Istituto Nazionale di Fisica Nucleare

ISOLPHARM_APEX

^{111}Ag-PSMA-617 Experiments

RL – Antonietta Donzella

ISOLPHARM: over 10 years of activity

INFN experiments

PRIN

2014 – 2017

Interdisciplinary study group on production of medical radioisotopes at SPES

2018 – 2019

Simulations and feasibility evaluation of Ag as radiopharmaceutical precursor

2020 – 2022

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

2023 – 2025

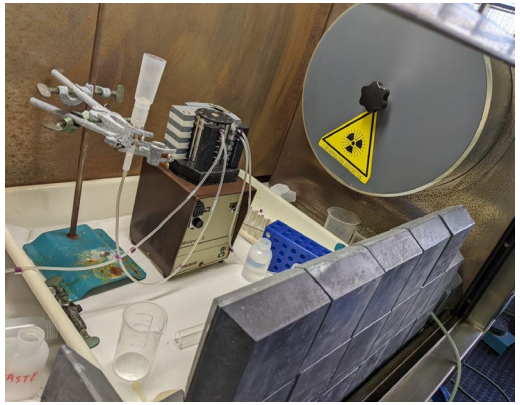
Characterizing the 2D/3D *in-vitro* therapeutic effect of ^{111}Ag and its imaging capabilities

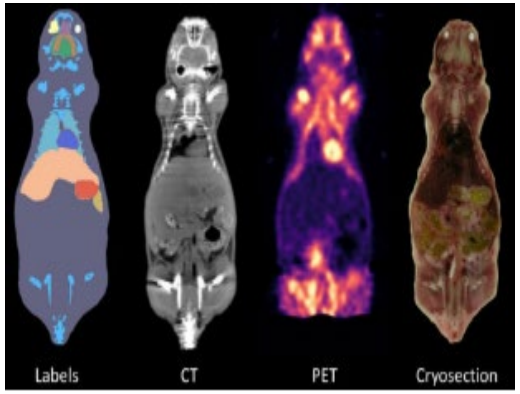
2025 – 2027

First nuclear measurements of radionuclide production at SPES

2024 – 2025

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

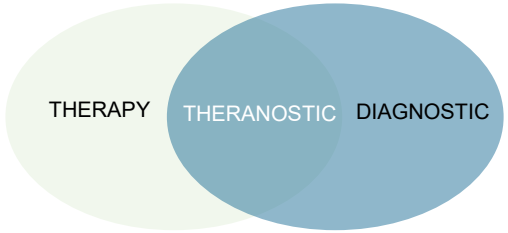




Why ^{111}Ag?

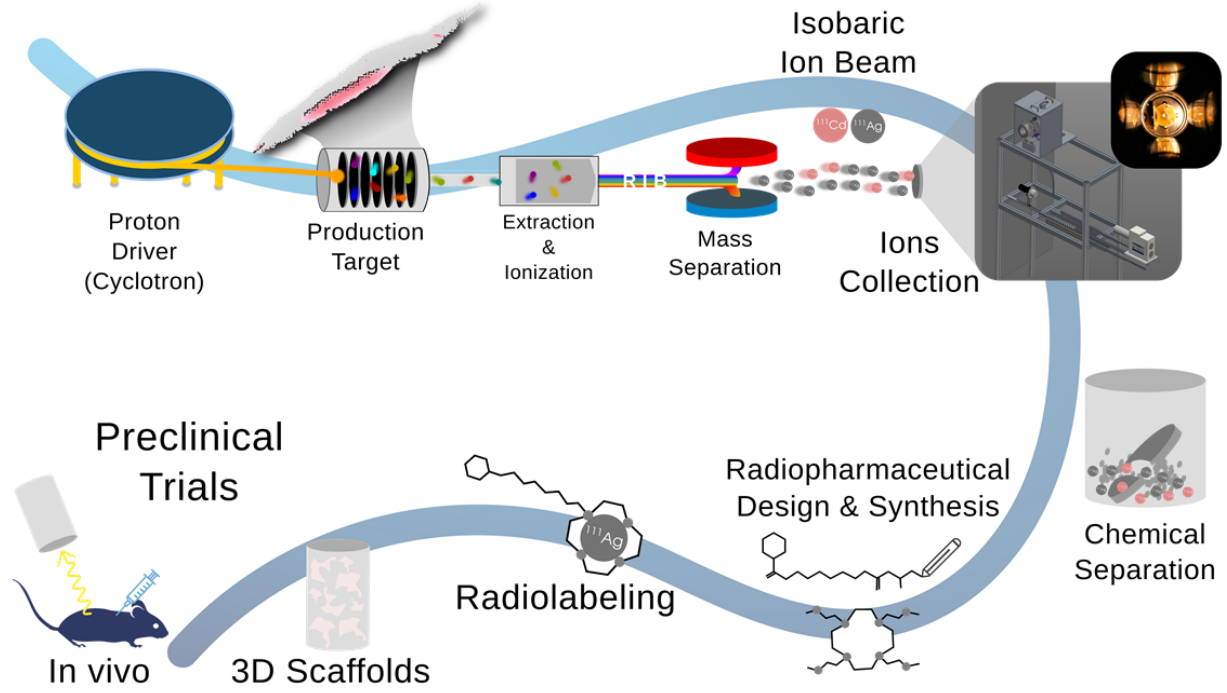
^{111}Ag properties

- **β⁻ emitter** (average energy **360 keV**)
- Medium half-life (**7.45 days**)
- Medium tissue penetration (1.5 mm)
- Medium energy **γ rays** -> SPECT?



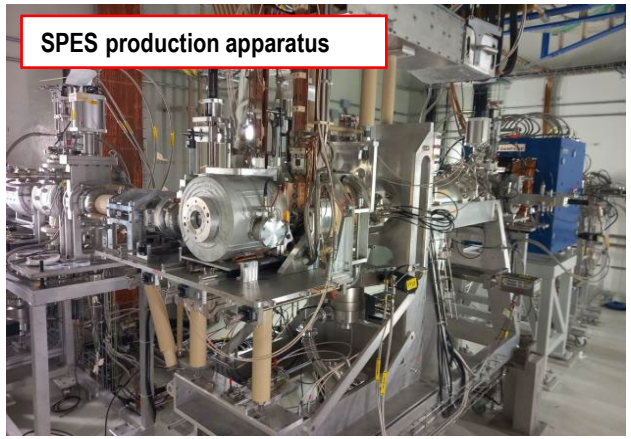
- In the market no radiopharmaceuticals radiolabeled with ^{111}Ag.
- ^{111}Ag exhibits theranostic properties similar to ^{177}Lu: the first ^{177}Lu-based radiopharmaceuticals are being approved by AIFA, EMA and FDA (^{111}Ag-PSMA-617)
- ^{111}Ag behaves similarly to ^{186}Re, recently studied in phase I/II clinical trials

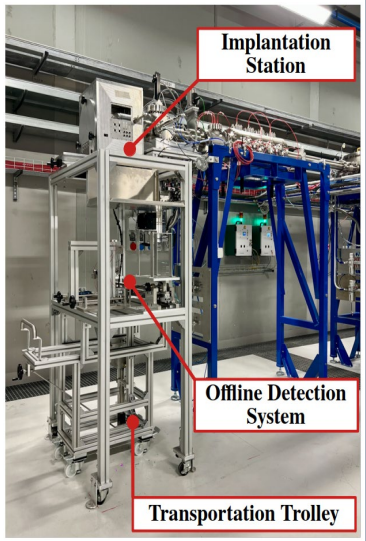
ISOL PHARM



ISOLPHARM method

^{111}Ag will be produced @ SPES-LNL with the ISOL method:
- with high purity & high production rate
- without isobaric radioactive contaminants





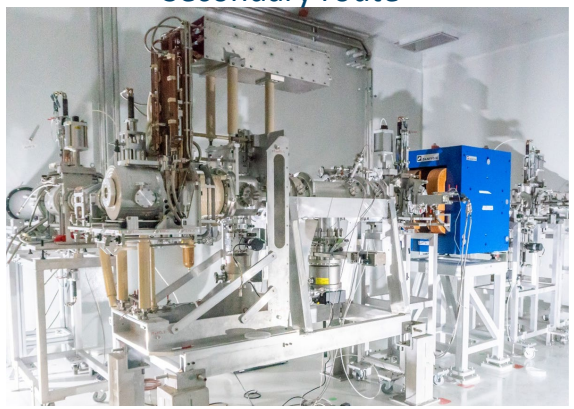
ISOLPHARM_APEX (2026-2028)

ISOLPHARM_APEX

^{111}Ag-PSMA-617 EXperiments

Main route

Secondary route



Radionuclide production at LENA and SPES

Main goals

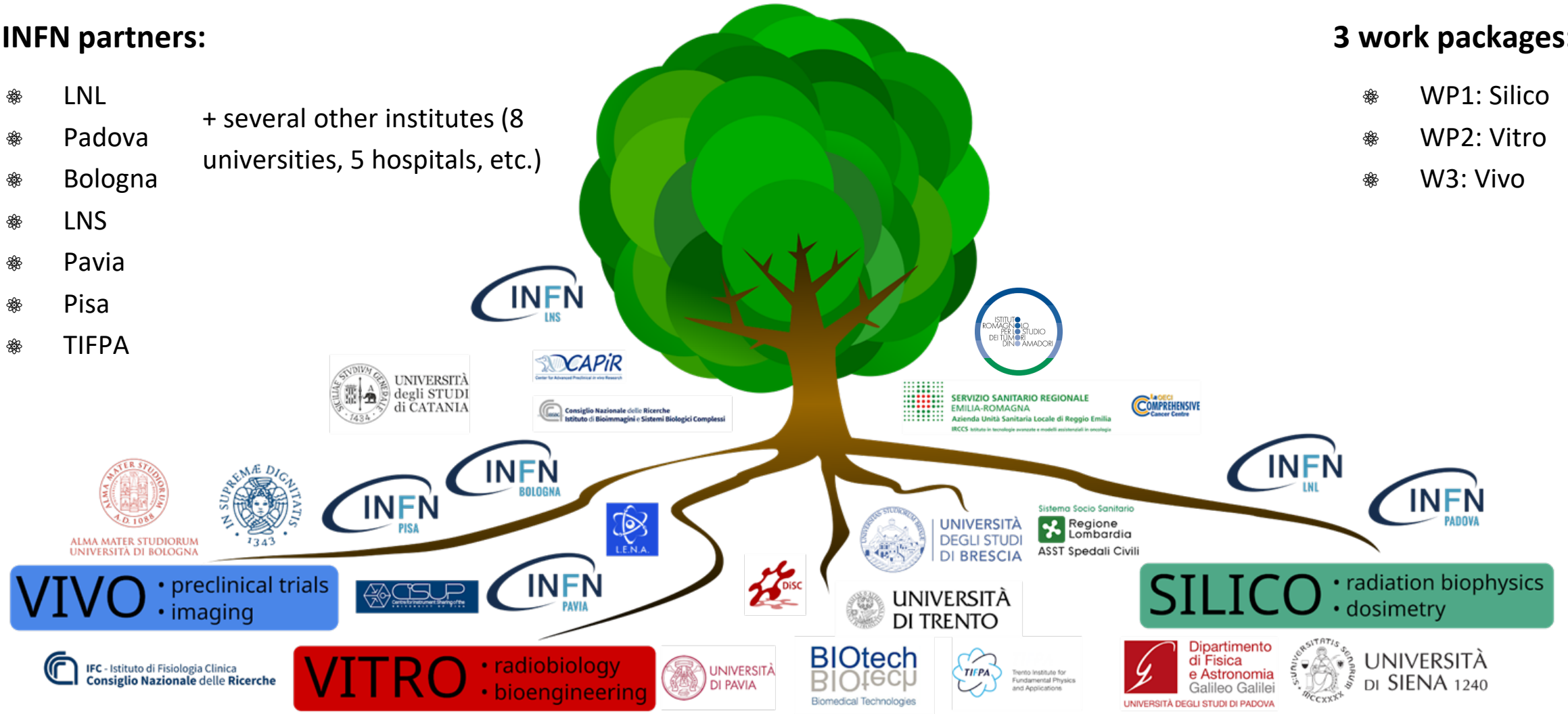
1) Understanding the dosimetry of ^{111}Ag-PSMA-617 in living systems such as cells, small animals and human patients.
2) Studying this radiopharmaceutical in cancer cell cultures in 2D monolayers and in 3D tissue-mimicking scaffolds.
3) Observing the biodistribution and the effects of theranostic ^{111}Ag-PSMA-617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

Project organization

7 INFN partners:

- LNL
- Padova
- Bologna
- LNS
- Pavia
- Pisa
- TIFPA

+ several other institutes (8 universities, 5 hospitals, etc.)



3 work packages:

- WP1: Silico
- WP2: Vitro
- W3: Vivo

Activities

WP1 – SILICO

Monte Carlo dosimetry for the assessment of the absorbed dose in cellular geometries and murine phantoms.
Divisions involved: PD, LNL, **PV**.

WP2 – VITRO

2D and 3D radiobiology using ^{111}Ag-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 ^{111}Ag-PSMA-617, radiomics and imaging using γ camera prototype, SPECT/CT and ARG. Imaging calibration using phantoms.
Divisions involved: LNS, PI, BO.

Endorsement of hospitals: Santa Maria Nuova (RE); Cannizzaro (CT); IRST D. Amadori (Meldola, FC); IFC-CNR (Pisa); **Spedali Civili (BS)**

International partners: **University of Freiburg** (PSMA-617 synthesis), **BIOEMTECH** (SPECT imaging), **CNEA** (currently studying ^{177}Lu-DTPA complexes)

Gantt diagram

		Year 1				Year 2				Year 3				Notes		
		M3	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	→	●											T2.1-T2.6	A, B	LNL, PD, PV
T1.2	Internal Monte Carlo dosimetry of biodistribution study with healthy mice	→			●									T3.5	C	LNL, PD, PV
T1.3	Internal Monte Carlo dosimetry of biodistribution study with tumor-bearing mice					→			●					T1.5, T3.6	D	LNL, PD, PV
T1.4	Biophysical model validation with radiobiological data			→					●						A	LNL, PD
T1.5	Dosimetric planning for preclinical studies with tumor-bearing mice							→			●			T3.6	E	LNL, PD, PV
T1.6	Validation of DNA damage models using radiobiological data and Geant4-DNA							→					●		F	LNL, PD
T1.7	Preliminary dosimetric predictions for human patients										→		●		E	LNL, PD, PV
	WP2 – VITRO (leader: D. Maniglio)															
T2.1	2D radiobiology of Ag-111-PSMA-617 on prostate cancer cells	→			●									T1.4	A	PV
T2.2	2D radiobiology of Lu-177-PSMA-617 on prostate cancer cells	→			●									T1.4	A	LNS
T2.3	β imaging of 2D cell culture uptake	→			●									T2.1	A	PD, PI
T2.4	3D radiobiology of Ag-111-PSMA-617 on prostate cancer cells					→			●						B	PV, TIFPA
T2.5	Microscopy and β imaging of 3D cell culture uptake					→			●					T2.4, T2.6	B	TIFPA, PD, PI
T2.6	3D radiobiology of Ag-111-PSMA-617 on prostate cancer cells in bioreactor									→			●		B	PV, TIFPA
T2.7	2D radiobiology of SPES radionuclides							→					●	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	→	●											T3.4-T3.6	-	PI, LNS
T3.2	γ camera and SPECT imaging of Ag-111 in phantoms	→			●									T3.7	G	BO, PI
T3.3	ARG imaging improvement using the γ camera collimator	→							●					T3.4-T3.6	G	BO, LNS
T3.4	γ imaging and *ex vivo* biodistribution study of Ag-111-PSMA-617 in healthy mice		→		●									T1.2	C	LNS, PI, LNL
T3.5	γ imaging and *ex vivo* biodistribution study of Ag-111-PSMA-617 in tumor-bearing mice					→			●					T1.3	D	LNS, PI, LNL
T3.6	Preclinical experiments and γ imaging using Ag-111-PSMA-617 on tumor-bearing mice							→					●	T1.7, T3.7	E	LNS, PI, BO
T3.7	Radiomic features evaluation from SPECT/CT of preclinical studies									→			●		H	LNS

→	Activity started
●	Deliverable/milestone reached

Pavia prospect

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

Total APEX
FTE 15.3

Pavia							
Type	ID	Item	WP	Year 1 [k€]	Year 2 [k€]	Year 3 [k€]	Total
Consumables	23	Chambers and electronics for "hot" bioreactor	2	0	2	0	2
	24	Radiobiology laboratory material	2	2	2	2	6
	25	Enriched Pd-110 targets	2, 3	5	5	0	10
	26	Laboratory material for LENA	2, 3	2	2	2	6
	27	Material for activation measurements (INRiM)	2, 3	2	0	0	2
Services	28	Target irradiation and chemical separation at LENA	2, 3	8	8	8	24
Shipping	29	Shipping of Ag-111, etc.	2, 3	5	4	5	14
Travels	30	Travels for research activities	1	2	2	2	6
Total PV				26	25	19	70

Fallout

- With successful preclinical trials using ^{111}Ag-PSMA-617 against prostatic tumors, **clinical trials** could begin
- Possible **commercialization** γ and β imaging prototypes, if their goals in terms of resolution and efficiency will be satisfied
- Production of low-dose-rate **radiobiological data** as benchmark for DNA damage and repair models with SPES_MED nuclides

Infrastrutture