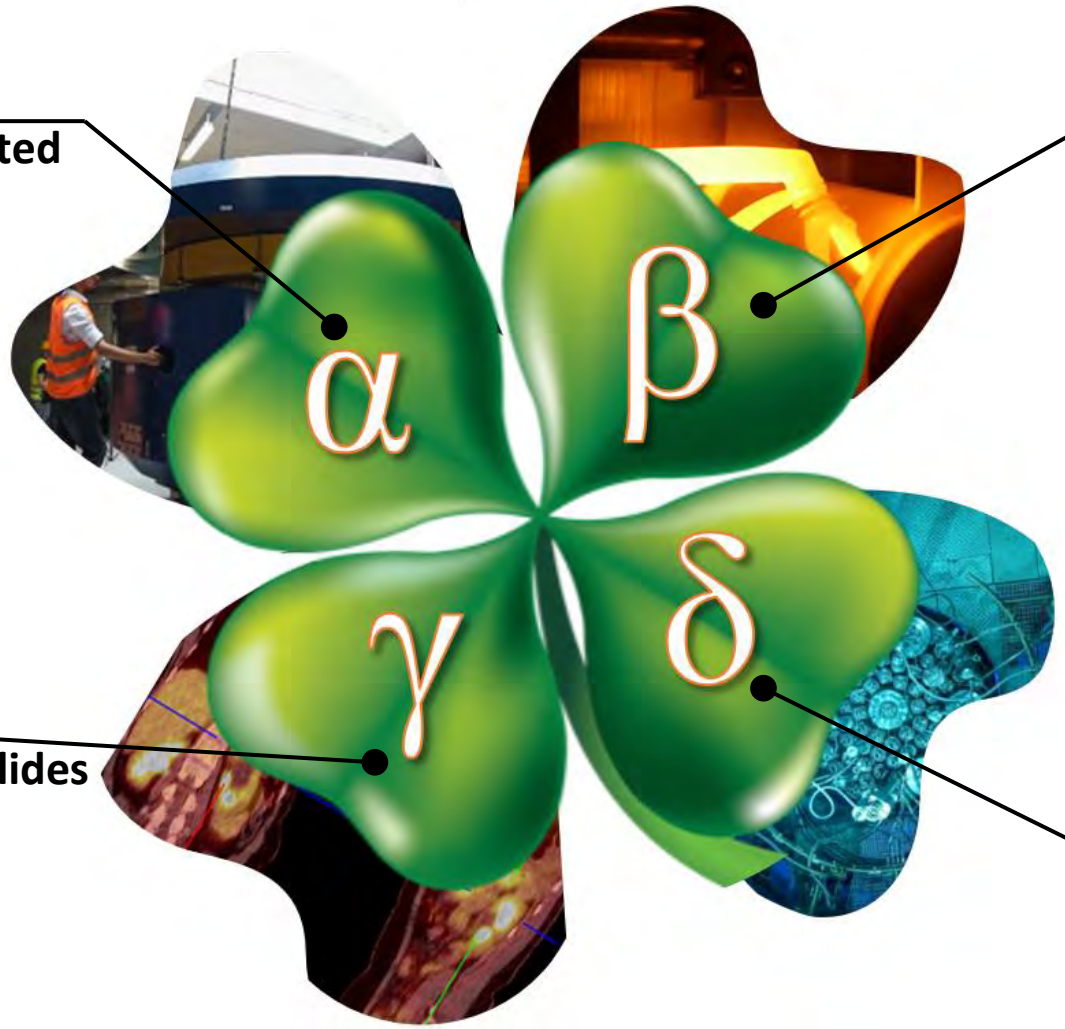
The SPES project

SPES-α

The cyclotron and related infrastructure.

SPES-β

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



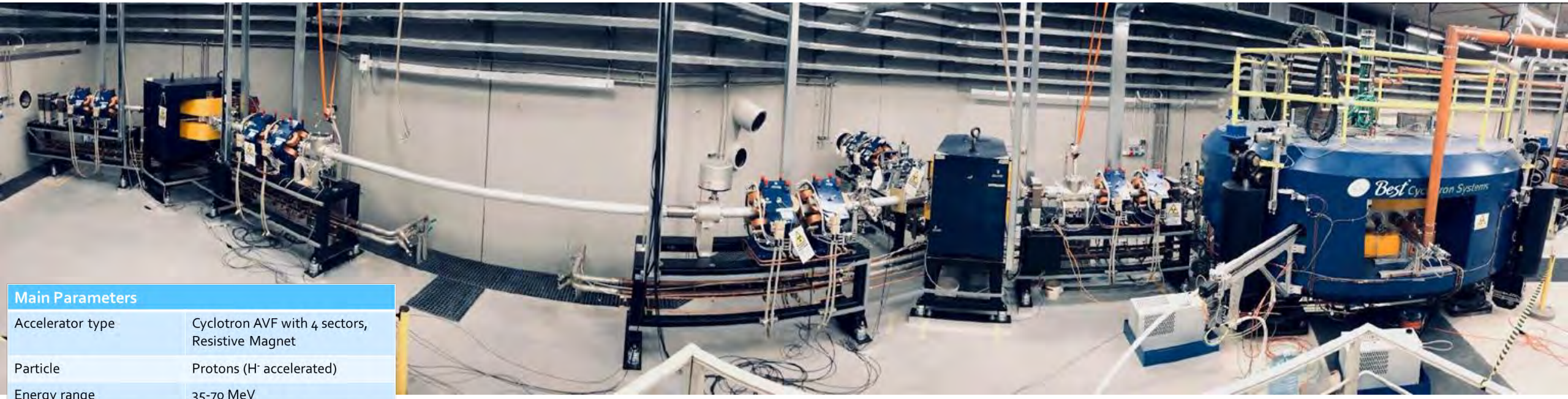
SPES-γ

The production of radionuclides for applications.

SPES-δ

The multidisciplinary neutron sources.

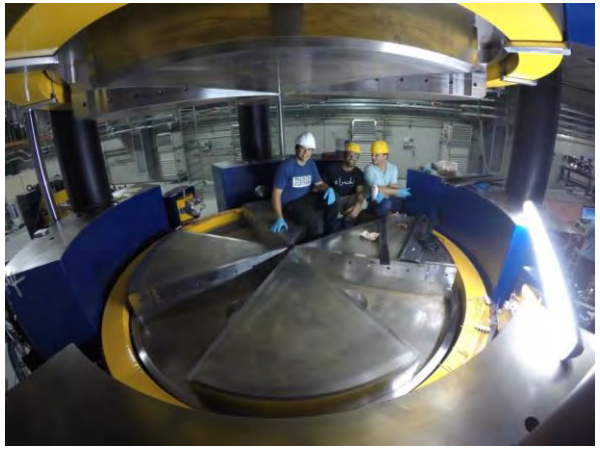
The SPES cyclotron



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

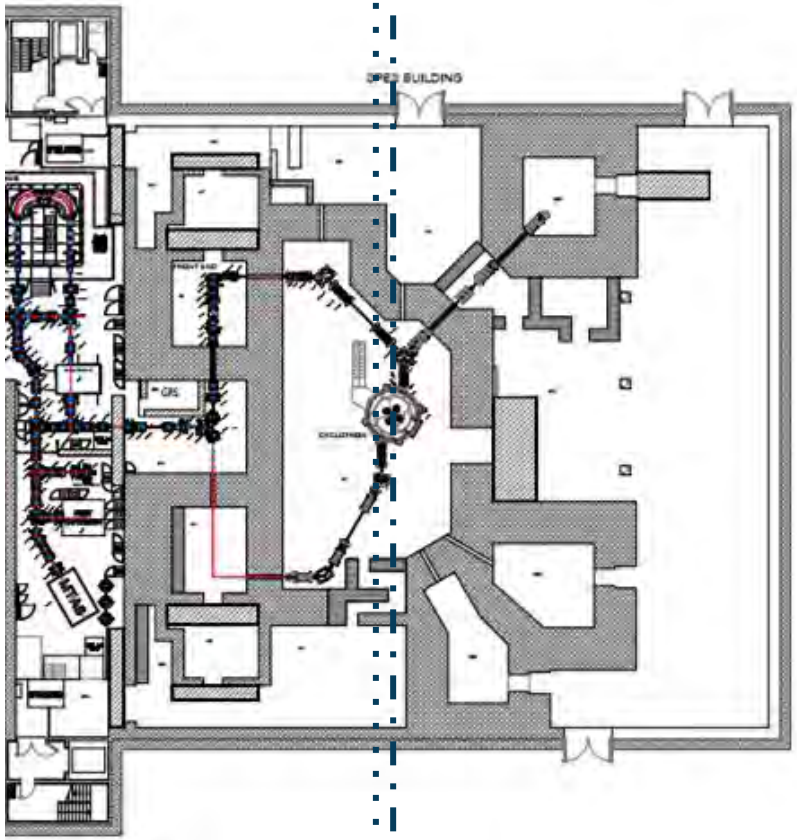
Dual extraction → Fundamental & Applied research



Medical radionuclides production

ISOLPHARM
SPES exotic beams for medicine

ISOL technique
A. Andrighetto
Resp. ISOLPHARM



LARA MED

Direct activation
J. Esposito
Resp. LARAMED

SPES-γ
The production of radionuclides for applications.

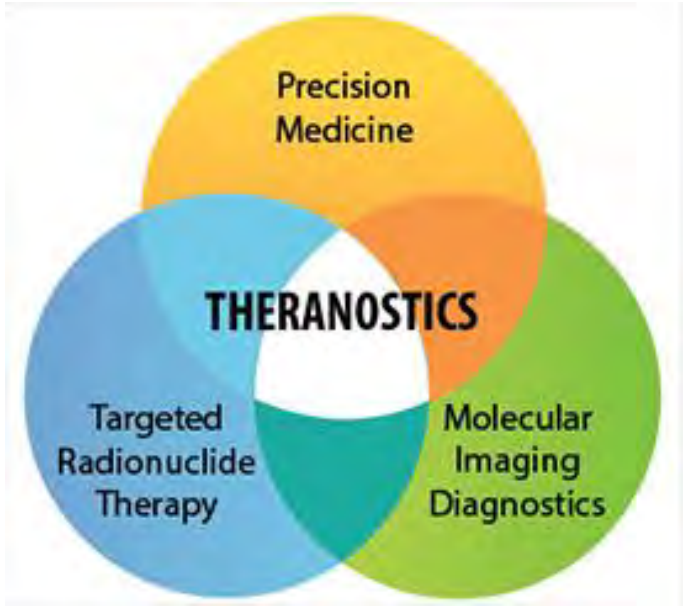
PRISMAP 27 EU
Medical Radionuclides

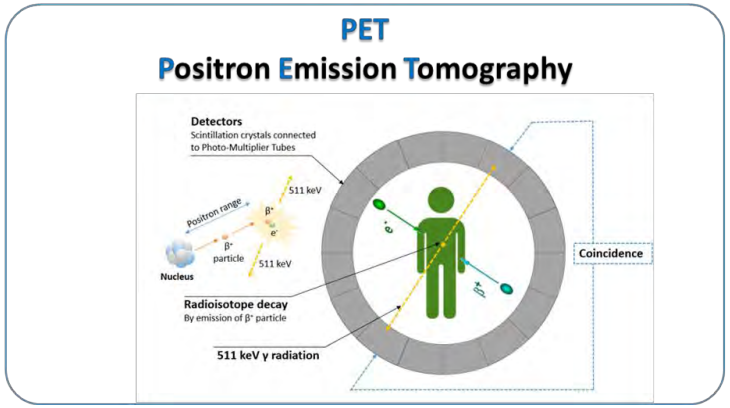
https://isolpharm.pd.infn.it/web/

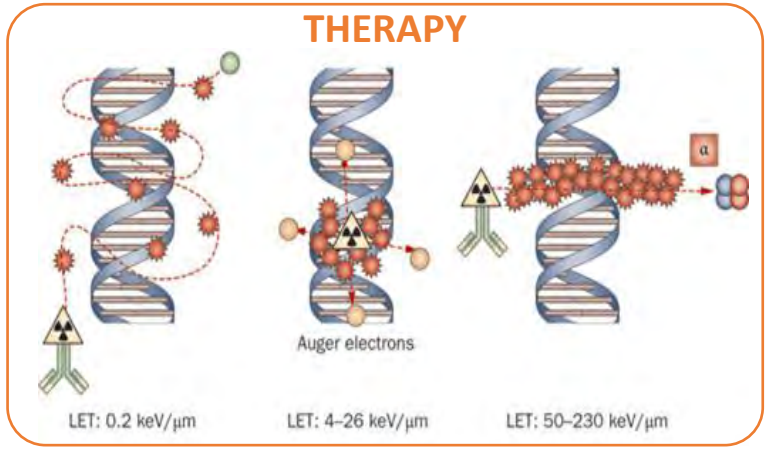
https://www.lnl.infn.it/en/spes-laramed-range

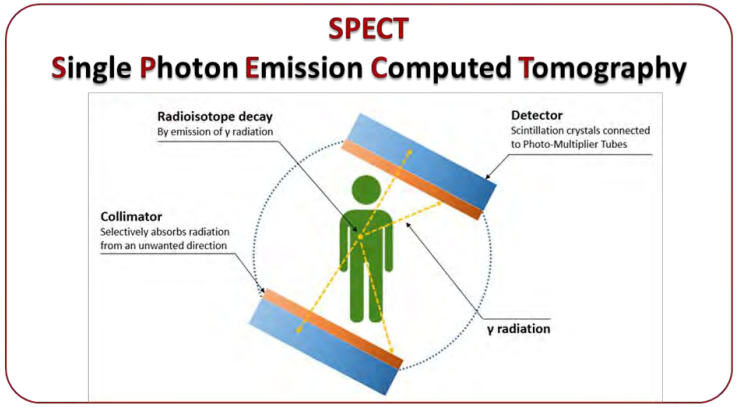

WHY?


Radiopharmaceutical
Radioisotope
responsible of signal emission
Targeting agent
Small molecule or biological agent (Ab, etc.)
Linker
joins the chelator to targeting agent
Chelator
molecule holding the radioisotope
Biological target
Better if overexpressed by the target cells


Precision Medicine
THERANOSTICS
Targeted Radionuclide Therapy
Molecular Imaging Diagnostics


PET
Positron Emission Tomography
Detectors
Scintillation crystals connected to Photo-Multiplier Tubes
511 keV
Positron range
β+
e-
β+ particle
511 keV
Nucleus
Coincidence
Radioisotope decay
By emission of β+ particle
511 keV γ radiation

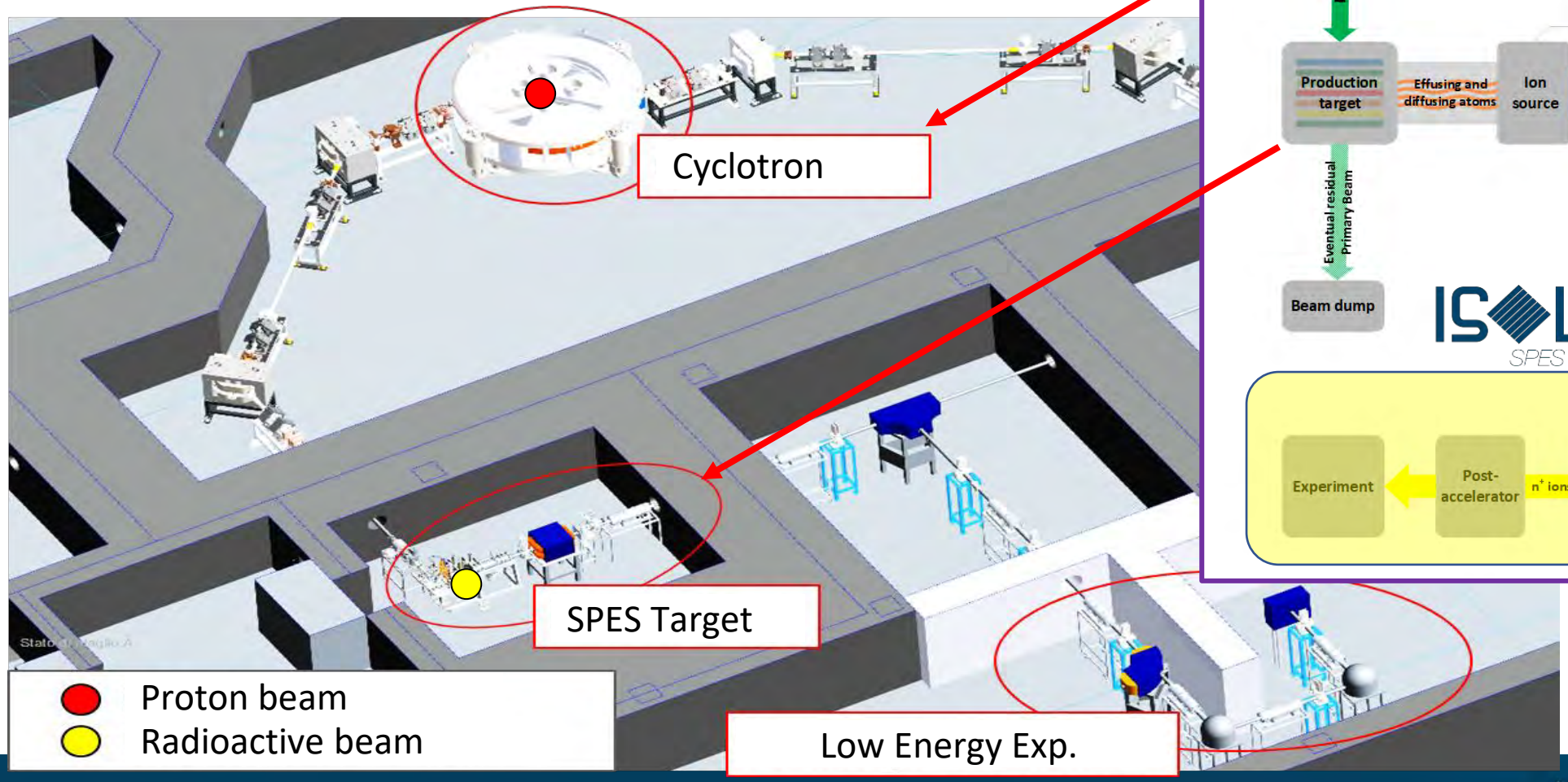

THERAPY
Auger electrons
α
LET: 0.2 keV/μm
LET: 4–26 keV/μm
LET: 50–230 keV/μm

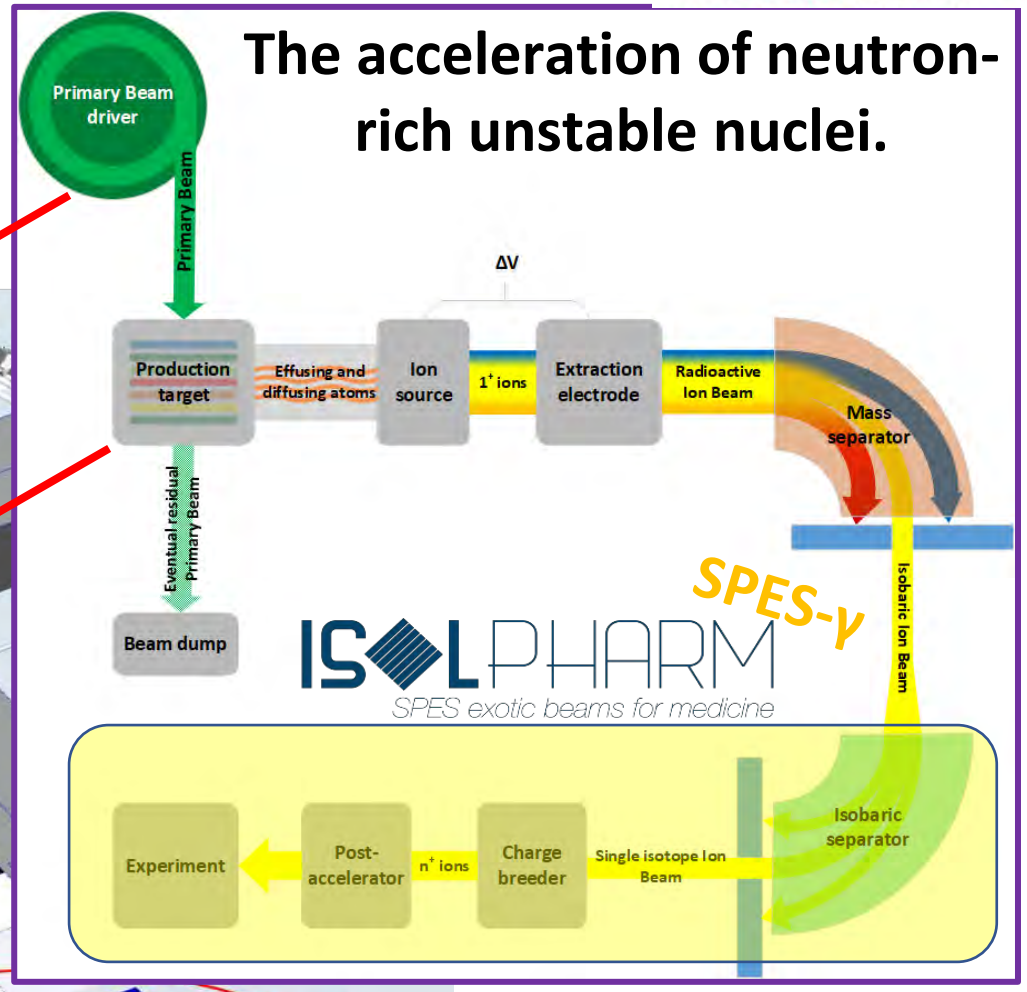

SPECT
Single Photon Emission Computed Tomography
Radioisotope decay
By emission of γ radiation
Detector
Scintillation crystals connected to Photo-Multiplier Tubes
Collimator
Selectively absorbs radiation from an unwanted direction
γ radiation

The ISOL facility

SPES-β

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





ISOLPHARM

SPES exotic beams for medicine

ISOLPHARM national collaboration

INFN LNL · INFN PADOVA · INFN BOLOGNA · INFN PISA · INFN PAVIA · INFN LNS

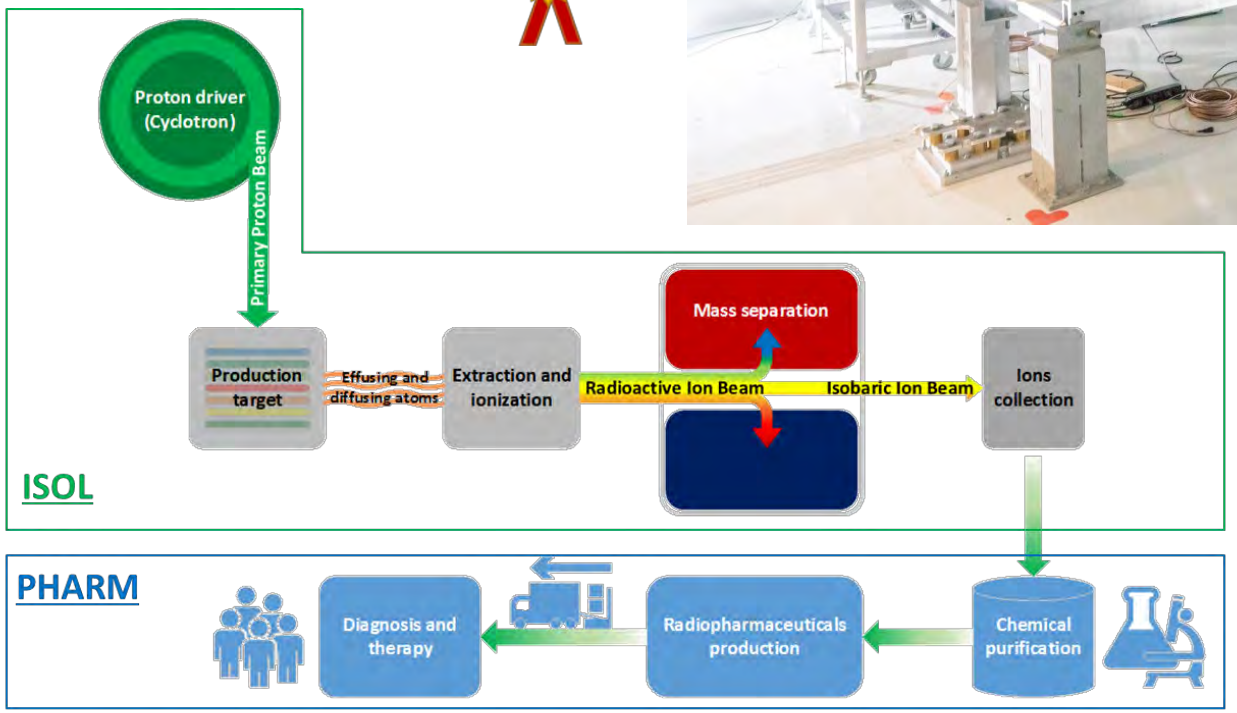
TIFPA Trento Institute for Fundamental Physics and Applications

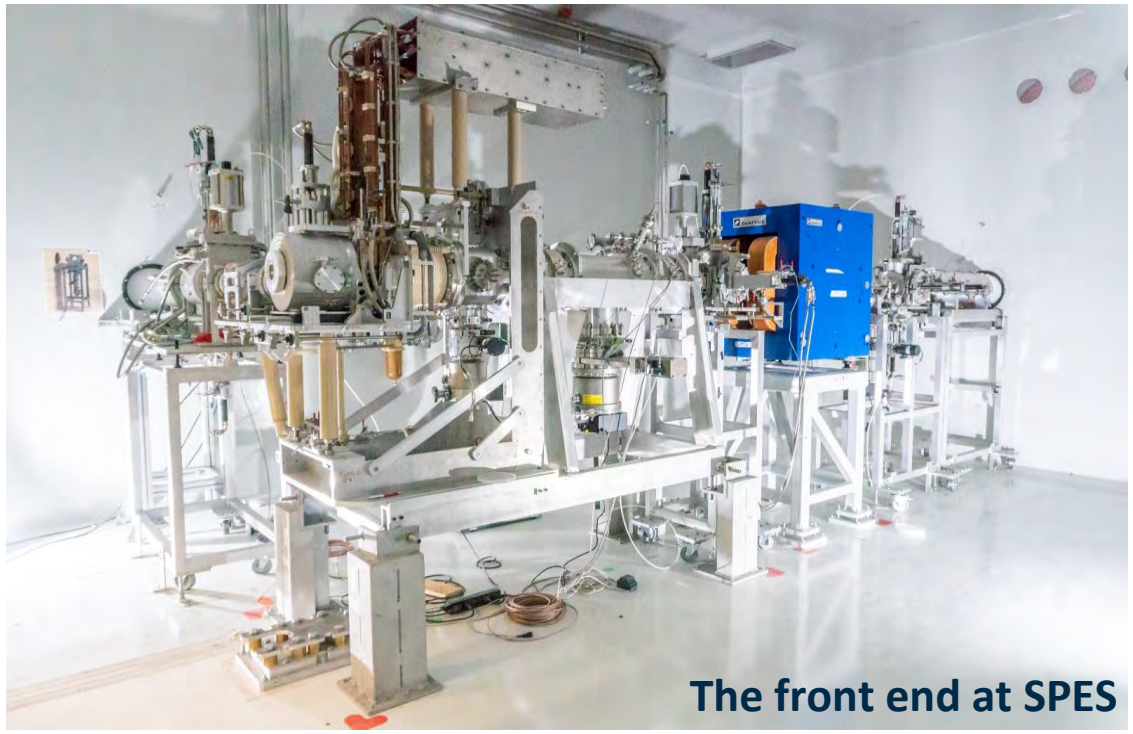
SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Reggio Emilia
Azienda Ospedaliera di Reggio Emilia
Arcispedale S. Maria Nuova
Istituto in tecnologie avanzate e modelli assistenziali in oncologia
Istituto di ricovero e cura a carattere scientifico

UNIVERSITÀ DEGLI STUDI DI PADOVA · UNIVERSITÀ DI TRENTO · UNIVERSITÀ DI PAVIA · UNIVERSITÀ degli STUDI di CATANIA · UNIVERSITÀ DI SIENA 1240 · UNIVERSITÀ DEGLI STUDI DI BRESCIA

IBFM · OSPEDALE CANNIZZARO CATANIA AZIENDA OSPEDALIERA PER L'EMERGENZA · REGIONE DEL VENETO ULSS2 MARCA TREVIGIANA

The ISOLPHARM method radiopharmaceuticals production is an INFN PATENT





The front end at SPES

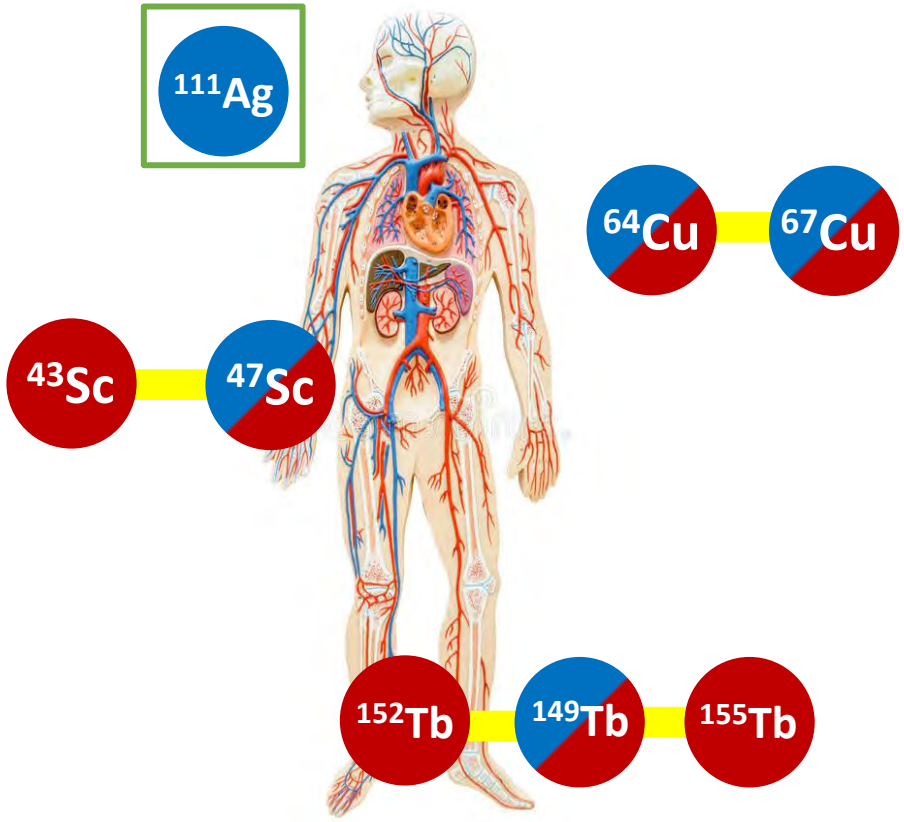
Flexible production, high specific activity & radionuclidic purity

International Conference on Accelerators for Research and Sustainable Development
#Accelerators2022
23–27 May 2022
IAEA, Vienna, Austria

ISOLPHARM
SPES exotic beams for medicine

The ISOLPHARM **ion collection target**

ISOLPHARM allows to produce unconventional medical radionuclides



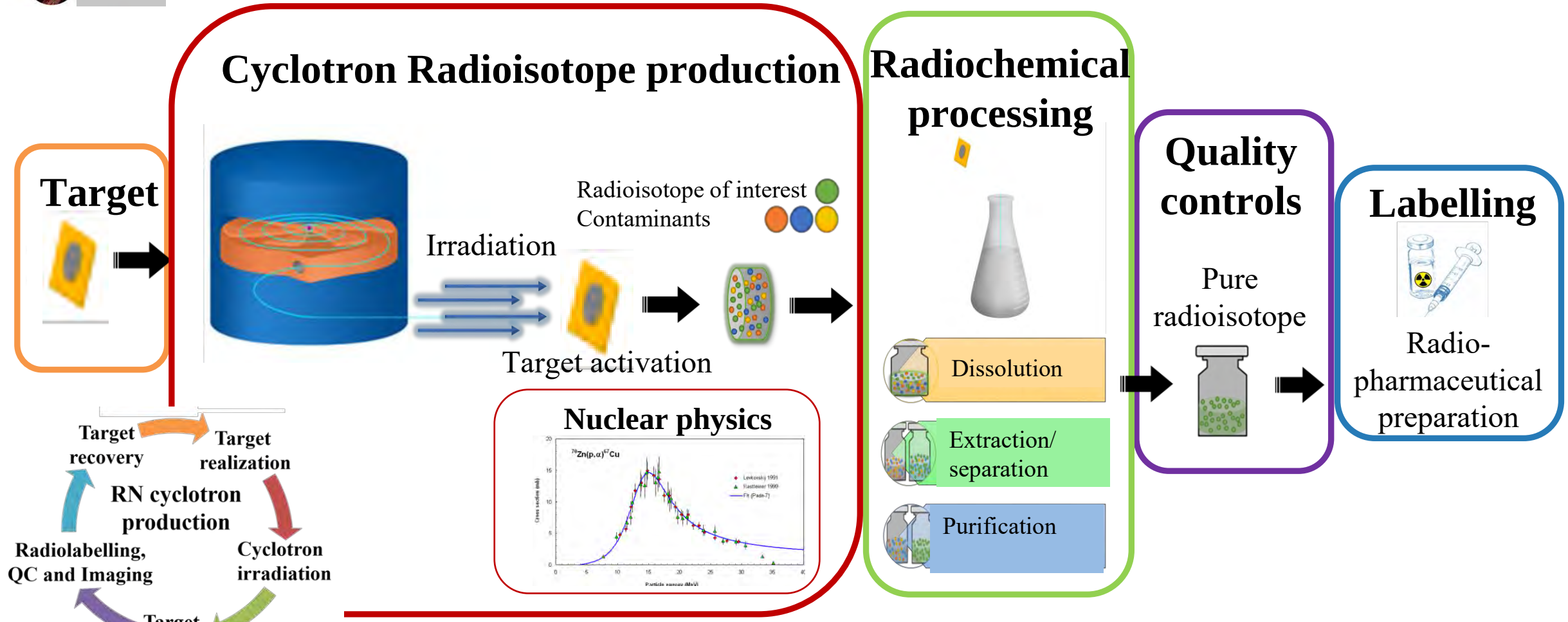
therapy diagnostics theranostics pairs

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

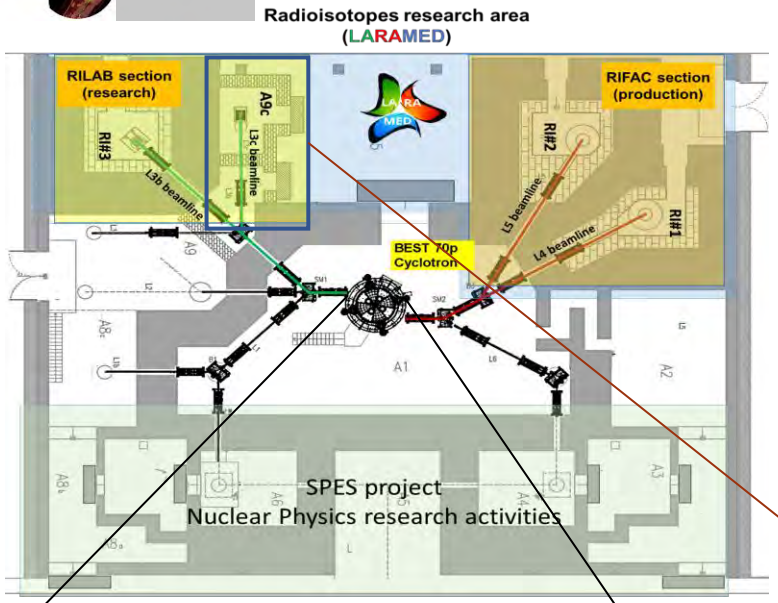
ISOLPHARM (2018-2019)

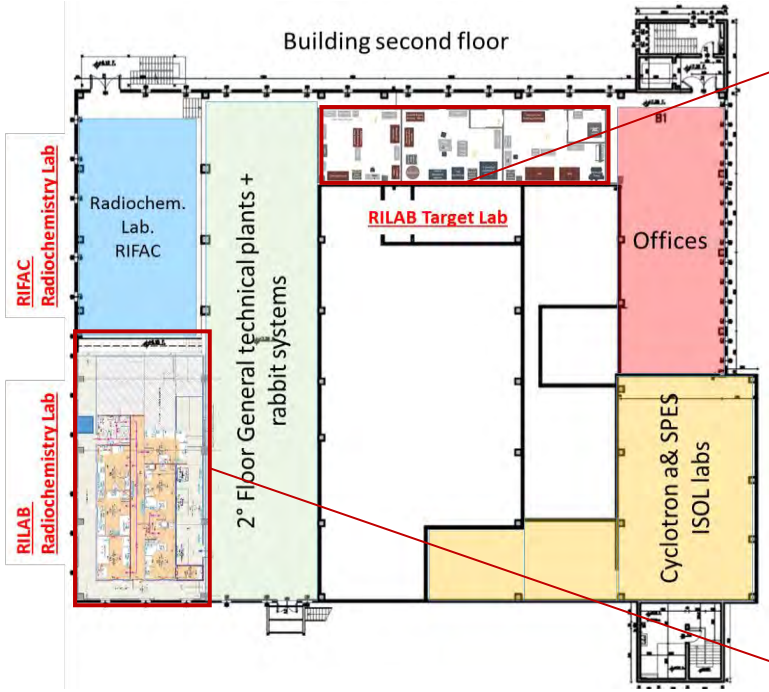
ISOLPHARM_EIRA (2020-2022)

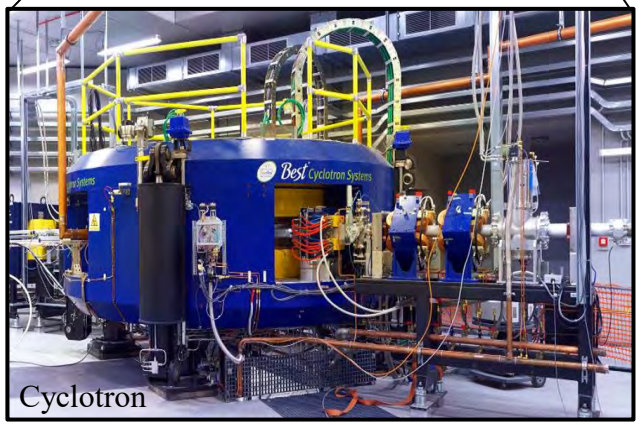
Cyclotron radiopharmaceutical production

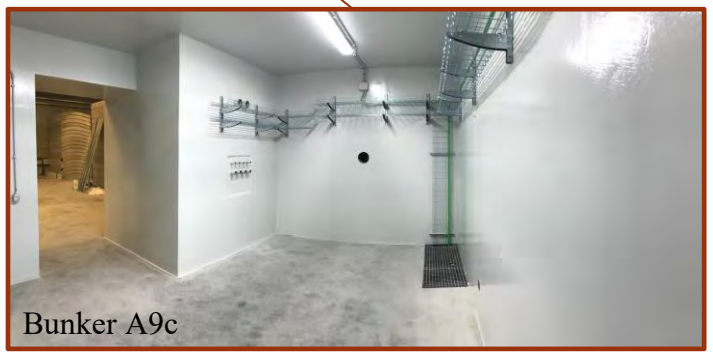


LARAMED facility @ LNL









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)

National collaboration

- Pavia Univ + INFN Pavia
- LENA Laboratory (PV)
- CNR Milan
- Ferrara Univ. /INFN-Fe
- Padua Univ. /INFN-Pd
- Milan Univ. /INFN Mi
- SC Hospital (VR)
- St. Orsola Hospital (BO)

International collaboration

- ARRONAX (Nantes, FRANCE)
- Univ. Winsconsin-MD (USA)
- IAEA

27 EU PRISMAP Medical Radionuclides

International Conference on Accelerators for Research and Sustainable Development #Accelerators2022 23–27 May 2022 IAEA, Vienna, Austria

^{99m}Tc production cycle

^{99m}Tc is the gold standard radionuclide for the SPECT procedures worldwide.
It's currently obtained with ^{99}Mo/^{99m}Tc generator systems

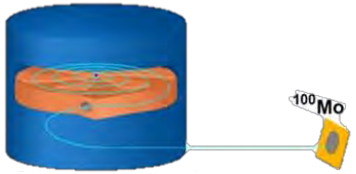
Target production

H. Skliarova et al. Molecules 2019, 24, 25

INFN patent PCT/IB2018/056826

TARGETRY
Sputtering on chemically inert baseplate

Cyclotron irradiation



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

Extraction separation purification

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

Radio-pharmaceuticals, QC, imaging

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

^{100}Mo recovery techniques

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

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

IAEA

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

Theranostic radionuclides

Cu-67
61.83 h
β^- : 100 %
(Zn-67)

SPECT

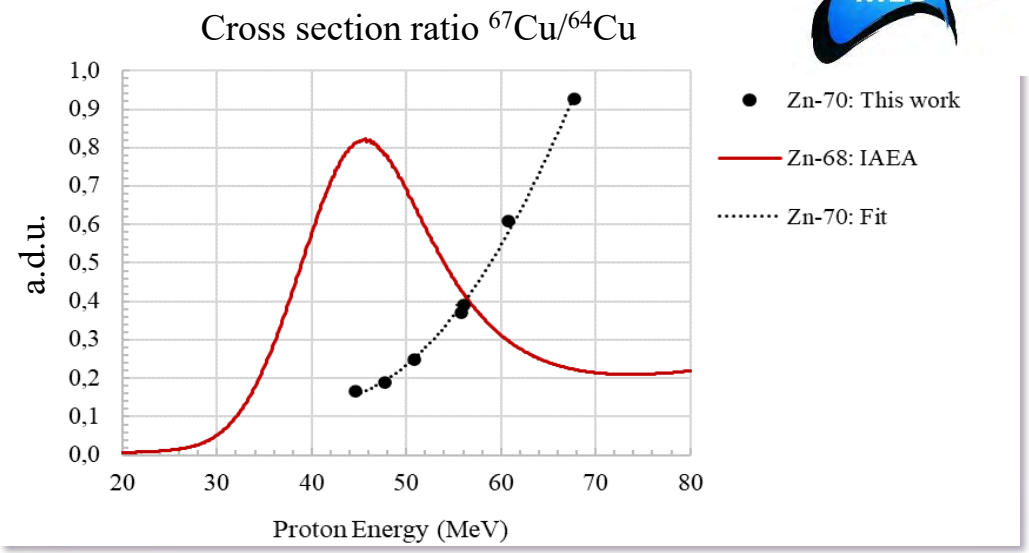
γ-ray [keV]	γ-ray [%]
184.6	48.7

THERAPY
Mean β^- : 141 keV

Nuclear cross section measurements of the $^{70}Zn(p,x)^{67}Cu,^{64}Cu$

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

COME (INFN, 2016)



"A method and a target for the production of ^{67}Cu"
Mou, Pupillo, Martini, Pasquali

International Patent n° WO 2019/220224 A1
November 2019

Sc-47
3.35 d
β^- : 100 %
(Ti-47)

SPECT

γ-ray [keV]	γ-ray [%]
159.4	68.3

THERAPY
Mean β^- : 162 keV

Nuclear cross section measurements of the $^{nat}V,^{48}Ti(p,x)^{47}Sc,^{xx}Sc$

PASTA (INFN, 2017-2018)
E_PLATE (INFN, 2018-2019)

G. Pupillo, L. Mou *et al.*, *Preliminary results of the PASTA project* (2019) Colloquia: EuNPC 2018, IL NUOVO CIMENTO 42 C 139

F. Barbaro *et al.*, *New results on proton induced reactions on Vanadium for ^{47}Sc production and the impact of level densities on t heoretical cross sections*, Physical Review C 2021

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

REMiX
(INFN, 2021-2023) Cross section measurements of $^{49,50}Ti(p,x)^{47}$**Sc** & **Tb-radionuclides**

Conclusions & perspectives

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

- **High potential impact** with the possibility to exploit both the ISOL and the DIRECT activation techniques at the INFN-LNL (70 MeV proton-cyclotron)

- **Wide national & international network** of collaboration (+ PRISMAP consortium)

Acknowledgements to all the people and the Institutions inolved.

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