CUPRUM-TTD (2023-25)

$^{67/64}$CU PRoduction and Use in Medicine – Target Technology Development

Padova, 26 Giugno 2025

INFN Istituto Nazionale di Fisica Nucleare
LABORATORI NAZIONALI DI LEGNARO

LARAMED

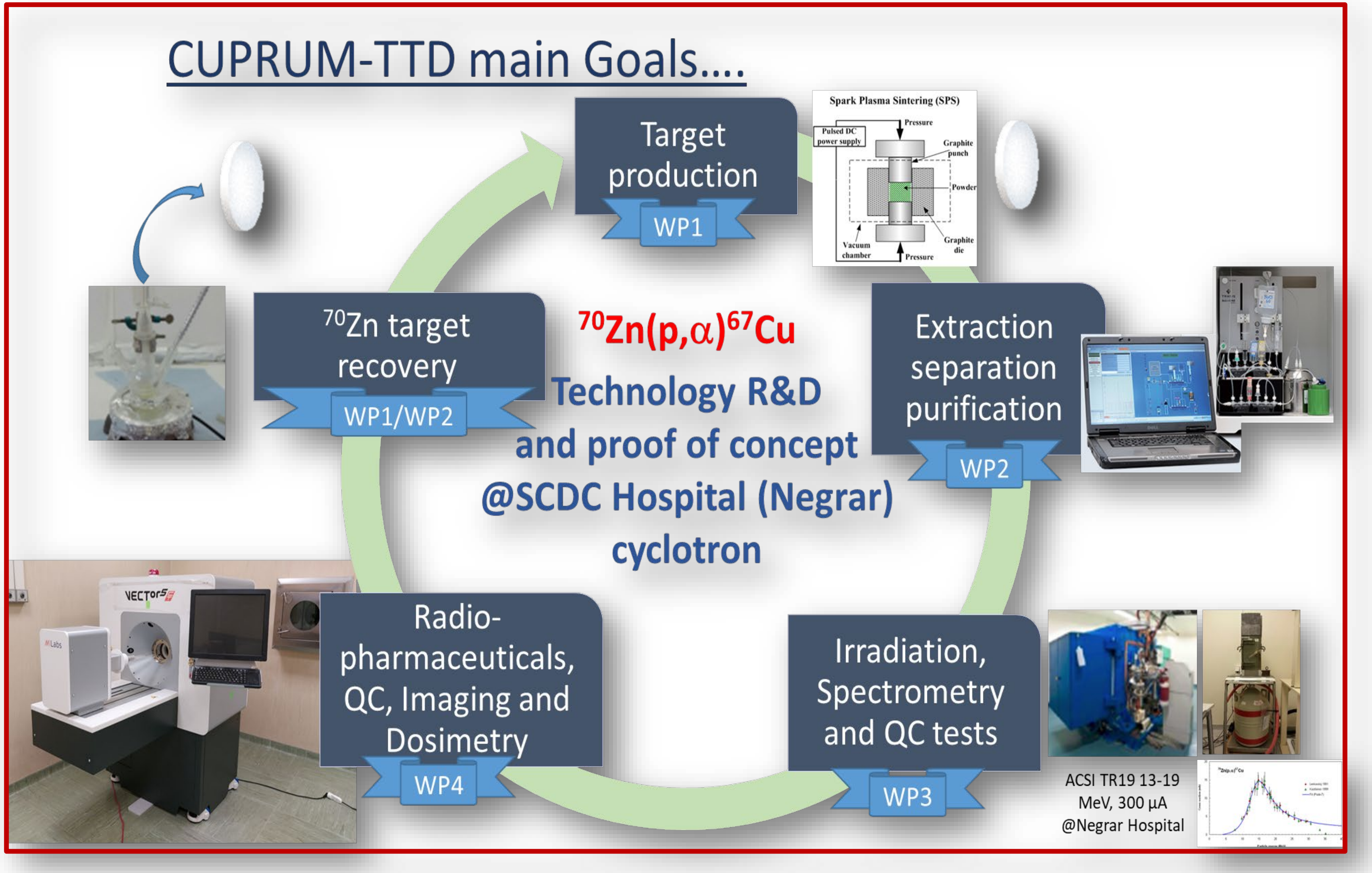
UNIVERSITÀ DI PAVIA

Università degli Studi di Ferrara

Università degli Studi di Padova

UNIVERSITÀ DEGLI STUDI DI MILANO

CUPRUM-TTD main Goals….



Target production
WP1

Extraction separation purification
WP2

Irradiation, Spectrometry and QC tests
WP3

Radio-pharmaceuticals, QC, Imaging and Dosimetry
WP4

^{70}Zn target recovery
WP1/WP2

$^{70}Zn(p,\alpha)^{67}Cu$

Technology R&D and proof of concept @SCDC Hospital (Negrar) cyclotron

ACSI TR19 13-19 MeV, 300 µA @Negrar Hospital

SACRO CUORE DON CALABRIA I R C C S

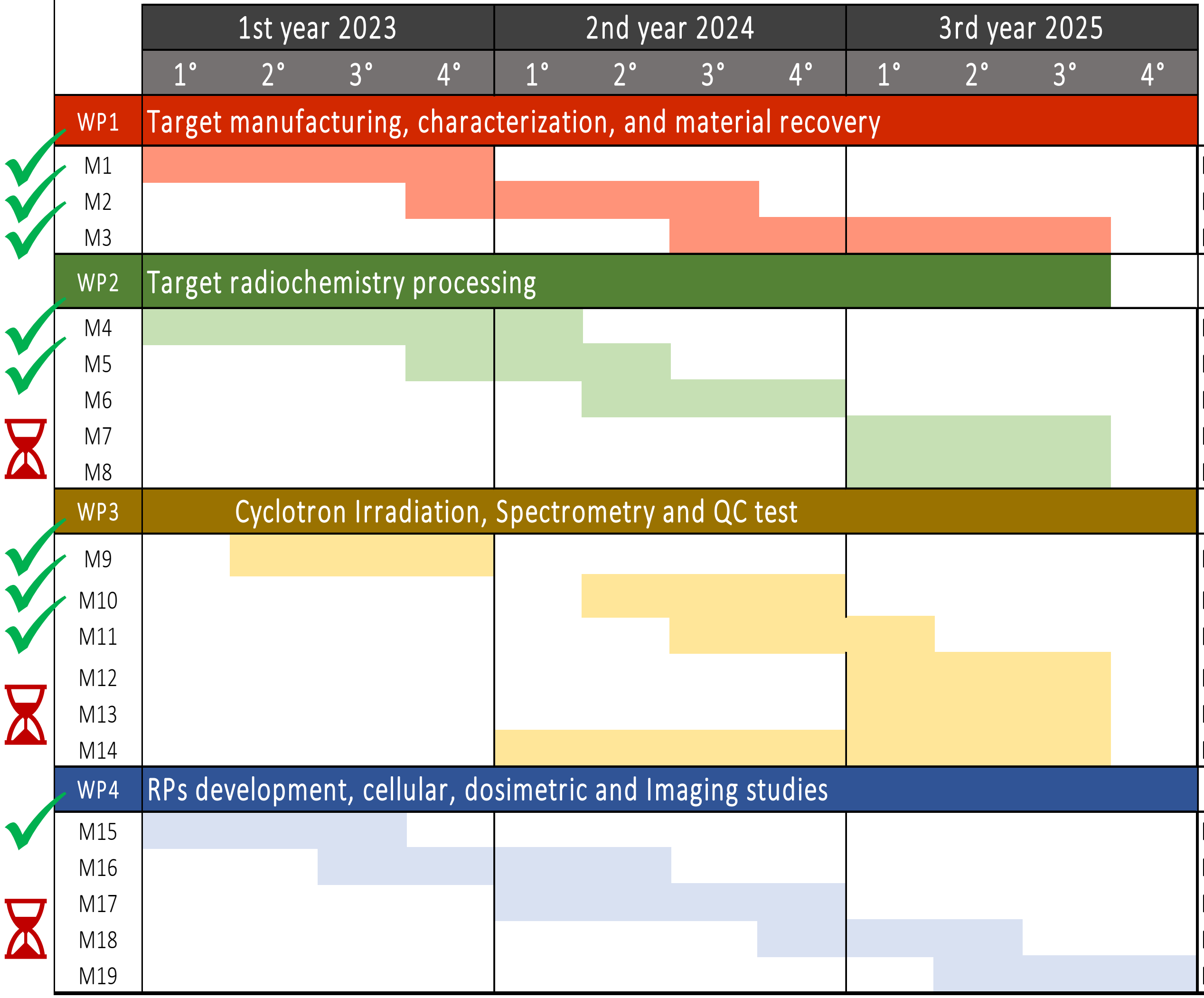
I.O.V. ISTITUTO ONCOLOGICO VENETO I.R.C.C.S.

ICMATE

CUPRUM-TTD Status attività 2025

GANTT chart

- Cronoprogramma del progetto CUPRUM_TTD (2023-2025)



		1st year 2023				2nd year 2024				3rd year 2025				
		1°	2°	3°	4°	1°	2°	3°	4°	1°	2°	3°	4°	
	WP1	Target manufacturing, characterization, and material recovery												
✓	M1	🟥	🟥	🟥	🟥									**M1:** SPS technique development for natZnO target manufacturing (Nb/Au/ZnO kind)
✓	M2				🟥	🟥	🟥	🟥						**M2:** recovery process development for natZnO, and material powders characterization (SEM, EDS, profilometer)
✓	M3							🟥	🟥	🟥	🟥	🟥		**M3:** target production with SPS technique starting from recovered natZnO;
	WP2	Target radiochemistry processing												
✓	M4	🟩	🟩	🟩	🟩	🟩								**M4** : development of separation and purification procedure using cold targets of natural ZnO
✓	M5				🟩	🟩	🟩							**M5** : development of a solid target dissolution reactor and optimization of automation of 6xCu separation,
	M6						🟩	🟩	🟩					**M6:** development of an automatic system for the separation and purification of Cu-67 from the target of ZnO and other contaminants,
⌛	M7									🟩	🟩	🟩		**M7** : productions tests of Cu-67 using enriched target and determination of the extraction yield and purity of the final product.
	M8									🟩	🟩	🟩		**M8:** Quality controls analysis on Cu-67 produced and isolated for pharmaceutical studies
	WP3	Cyclotron Irradiation, Spectrometry and QC test												
✓	M9		🟨	🟨	🟨									**M9** : ^{nat}ZnO targets irradiation for thermomechanical stability tests
✓	M10						🟨	🟨	🟨					**M10:** ^{nat}ZnO targets irradiations for radiochemical separation optimization
✓	M11							🟨	🟨	🟨				**M11:** perform γ-spectrometry measurements to estimate the efficiency of the radiochemical procedure (natZn targets)
⌛	M12									🟨	🟨	🟨		**M12:** three long irradiations for Cu-67 production on enriched ^{70}ZnO targets.
	M13									🟨	🟨	🟨		**M13:** perform γ-spectrometry measurements to estimate the activity and RNP of the 67Cu produced by irradiation of 70Zn targets
	M14					🟨	🟨	🟨	🟨	🟨	🟨	🟨		**M14:** xs measurements for alternative67-61 Cu nuclear reaction routes 64Ni(α,p)67Cu and 59Co(α,2n)61Cu
	WP4	RPs development, cellular, dosimetric and Imaging studies												
✓	M15	🟦	🟦	🟦										**M15** : synthesis and characterizatoin of NOTA-PSMA conjugates
	M16			🟦	🟦	🟦	🟦							**M16** : Radiolabeling and stability studies of synthetized conjugates
⌛	M17					🟦	🟦	🟦	🟦					**M17:** Determination of specific binding of Cu-PSMA RPs to PSMA receptors naturally expressed by PCa tumor cells, uptake % and internalization
	M18								🟦	🟦	🟦			**M18** : Determination of cell absorbed dose and the surviving fraction after the treatment with 6xCu-NOTA RPs
	M19										🟦	🟦	🟦	**M19** : Determination of contrast, sensitivity, and spatial resolution of the SPECT/PET imaging of the produced 64-67Cu

Richiesta prolungamento di un anno (3+1)

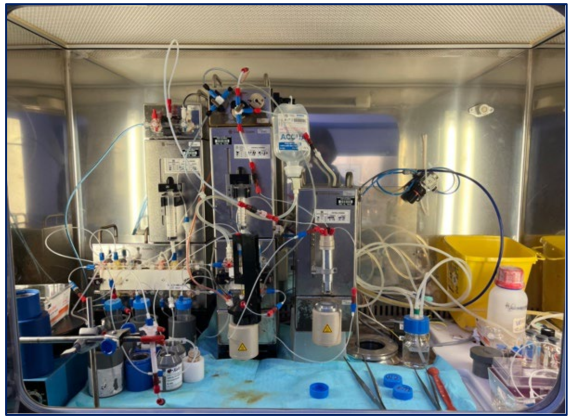
Motivazione: **due aspetti (milestone) chiave per il progetto** molto probabilmente non potranno essere raggiunti entro la fine del 2025.

1) L'esportazione (**trasporto autorizzato fino ai LNL**) del Cu67 che produrremo con i ns. bersagli al ciclotrone del IRCSS Sacro Cuore Don Calabria - SCDC di Negrar (VR)

Irraggiamento

ACSI TR19/300, SCDCH, Negrar

Separazione



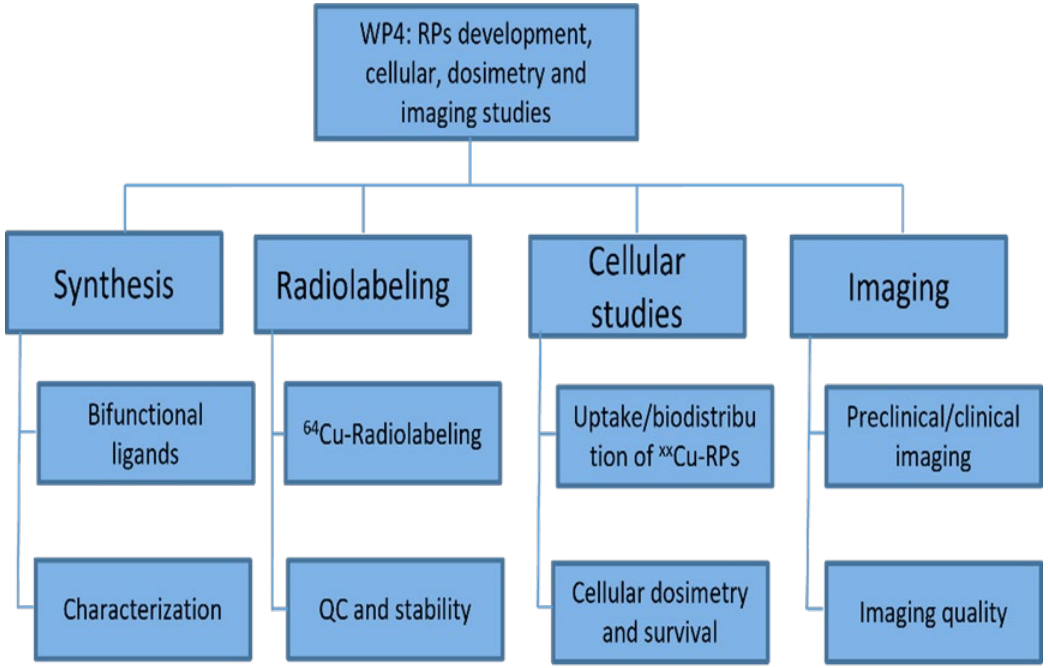
Moduli a cassetta per l'automazione del processo di separazione

→ ^{67}Cu → **trasporto autorizzato fino ai LNL** → **laboratorio LARIM ai LNL**

- Autorizzazione per <u>ottobre/novembre 2025?</u>

Richiesta prolungamento di un anno (3+1)

2) la possibilità di poter svolgere le attività pianificate al **laboratorio LARIM ai LNL**.



WP4: RPs development, cellular, dosimetry and imaging studies

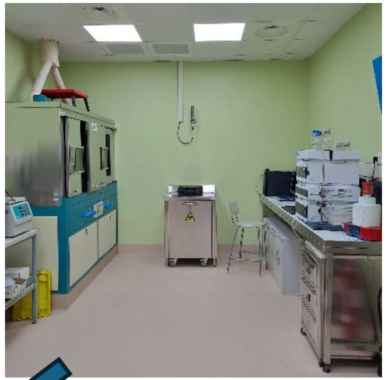
- Synthesis
  - Bifunctional ligands
  - Characterization
- Radiolabeling
  - ^{64}Cu-Radiolabeling
  - QC and stability
- Cellular studies
  - Uptake/biodistribution of ^{xx}Cu-RPs
  - Cellular dosimetry and survival
- Imaging
  - Preclinical/clinical imaging
  - Imaging quality

Le operazioni di collaudo impiantistico della macchina trattamento aria/depressurizzazione (UTA) del laboratorio LARIM **stanno impiegando molto più tempo del previsto**.

Seguirà poi la fase di verifica da parte dei VVF del comando di Padova per il rilascio del CPI, necessario per poter entrare in esercizio con uso di radioattivo.

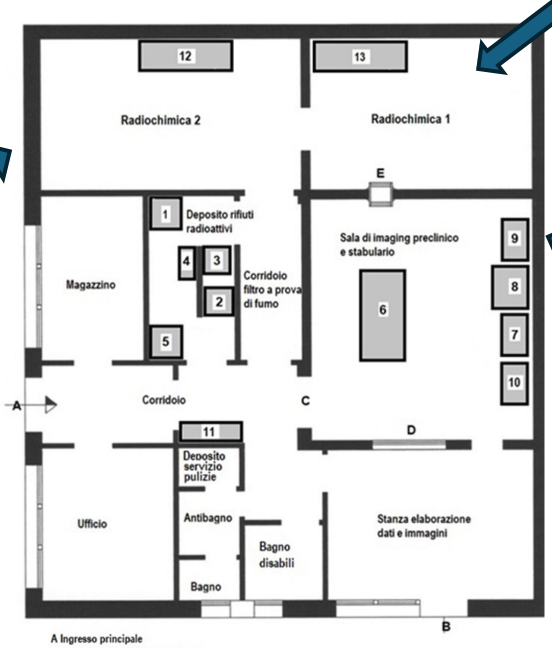
LARIM: Laboratory of Radionuclides and Molecular Imaging


Laboratorio radiochimica freddo


Laboratorio radiochimica caldo

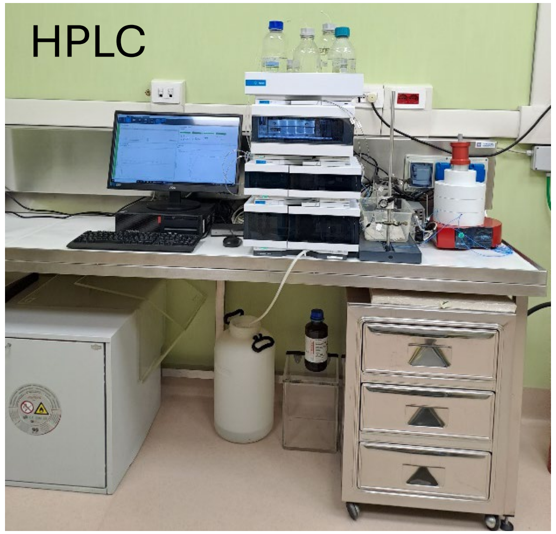

Cappa caldo


Cappa cellule



A Ingresso principale
B Entrata/Uscita materiali e animali
C Porta a chiusura automatizzata per accesso stanza di imaging preclinico e stabulario
D Finestra di vetro
E Passbox per il passaggio bidirezionale degli animali
1 Congelatore a -18 °C schermato
2 Armadio schermato
3 Doccia filtro
4 Lavello in acciaio con scarico controllato
5 Frigorifero combinato per prodotti chimici
6 Micro-tomografo preclinico PET/SPET/CT
7,9 Armadi ventilati per roditori
8 Cappa stazione di cambio Biohazard
10 Armadio stoccaggio gabbie pulite monouso
11 Angolo attrezzato uso spogliatoio
12 Cappa chimica dove gli animali saranno anestetizzati e iniettati con il radiofarmaco
13 Tavolo di acciaio inox dove saranno eseguiti gli espianti degli organi da cadavere

HPLC



Stanza PET


Small animal scanner:
MILABS Vector 5 CT

Stabulario topi

WP 1: Target manufacturing, characterization, and material recovery (WP2)

Responsabile WP1: Sara Cisternino

	1st year 2023				2nd year 2024				3rd year 2025			
	1°	2°	3°	4°	1°	2°	3°	4°	1°	2°	3°	4°
WP1	Target manufacturing, characterization, and material recovery											
M1	▨	▨	▨	▨								
M2				▨	▨	▨	▨					
M3							▨	▨	▨	▨	▨	

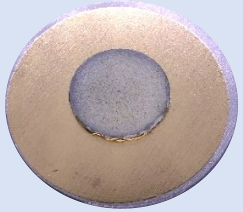
D1: no. 2-3 ZnO targets for surface analyses investigations (WP2);
D2: no. 5 ZnO targets for cold test chemical processing optimization (WP2);
D3: 3 ^{70}ZnO targets for production test;
D4: recovered ^{nat}ZnO powders.

✓ M1: SPS technique development for natZnO target manufacturing (Nb/Au/ZnO kind)
✓ M2: recovery process development for natZnO, and material powders characterization (SEM, EDS, profilometer)
✓ M3: target production with SPS technique starting from recovered natZnO;

Recycling process WP1 and WP2 powder

First Irradiation of recovered ZnO target:

New recovery processes



PLANNED

Targets ready to be tested under irradiation when IRCCS SCDC hospital will be available

SPS target manufacturing ***(efficiency 98%)***

- Thermomechanical tests: Irradiation @ medical cyclotron ***(18 MeV, 50 μA)***
- ^{61}Cu production

Dissolution (complete ZnO dissolution)

Recovery process ***(Yield 94%)***

Target with recovered powder

S. Cisternino, et al., Spark plasma sintering in manufacturing and recycling of ZnO targets for medical radioisotopes cyclotron-based production, Ceramics International (2025). https://doi.org/10.1016/j.ceramint.2025.04.262.

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Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali di Legnaro

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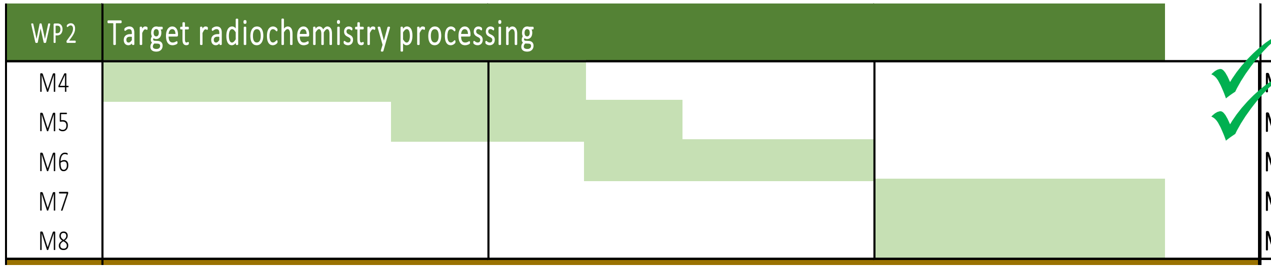
PLANNED D3: 3 ^{70}ZnO targets for production test

WP2 activities (Radiochemistry)

Responsabile WP2: Petra Martini



M4 : development of separation and purification procedure using cold targets of natural ZnO
M5 : development of a solid target dissolution reactor and optimization of automation of 6xCu separation,
M6: development of an automatic system for the separation and purification of Cu-67 from the target of ZnO and other contaminants,
M7 : productions tests of Cu-67 using enriched target and determination of the extraction yield and purity of the final product.
M8: Quality controls analysis on Cu-67 produced and isolated for pharmaceutical studies

2024

- Determine the best Zn/Ga/Cu chemical separation and purification with CU and TK201 resins
- Development of a semi-automatic module
- First radiochemical separation/purification procedures with irradiated with ^{nat}ZnO targets
- Cu-61 labeling studies DOTA/NODAGA-RGD
- ZnO recovery refinement

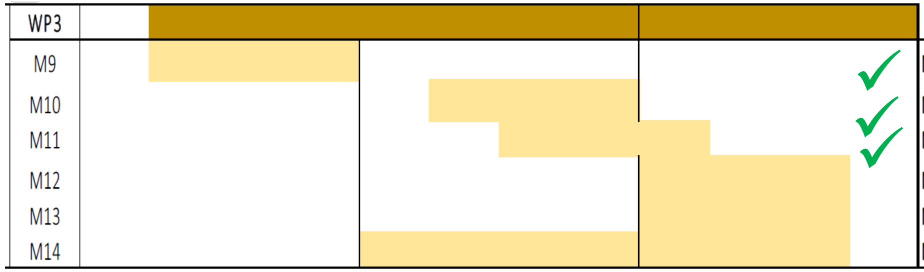
2025/2026 - <u>INFN - FE unit</u>

PLANNED

- Determination of recovery yield and quality
- Automation with the new module
- First ^{67}Cu production with enriched ^{70}ZnO target irradiation and processing
- Finalize the ZnO recovery with the new instruments
- Investigating Zn/Cu electrochemical separation
- Recovery of ZnO nanoparticles

WP2 activities (Radiochemistry) + irradiation WP3

Responsabile WP3: Liliana Mou



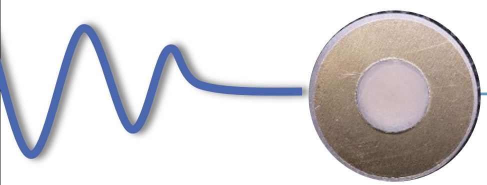
M9 : ${}^{nat}ZnO$ targets irradiation for thermomechanical stability tests
M10: ${}^{nat}ZnO$ targets irradiations for radiochemical separation optimization
M11: perform γ-spectrometry measurements to estimate the efficiency of the radiochemical procedure (natZn targets)
M12: three long irradiations for Cu-67 production on enriched ${}^{70}ZnO$ targets.
M13: perform γ-spectrometry measurements to estimate the activity and RNP of the 67Cu produced by irradiation of 70Zn targets
M14: xs measurements for alternative67-61 Cu nuclear reaction routes 64Ni(α,p)67Cu and 59Co(α,2n)61Cu

IRRAGGIAMENTO

${}^{64}Zn(p,\alpha){}^{61}Cu$

(Energia: 17,9 MeV; Corrente: variabile; Tempo: variabile)

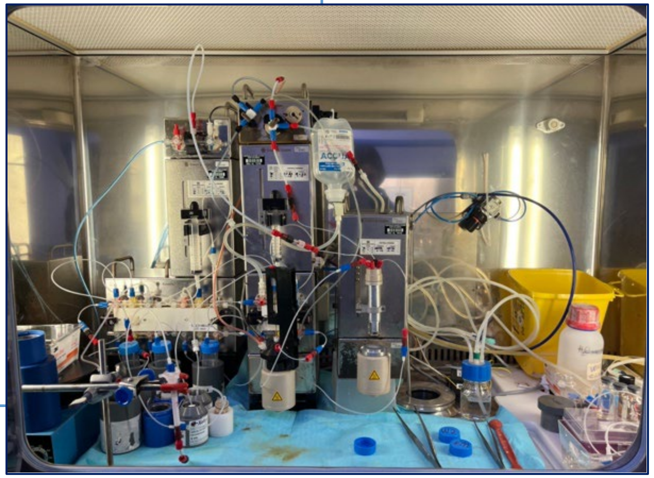
ACSI TR19/300, SCDCH, Negrar



${}^{nat}ZnO$

AUTOMAZIONE

REATTORE AUTOMATICO DI DISSOLUZIONE DEL TARGET SOLIDO



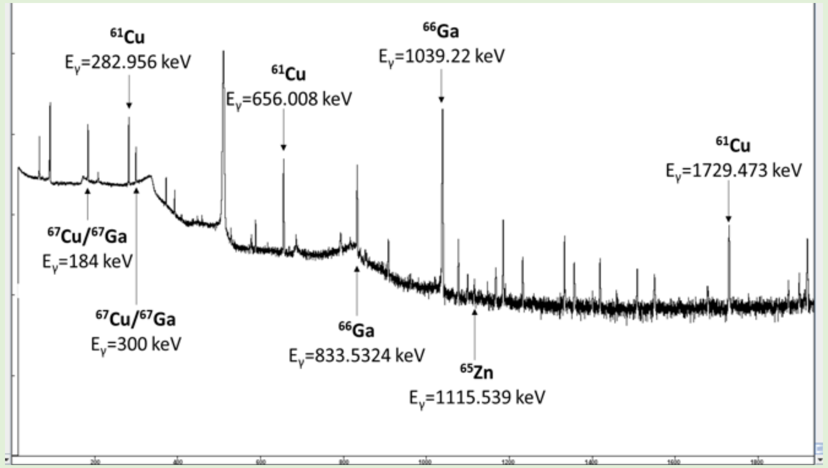
MODULI A CASSETTA PER L'AUTOMAZIONE DEL PROCESSO DI SEPARAZIONE

Campioni per analisi γ-spettrometrica

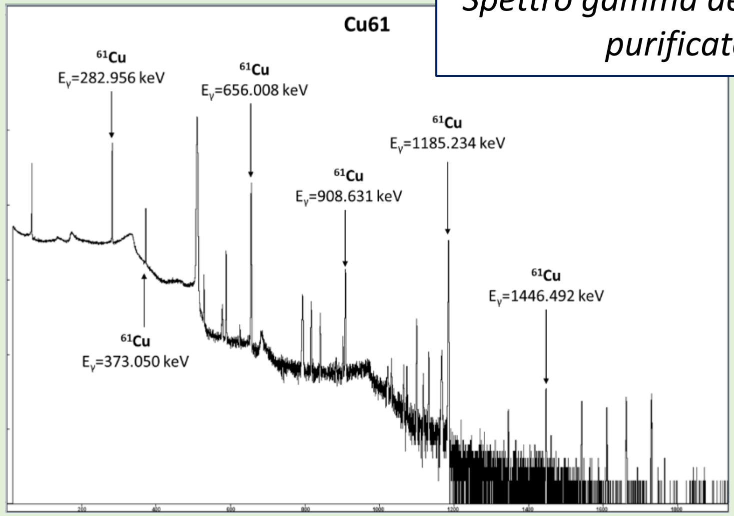
WP2 activities (Radiochemistry) + irradiation WP3

Gamma spectrometry

Spettro gamma del bersaglio post dissoluzione, prima del processo di purificazione

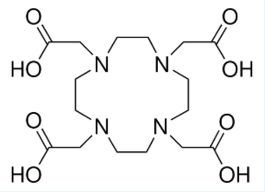


Spettro gamma del prodotto purificato

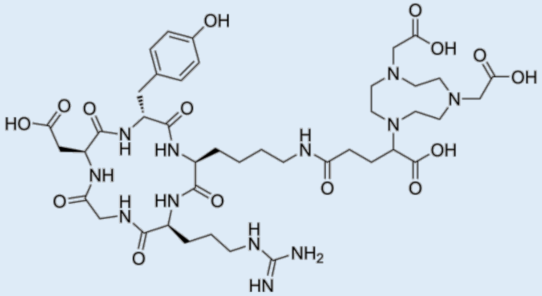


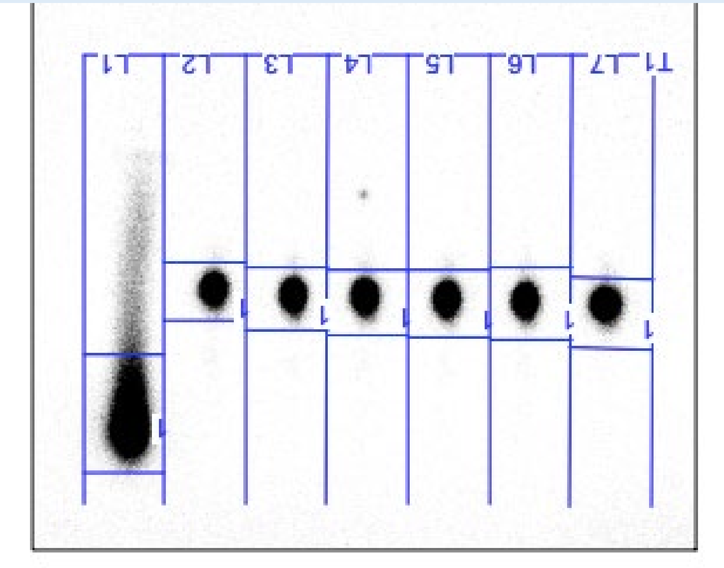
Labelling

DOTA



NODAGA-RGD

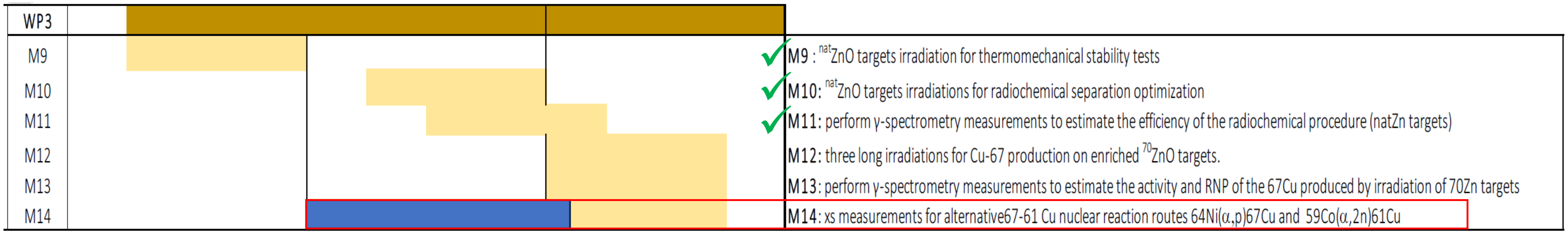




Condizioni:
95°C x 15 minuti.
TLC Al silica
Fase mobile: EtOH/NH4Ac 1:1

Resa > 99%

WP 3: xs measurements for alternative Cu67/Cu61 nuclear reaction route with alpha beams



WP3	
M9	✓ M9 : ^{nat}ZnO targets irradiation for thermomechanical stability tests
M10	✓ M10: ^{nat}ZnO targets irradiations for radiochemical separation optimization
M11	✓ M11: perform γ-spectrometry measurements to estimate the efficiency of the radiochemical procedure (natZn targets)
M12	M12: three long irradiations for Cu-67 production on enriched ^{70}ZnO targets.
M13	M13: perform γ-spectrometry measurements to estimate the activity and RNP of the 67Cu produced by irradiation of 70Zn targets
M14	M14: xs measurements for alternative67-61 Cu nuclear reaction routes 64Ni(α,p)67Cu and 59Co(α,2n)61Cu

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State of the activities

M14 is divided into two main activities:

- **^{59}Co(α,2n)^{61}Cu**: irradiation and analysis completed, article under internal revision, additional irradiations at low energy to be planned at CAS
- **^{64}Ni(α,p)^{67}Cu**: enriched material arrived at LASA, target and irradiations at CAS to be done

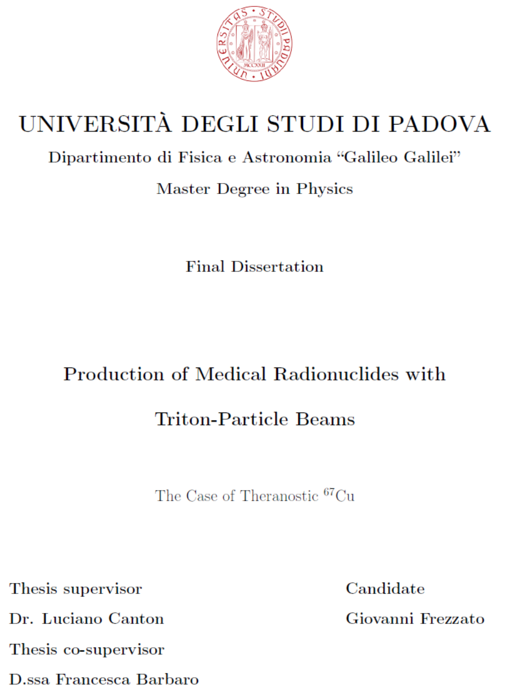
PLANNED

Irradiation at CAS is planned for September-December 2025.

WP3: theoretical activities on alternative nuclear reaction routes to yield ^{67}Cu

UniPD/INFN-PD
F. Barbaro
L. Canton
Y. Lashko

^{68}Zn(t,2n2p)^{67}Cu



UNIVERSITÀ DEGLI STUDI DI PADOVA
Dipartimento di Fisica e Astronomia "Galileo Galilei"
Master Degree in Physics

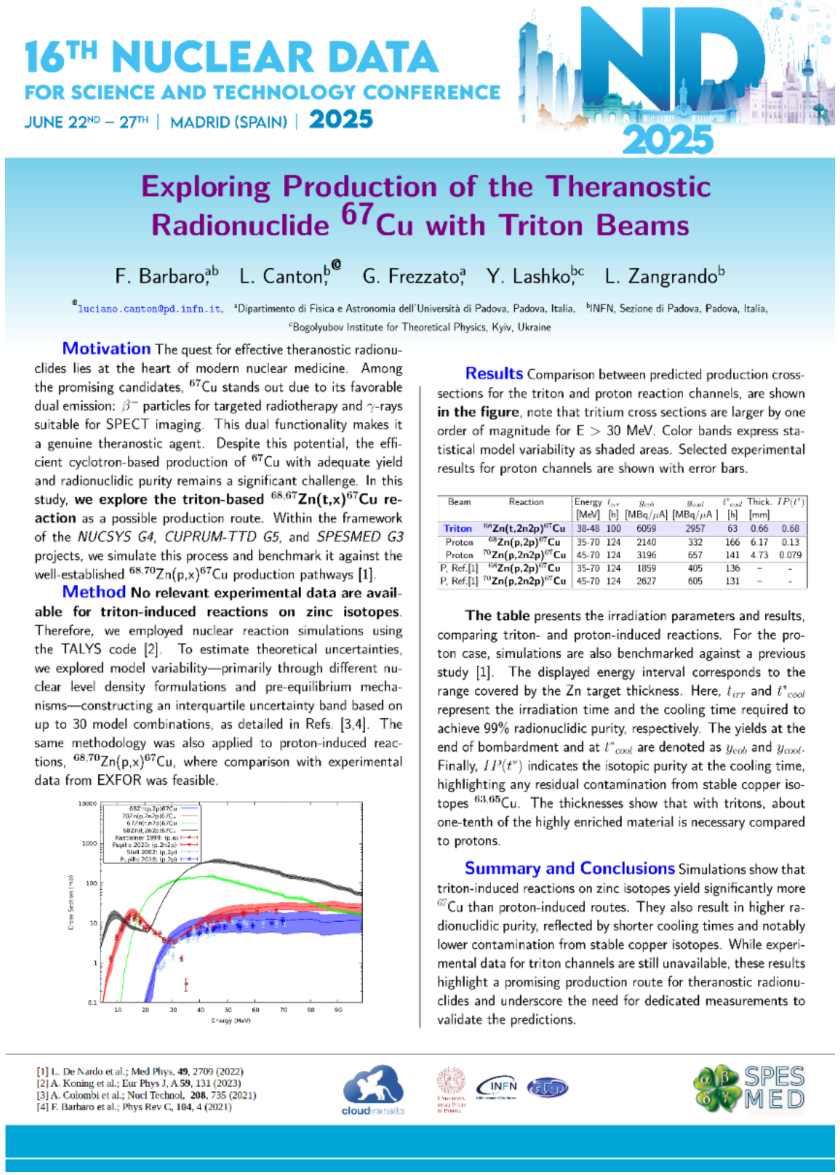
Final Dissertation

Production of Medical Radionuclides with
Triton-Particle Beams

The Case of Theranostic ^{67}Cu

Thesis supervisor	Candidate
Dr. Luciano Canton	Giovanni Frezzato
Thesis co-supervisor	
D.ssa Francesca Barbaro	

Academic Year 2023/2024



16TH NUCLEAR DATA
FOR SCIENCE AND TECHNOLOGY CONFERENCE
JUNE 22ND – 27TH | MADRID (SPAIN) | 2025

Exploring Production of the Theranostic Radionuclide ^{67}Cu with Triton Beams

F. Barbaro[a,b] L. Canton[b,@] G. Frezzato[a] Y. Lashko[b,c] L. Zangrando[b]

[@] luciano.canton@pd.infn.it, [a] Dipartimento di Fisica e Astronomia dell'Università di Padova, Padova, Italia, [b] INFN, Sezione di Padova, Padova, Italia, [c] Bogolyubov Institute for Theoretical Physics, Kyiv, Ukraine

Motivation The quest for effective theranostic radionuclides lies at the heart of modern nuclear medicine. Among the promising candidates, ^{67}Cu stands out due to its favorable dual emission: β^- particles for targeted radiotherapy and γ-rays suitable for SPECT imaging. This dual functionality makes it a genuine theranostic agent. Despite this potential, the efficient cyclotron-based production of ^{67}Cu with adequate yield and radionuclidic purity remains a significant challenge. In this study, **we explore the triton-based ^{68,67}Zn(t,x)^{67}Cu reaction** as a possible production route. Within the framework of the *NUCSYS G4*, *CUPRUM-TTD G5*, and *SPESMED G3* projects, we simulate this process and benchmark it against the well-established ^{68,70}Zn(p,x)^{67}Cu production pathways [1].

Method **No relevant experimental data are available for triton-induced reactions on zinc isotopes**. Therefore, we employed nuclear reaction simulations using the TALYS code [2]. To estimate theoretical uncertainties, we explored model variability—primarily through different nuclear level density formulations and pre-equilibrium mechanisms—constructing an interquartile uncertainty band based on up to 30 model combinations, as detailed in Refs. [3,4]. The same methodology was also applied to proton-induced reactions, ^{68,70}Zn(p,x)^{67}Cu, where comparison with experimental data from EXFOR was feasible.

Results Comparison between predicted production cross-sections for the triton and proton reaction channels, are shown **in the figure**, note that tritium cross sections are larger by one order of magnitude for E > 30 MeV. Color bands express statistical model variability as shaded areas. Selected experimental results for proton channels are shown with error bars.

Beam	Reaction	Energy [MeV]	t_{irr} [h]	y_{eob} [MBq/μA]	y_{cool} [MBq/μA]	t^*_{cool} [h]	Thick. [mm]	$IP(t^*)$
Triton	^{68}Zn(t,2n2p)^{67}Cu	38-48	100	6059	2957	63	0.66	0.68
Proton	^{68}Zn(p,2p)^{67}Cu	35-70	124	2140	332	166	6.17	0.13
Proton	^{70}Zn(p,2n2p)^{67}Cu	45-70	124	3196	657	141	4.73	0.079
P, Ref.[1]	^{68}Zn(p,2p)^{67}Cu	35-70	124	1859	405	136	–	-
P, Ref.[1]	^{70}Zn(p,2n2p)^{67}Cu	45-70	124	2627	605	131	–	-

The table presents the irradiation parameters and results, comparing triton- and proton-induced reactions. For the proton case, simulations are also benchmarked against a previous study [1]. The displayed energy interval corresponds to the range covered by the Zn target thickness. Here, t_{irr} and t^*_{cool} represent the irradiation time and the cooling time required to achieve 99% radionuclidic purity, respectively. The yields at the end of bombardment and at t^*_{cool} are denoted as y_{eob} and y_{cool}. Finally, $IP(t^*)$ indicates the isotopic purity at the cooling time, highlighting any residual contamination from stable copper isotopes ^{63,65}Cu. The thicknesses show that with tritons, about one-tenth of the highly enriched material is necessary compared to protons.

Summary and Conclusions Simulations show that triton-induced reactions on zinc isotopes yield significantly more ^{67}Cu than proton-induced routes. They also result in higher radionuclidic purity, reflected by shorter cooling times and notably lower contamination from stable copper isotopes. While experimental data for triton channels are still unavailable, these results highlight a promising production route for theranostic radionuclides and underscore the need for dedicated measurements to validate the predictions.

[1] L. De Nardo et al.; Med Phys, **49**, 2709 (2022)
[2] A. Koning et al.; Eur Phys J, A **59**, 131 (2023)
[3] A. Colombi et al.; Nucl Technol, **208**, 735 (2021)
[4] F. Barbaro et al.; Phys Rev C, **104**, 4 (2021)

Beam	Reaction	Energy [MeV]	t_{irr} [h]	y_{eob} [MBq/μA]	y_{cool} [MBq/μA]	t^*_{cool} [h]	Thick. [mm]	$IP(t^*)$
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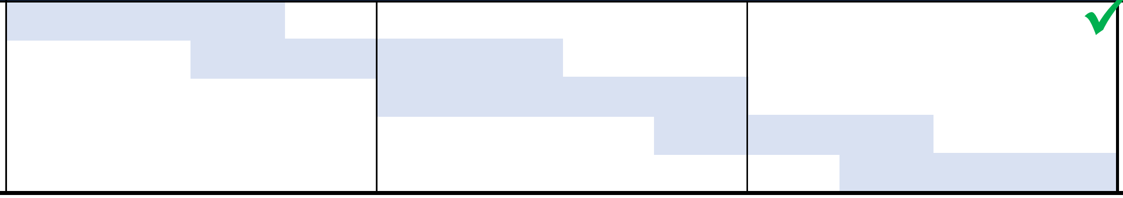
WP4 : RPs development, cellular, dosimetry and Imaging studies

Responsabile WP4: Laura De Nardo/Laura Melendez

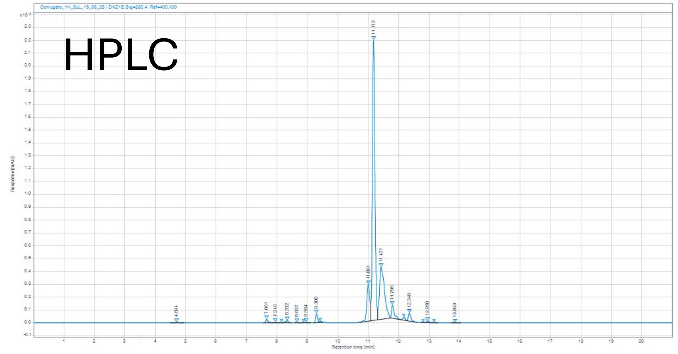
Università degli Studi di Padova

Istituto Oncologico Veneto I.R.C.C.S



WP4	RPs development, cellular, dosimetric and Imaging studies	
M15		✓ M15 : synthesis and characterizatoin of NOTA-PSMA conjugates
M16		M16 : Radiolabeling and stability studies of synthetized conjugates
M17		M17: Determination of specific binding of Cu-PSMA RPs to PSMA receptors naturally expressed by PCa tumor cells, uptake % and internalization
M18		M18 : Determination of cell absorbed dose and the surviving fraction after the treatment with 6xCu-NOTA RPs
M19		M19 : Determination of contrast, sensitivity, and spatial resolution of the SPECT/PET imaging of the produced 64-67Cu

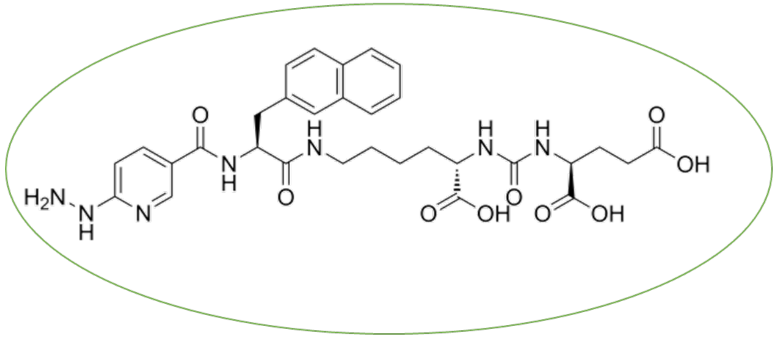
RP activities (Synthesis of new conjugates)



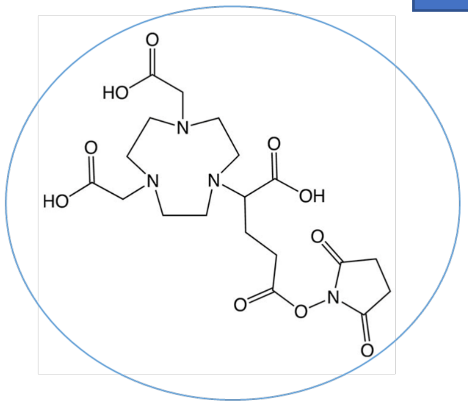
MOLAR RATIO iPSMA:NODAGA

1 : 0.9

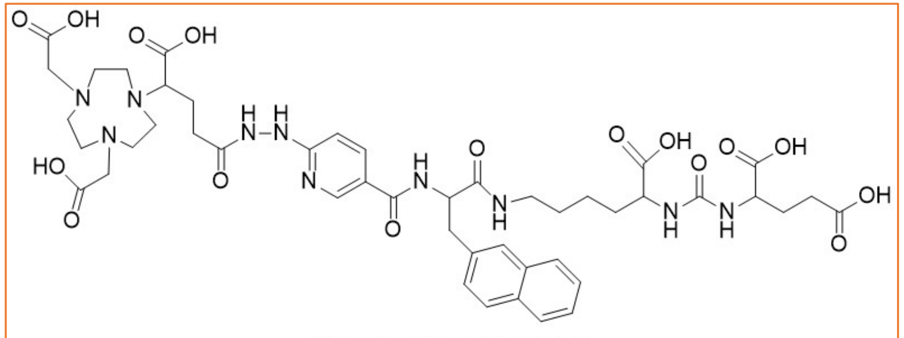
37 °C for 1.5 h in DMF and 5% DIPEA



iPSMA



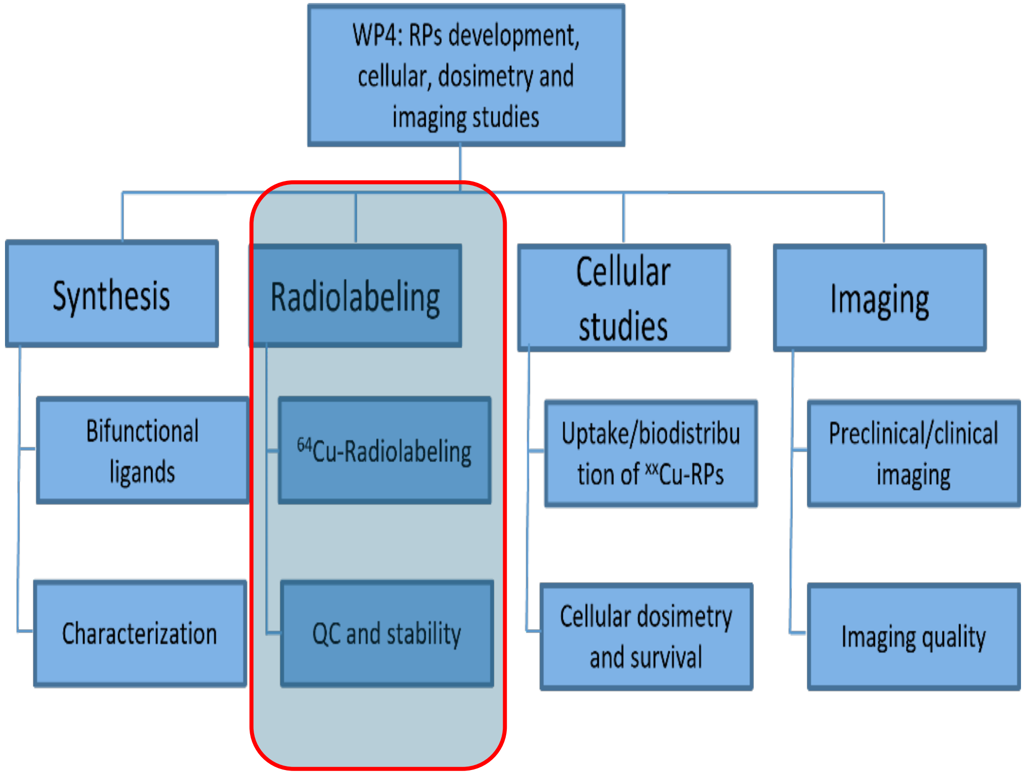
NODA-GA-NHS



Molecular Weight: 1009.04

iPSMA-NODAGA conjugate

WP4 : RPs development, cellular, dosimetry and Imaging studies



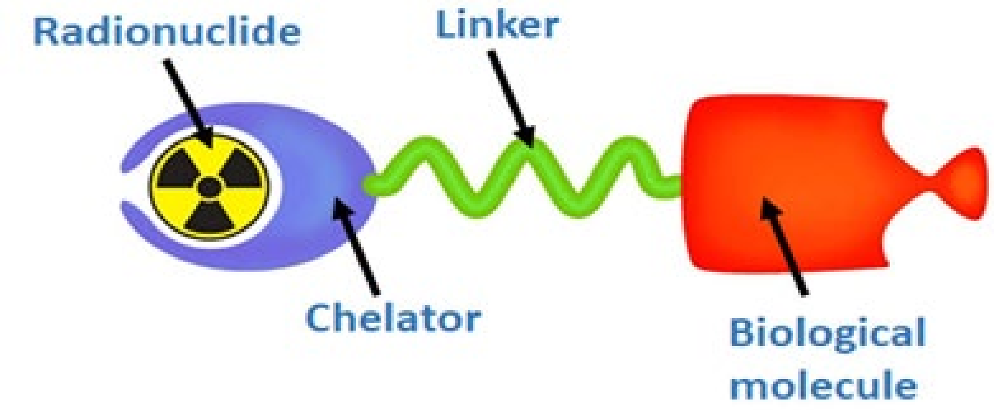
WP4: RPs development, cellular, dosimetry and imaging studies

Synthesis
- Bifunctional ligands
- Characterization

Radiolabeling
- ^{64}Cu-Radiolabeling
- QC and stability

Cellular studies
- Uptake/biodistribution of ^{xx}Cu-RPs
- Cellular dosimetry and survival

Imaging
- Preclinical/clinical imaging
- Imaging quality

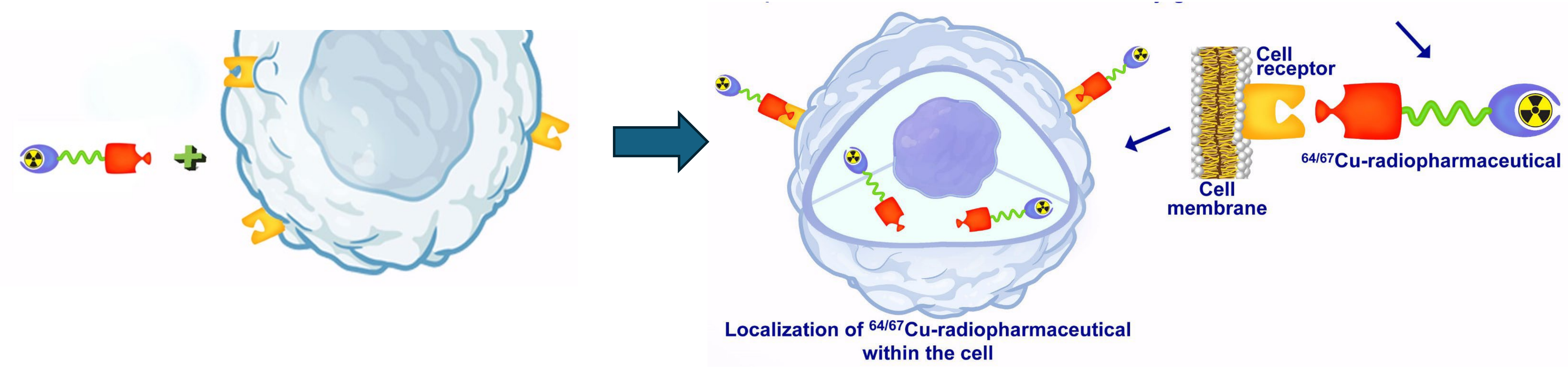


⌛ Radiolabeling

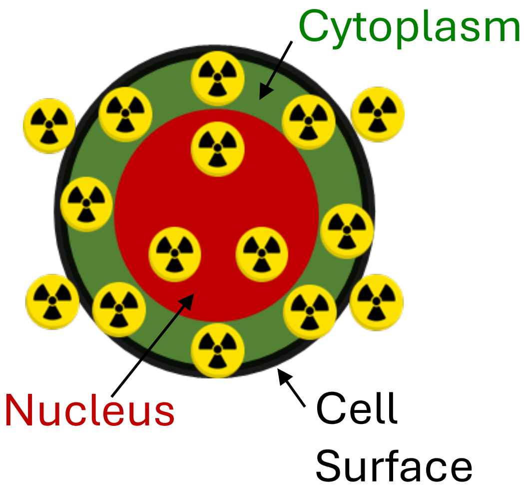
Cu-64

Cu-67 Not yet available

WP4 : cellular dosimetry



- Cellular dosimetry calculations require evaluation of specific uptake and internalization in both PSMA-positive and –negative PCa cells.


Cytoplasm

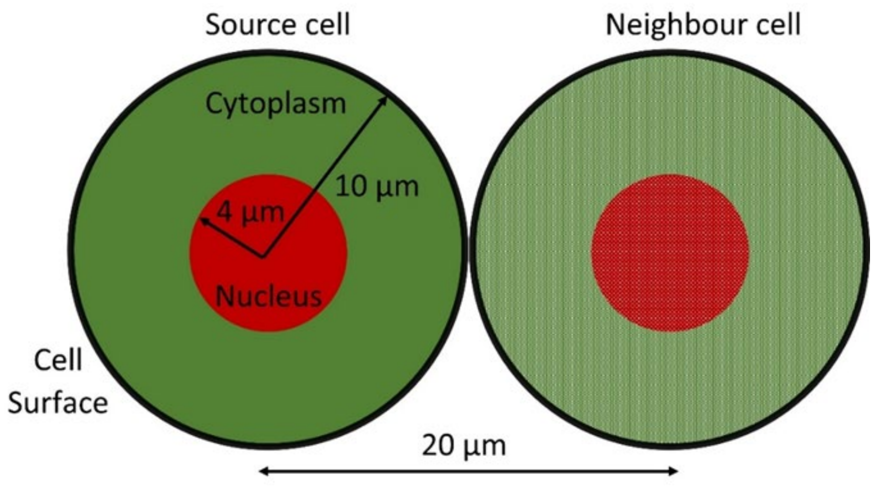
Nucleus

Cell Surface

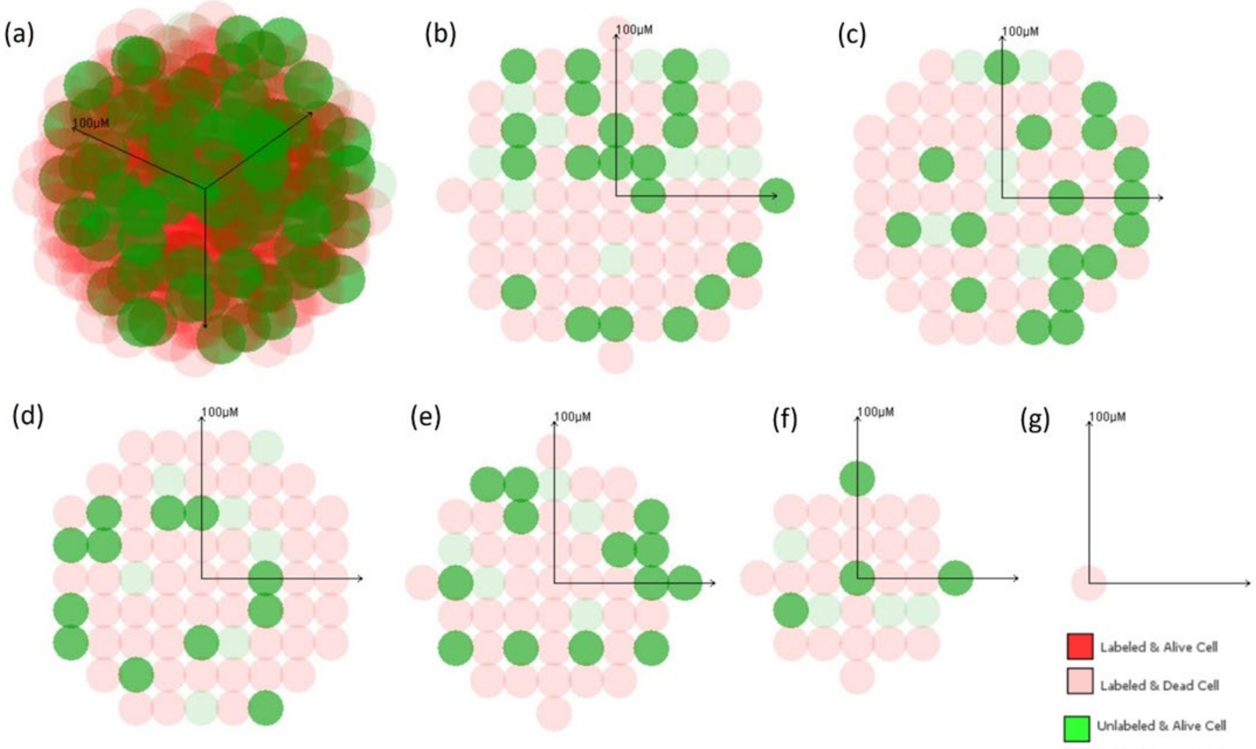
WP4 : cellular dosimetry calculations

- **Preliminary calculations** with ^{67}Cu and ^{64}Cu performed with the MIRDCell software in tumour models represented as isolated spheres of water density with a uniform distribution of radioactivity or as spherical clusters of cells by assuming different:
- subcellular distribution of radionuclides (100% in Cytoplasm, Nucleus or Cell Surface)
- cluster cell dimension ($r_{cluster}$= 50, 150, 290, 625, 1350 µm)
- percentage of labelled cells (10, 30, 50, 80, 100%)

➢ **Article in publication (Cellular and Multicellular Dosimetry of two copper radioisotopes: ^{67}Cu and ^{64}Cu)**



1D Cell model



3D spherical cell cluster model

CUPRUM-TTD Padova: richieste finanziarie e FTE

INFN-PD	FTE
De Nardo L. (R. Loc)	0.80
Canton L.	0.20
Bolzati C.	0.20
Paiusco M.	0.20
Zorz A.	0.20
Barbaro F.	?

Sezioni / Lab	Missioni	Consumo/ Altri consumo	Tot. per sez/lab	FTE previsto
PD	1.0	5.5**	**6,5**	**1.60**

**richiesta riassegnazione

Consumables: 64Cu to radiolabel the developed Radiopharmaceuticals (2x10mCi) (3 keuro)
Solvents for HPLC analysis, reagents for stability test, buffers and cell culture media, Sep-Pack cartridges for radiopharmaceutical purification (2.5 Keuro).