

Laboratori Nazionali di Legnaro - INFN

A new CSN5 experiment proposal

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Radiopharmaceutical frame





PES exotic beams



Experiments: why ¹¹¹Ag?



¹¹¹Ag properties

- **β⁻ emitter** (average energy **360 keV**)
- Good half-life (**7.45 days**)
- Average tissue penetration (1.8 mm)
- Medium energy γ rays -> SPECT?

 \rightarrow In the market no radiopharmaceuticals radiolabeled with silver-111

- ightarrow Silver-111 can be produced @ SPES with high purity & high production rate
- \rightarrow No isobaric radioactive contamination in the implantation foil (also with LASER off!)
- ightarrow ¹¹¹Ag exhibits theranostic properties similar to ¹⁷⁷Lu which was recently approved by FDA
- \rightarrow ¹¹¹Ag behaves similarly to ¹⁸⁶Re, recently studied in phase I/II clinical trials







ISOLPHARM: over 10 years of activity







ISOLPI IARM EIRA



Interdisciplinary study group on production of medical radioisotopes at SPES

Simulations and feasibility evaluation of Ag as radiopharmaceutical precursor

First production of ¹¹¹Ag in reactor and beginning of *in-vitro* and *in-vivo* testing

Characterizing the 2D/3D *in-vitro* therapeutic effect of ¹¹¹Ag and its imaging capabilities First nuclear measurements of radionuclide

production at SPES

Technological aspects of radionuclide production (target, ion source, implantation...)







Collaboration infrastructures





























First nuclear measurements at SPES financed by INFN-CSN3!



Work packages

- 1) Cross-section measurements (LARAMED project)
- 2) ISOL production yield measurements (ISOLPHARM project)
- 3) Theory and simulations



The SPES_MED scenario



WP2 aim: measuring the **ISOL production yields of radiotracers** with applications in biology, medicine, environment, industry.

2025: ²⁴Na and ⁷Be from SiC target (currently out of SPES_MED)
2026: ²⁸Mg from SiC target (low activity expected)
2027: ⁵¹Cr (low activity expected), ⁴³K from TiC target + ¹¹¹Ag from UC_x



High-production nuclides could be used in a CSN5 experiment!



Radiobiology lab at LNL?



Open questions after ADMIRAL



- 1) Which are the radiobiological advantages of $^{111}\mbox{Ag}$ with respect to other β^{-} emitters?
- 2) Can ¹¹¹Ag be used in radiopharmaceutical therapy against prostatic tumors with PSMA-617 (already used with ¹⁷⁷Lu) as a targeting agent?
- 3) Can its γ imaging be used in a SPECT?
- 4) Can its β imaging be used for cell uptake measurements?
- 5) Can the SPES_MED nuclides provide interesting radiobiological data?



ISOLPHARM_APEX (2026-2028)



IS LPHARM_APEX

¹¹¹Ag-PSMA-617 EXperiments



Radionuclide production at LENA and SPES

Main goals

- Understanding the dosimetry of ¹¹¹Ag-PSMA-617 in living systems such as cells, small animals and human patients.
- 2) Studying this radiopharmaceutical in cancer cell cultures in 2D monolayers and in 3D tissue-mimicking scaffolds.
- 3) Observing the biodistribution and the effects of theranostic ¹¹¹Ag-PSMA-617 on small animals.
- 4) Investigating the radiobiological response to low-doserate radiation using the first nuclides obtainable at SPES.

IS LPHARM The long road to (radio)pharmaceuticals







WP1 – SILICO



- Computational dosimetry at cell and organ level
- Survival models and DNA damage study
- Monte Carlo simulations for imaging prototypes



















Silico for vitro

Silico for vivo





Cell shape and dimensions are retrieved from microscopy via image-processing software.

Monte Carlo simulations compute the absorbed dose per activity unit (*S-value*) and the consequent **DNA damage**.



Biophysical models help understanding the **dose-rate curve** and the **DNA repair dynamics**.





Simulations can provide organ S-values for treatment plans as well as imaging previews to tune the devices.



WP2 – VITRO









DNA damage and cell survival



3D tissue-mimicking scaffolds are optimized for the cell lines under study.



Cell death and vitality are evaluated by means of **clonogenic survival assays**.



2D/3D **foci assays** visualize the real-time DNA damage imparted by the treatment.

Uptake measurements



The **uptake** of radiopharmaceutical is generally evaluated with γ counters analyzing pellets of cells and is fundamental for dosimetric assessments.



High-resolution **β imagers** allow to discriminate membrane and cytoplasm absorption and can be used on 3D scaffolds.



WP2 – VITRO





The CMOS camera

Glioblastoma cells imaging



Brightfield image



Positron image



WP3 – VIVO



- Biodistribution ex vivo of ¹¹¹Ag-PSMA-617
- Preclinical experiments *in vivo* with ¹¹¹Ag-PSMA-617 and ¹⁷⁷Lu-PSMA-617 for comparison
- \circledast γ imaging and radiomics



















Preclinical experiments



The **ex-vivo biodistribution** is preliminarily evaluated with free, chelated and targeted nuclide in healthy mice.



transfected with tumors expressing or not expressing the target receptor.



Imaging and radiomics







The real-time biodistribution can be visualized via 2D **autoradiography** and 3D **PET/CT** or **SPECT/CT** imaging; a ¹¹¹Ag-tailored **\gamma** camera is also available from ADMIRAL.







Large field-of-view full-ring stationary detectors for magnified PET- SPECT

MiLabs SPECT/CT/OI

Stationary multi-pinhole SPECT

Variable magnification microCT

Optical imaging

2D fluorescence/bioluminescence/ cherenkov

3D FLT/BLT



EUROBBIOIMAGING

See-Life Laboratorio di Imaging Biomedico









See-Life Laboratorio di Imaging Biomedico





Multi-pinhole concept



Freek J. Beekman et al., Journal of Nuclear Medicine Jul 2005, 46 (7) 1194-1200;





See-Life Laboratorio di Imaging Biomedico





Gantt diagram



		Year 1				Yea	ır 2			Year 3			Notes			
		М3	M6	M9	M12	M15	M18	M21	M24	M27	M30	M33	M36	Required for	Publications	Divisions
	WP1 – SILICO (leader: S. Bortolussi)															
T1.1	Image-based Monte Carlo dosimetry for prostate cancer cells	Ť												T2.1-T2.6	А, В	LNL, PD, PV
T1.2	Internal Monte Carlo dosimetry of biodistribution study with healthy mice	\rightarrow												T3.5	С	LNL, PD, PV
T1.3	Internal Monte Carlo dosimetry of biodistribution study with tumor-bearing mice					\rightarrow								T1.5, T3.6	D	LNL, PD, PV
T1.4	Biophysical model validation with radiobiological data			\rightarrow											Α	LNL, PD
T1.5	Dosimetric planning for preclinical trials with tumor-bearing mice and dosiomics							\rightarrow						T3.6	E	LNL, PD, PV
T1.6	Validation of DNA damage models using radiobiological data and Geant4-DNA							\rightarrow							F	LNL, PD
T1.7	Preliminary dosimetric predictions for human patients										\rightarrow				E	LNL, PD, PV
	WP2 – VITRO (leader: D. Maniglio)															
T2.1	2D radiobiology of Ag-111-PSMA-617 on prostate cancer cells	\rightarrow												T1.4	Α	PV
T2.2	2D radiobiology of Lu-177-PSMA-617 on prostate cancer cells	\rightarrow												T1.4	Α	LNS
T2.3	eta imaging of 2D cell culture uptake	\rightarrow												T2.1	A	FD, PI
T2.4	3D radiobiology of Ag-111-PSMA-617 on prostate cancer cells					\rightarrow									В	PV, TIEPA
T2.5	Microscopy and eta imaging of 3D cell culture uptake					\rightarrow								T2.4, T2.6	В	TIFPA, PD, PI
T2.6	3D radiobiology of Ag-111-PSMA-617 on prostate cancer cells in bioreactor									\rightarrow					В	PV, TIFPA
T2.7	2D radiobiology of SPES radionuclides							\rightarrow						T1.6	F	LNL
	WP3 – VIVO (leader: F. P. Cammarata)															
T3.1	Authorization request to work with Ag-111 in mice at CAPiR and CISUP	\rightarrow												T3.4-T3.6	-	PI, LNS
T3.2	γ camera and SPECT imaging of Ag-111 in phantoms			Pub	licatio	n/reno	rt sche	dule						T3.7	G	BO, PI
T3.3	ARG imaging improvement using the γ camera collimator	Inc	dex		meatro	ii) iepo	Them							T3.4-T3.6	G	BO, LNS
T3.4	γ imaging and <i>ex vivo</i> biodistribution study of Ag-111-PSMA-617 in healthy mice				2D rad	iobiolo	gy of A	z-111-6	PSMA-	517				T1.2	с	LNS, PI, LNL
T3.5	γ imaging and <i>ex vivo</i> biodistribution study of Ag-111-PSMA-617 in tumor-bearing mice		A 2027 2D radiobiology of Ag-111-PSMA-617 B 2029 3D radiobiology of Ag-111-PSMA-617						T1.3	D	LNS, PI, LNL					
T3.6	Preclinical experiments and γ imaging using Ag-111-PSMA-617 on tumor-bearing mice		C 2027 Biodistribution in healthy mice					\bullet	T1.7, T3.7	E	LNS, PI, BO					
T3.7	Radiomic features evaluation from SPECT/CT of preclinical studies		D 2028 Biodistribution in tumor-bearing mice		nice					н	LNS					
\rightarrow	Activity started		E 2	2029	Preclin	ical tria	als of A	g-111-6	PSMA-	517						
	Deliverable/milestone reached	1	F 2029 Validation of DNA damage models		ls											
-		' 🗖	G i	2029	Scinti	graphy	with A	g-111	y came	ra						
			н :	2029			Radiom	nics								



Endorsement of hospitals





Santa Maria Nuova Cannizzaro (Catania) IRST D. Amadori (Meldola, FC) IFC-CNR Pisa Spedali Civili (Brescia) (Reggio Emilia)



Pisa prospect



	Pisa										
	Name	WP	FTE	Status							
UNIPI	Nicola Belcari (PI local resp.)	2, 3	0.4	Experimental physicist, associate professor at UNIPI							
UNISI	Emilio Mariotti	3	0.1	Experimental physicist, associate professor at UNISI							
UNIPI	Giancarlo Sportelli	2, 3	0.3	Experimental physicist, associate professor at UNIPI							
IFC-CNR	Luca Menichetti	3	0.2	Radiochemist, CNR researcher							
IFC-CNR	Daniele Panetta	3	0.2	Medical physicist, CNR researcher							
	Total PI FTE		1.2	T=0; R=1.2							

	Pisa									
Туре	ID	Item	WP	Year 1 [k€]	Year 2 [k€]	Year 3 [k€]	Total			
	17	Laboratory material	3	1	1	1	3			
Consumables	18	New components for β detector	2	1	0	0	1			
	19	Mice for in-vivo experiments	3	2	5	5	12			
Services	rvices 20 Access to the Eurobioimaging facility		3	2	3	3	8			
Shipping	Shipping 21 Shipping of Ag-111, etc.		3	1	1	1	3			
Travels 22 Travels for experimental activity				1	1	1	3			
	Total PI 8 11 11 30									



Pisa prospect



	Pisa										
	Name	WP	FTE	Status							
UNIPI	Nicola Belcari (PI local resp.)	2, 3	0.4	Experimental physicist, associate professor at UNIPI							
UNISI	Emilio Mariotti	3	0.1	Experimental physicist, associate professor at UNISI							
UNIPI	Giancarlo Sportelli	2, 3	0.3	Experimental physicist, associate professor at UNIPI							
IFC-CNR	Luca Menichetti	3	0.2	Radiochemist, CNR researcher							
IFC-CNR	Daniele Panetta	3	0.2	Medical physicist, CNR researcher							
	Total PI FTE		1.2	T=0; R=1.2							

Altre richieste di servizi in sezione

- Laboratorio di Alte tecnologie (2 settimane anno)
- Progettazione meccanica / prototipazione (2 settimane anno)







WP1 – SILICO

Monte Carlo dosimetry in murine and cellular geometries; development of models for DNA damage repair and cell survival. Divisions involved: PD, LNL, PV.

WP2 – VITRO

2D and 3D radiobiology using ¹¹¹Ag-PSMA-617, other nuclides for comparison and radiotracers, including also cold studies for the 3D part. β imaging for cell uptake measurements. Divisions involved: PV, TIFPA, LNS, LNL, PD, PI.

WP3 – VIVO

In vivo experiments with ¹¹¹Ag-PSMA-617, radiomics and imaging using γ camera prototype, SPECT/CT and ARG. Imaging calibration using phantoms. Divisions involved: LNS, PI, BO.

Possible international partners: **BIOEMTECH** (SPECT imaging), **CNEA** (currently studying ¹⁷⁷Lu-DTPA complexes)







With successful preclinical trials using ¹¹¹Ag-PSMA-617 against prostatic tumors, <u>clinical trials</u> could begin

- Possible <u>commercialization</u> γ and β imaging prototypes, if their goals in terms of resolution and efficiency will be satisfied
- Production of low-dose-rate <u>radiobiological data</u> as benchmark for DNA damage and repair models with SPES_MED nuclides







Thank you!





Backup slides



The ISOLPHARM facility





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IRIS: ISOLPHARM Radionuclide Implantation Station



Implantation Station



Transportation Trolley

Offline Detection System



ADMIRAL achievements



WP1 - Radiopharmaceutical production

- Optimization of chelators for Ag
- Optimization of Ag production and separation
- Development of 3D scaffolds for prostatic cancer cells

WP2 - β imaging

- # 2D β imager "DUMBO" construction
- Characterization tests with ¹¹¹Ag

WP3 - γ imaging

- ^β ¹¹¹Ag γ camera prototype development
- Characterization tests with ¹¹¹Ag

WP4 - Targeted radiobiology

- 2D survival of different cell lines treated with free ¹¹¹Ag
- Protocol for experiments in 3D scaffolds
- Cell dosimetry and DNA damage/repair models













ISOLPHARM_EIRA achievements



Task 1 - Physics

- Production of ¹¹¹Ag via radiative neutron capture using ¹¹⁰Pd or ^{nat}Pd targets
- Spectroscopic system for radiation measurements at the reactor and ex vivo
- * Study of laser photo-ionization schemes of Ag for SPES laser ion source

Task 2 - Chemistry

- Ag/Pd separation protocol after irradiation at LENA
- Development of stable chelators for Ag





Task 3 - Biology

- Synthesis of linkers and targeting agents for CCK2R
- "Cold" affinity tests in vitro
- Biodistribution and stability tests in vivo using PET/SPECT radionuclides







SPES_MED vs ISOLPHARM_APEX

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SPES_MED: nuclear measurements (approved by CSN3)



- After measurements, either:
 - dispose of the radionuclide
 - reuse it for applications

ISOLPHARM_APEX: application to radiobiology and medicine (to be submitted to CSN5)





Project FTE



LNL								
Name	WP	FTE	Status					
Alberto Andrighetto (National resp.)	2	0.5	Experimental physicist, technology executive					
Stefano Corradetti (LNL local resp.)	2	0.1	Materials engineer, technologist					
Valerio Di Marco	2, 3	1	Chemist, associate professor at UNIPD					
Laura Orian	2, 3	1	Chemist, associate professor at UNIPD					
Omorjit Singh Khwairakpam	2	0.1	Experimental physicist, post-doc					
Total LNL FTE		2.7	T=0.6; R=2.1					

Padova							
Name	WP	FTE	Status				
Alberto Arzenton (National resp.)	1, 2	0.6	Theoretical physicist, research scholar at UNIPD				
Marcello Lunardon (PD local resp.)	2, 3	0.5	Experimental physicist, associate professor at UNIPD				
Sandra Moretto	2, 3	0.1	Experimental physicist, associate professor at UNIPD				
Lisa Zangrando	1	0.1	Computer scientist, technologist				
Total PD FTE		1.3	T=0.1; R=1.2				

Bologna							
Name	WP	FTE	Status				
Matteo Negrini (BO local resp.)	3	0.2	Experimental physicist, researcher				
Anselmo Margotti	3	0.2	Experimental physicist, technology executive				
Carla Sbarra	3	0.2	Experimental physicist, researcher				
Giuseppe Baldazzi	3	0.3	Experimental physicist, associate professor at UNIBO				
Edoardo Borciani	3	0.5	Physics PhD student at UNIBO				
Total BO FTE		1.4	T=0.2; R=1.2				

LNS								
Name	WP	FTE	Status					
Giorgio Russo (LNS local resp.)	3	0.3	Experimental physicist, CNR researcher					
Francesco Paolo Cammarata	3	0.5	Biologist, CNR researcher					
Cristiana Alberghina	3	1	Biologist, post-doc at UNICT					
Alessandro Stefano	3	0.3	Computer engineer, CNR researcher					
Total LNS FTE		2.1	T=0; R=2.1					

	Pavia							
Name	WP	FTE	Status					
Antonietta Donzella (PV local resp.)	1, 3	0.6	Computational physicist, technologist at UNIBS					
Giorgio Biasiotto	2	0.2	Biochemist, associate professor at UNIBS					
Roberto Bresciani	2	0.2	Biochemist, associate professor at UNIBS					
Carlo Rodella	1, 2	0.4	Medical physicist at Spedali Civili di Brescia					
Federica Saiani	1, 2	0.4	Medical physicist at Spedali Civili di Brescia					
Andrea Salvini	2, 3	0.3	Radiochemist, technologist at UNIPV-LENA					
Andrea Gandini	2, 3	0.3	Radiochemist, technologist at UNIPV-LENA					
Fabio Zelaschi	2, 3	0.2	Radiochemist, technologist at UNIPV-LENA					
Silva Bortolussi	1, 2	0.2	Experimental physicist, associate professor at UNIPV					
Marco Di Luzio	2	0.5	Metrologist, INRiM researcher					
Giancarlo D'Agostino	2	0.5	Metrologist, INRiM researcher					
Laura Cansolino	2	0.3	Biologist, technologist at UNIPV					
Cinzia Ferrari	2	0.4	Biologist, technologist at UNIPV					
Total PV FTE		4.5	T=2.1; R=2.4					

Pisa								
Name	WP	FTE	Status					
Nicola Belcari (PI local resp.)	2, 3	0.4	Experimental physicist, associate professor at UNIPI					
Emilio Mariotti	3	0.1	Experimental physicist, associate professor at UNISI					
Giancarlo Sportelli	2, 3	0.3	Experimental physicist, associate professor at UNIPI					
Luca Menichetti	3	0.2	Radiochemist, CNR researcher					
Daniele Panetta	3	0.2	Medical physicist, CNR researcher					
Total PI FTE		1.2	T=0; R=1.2					

TIFPA							
Name	WP	FTE	Status				
Devid Maniglio (TIFPA local resp.)	2	0.5	Experimental physicist, associate professor at UNITN				
Alessio Bucciarelli	2	0.7	Material scientist, researcher at UNITN				
Annalisa Tirella	2	0.7	Biomedical engineer, associate professor at UNITN				
Antonella Motta	2	1	Biomedical engineer, full professor at UNITN				
Total TIFPA FTE		2.9	T=0; R=2.9				

16.1

Total project FTE

T=