Istituto Nazionale di Fisica Nucleare
LABORATORI NAZIONALI DI LEGNARO

Laboratori Nazionali di Legnaro – INFN

A new CSN5 experiment proposal

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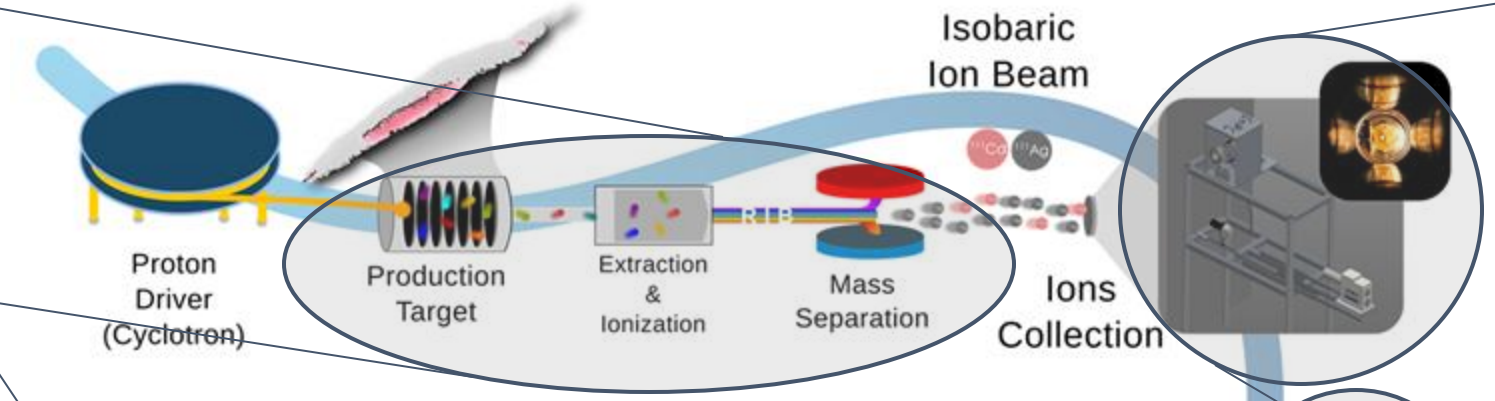
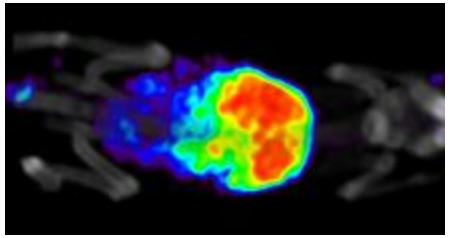
Collaboration infrastructures

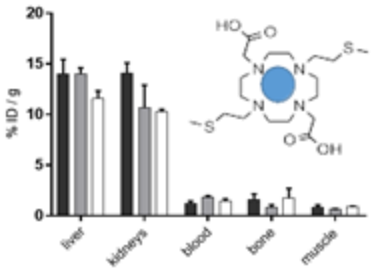
ISOLPHARM method



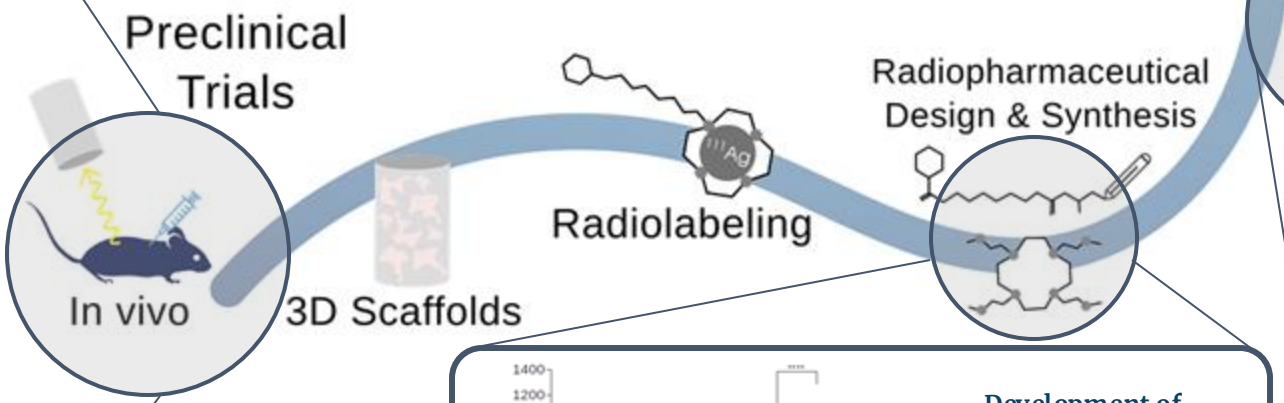
Design & construction of the IRIS system for radioisotope deposition and spectroscopic characterization

PET/CT fused image 24 h after the radiolabeled compound injection

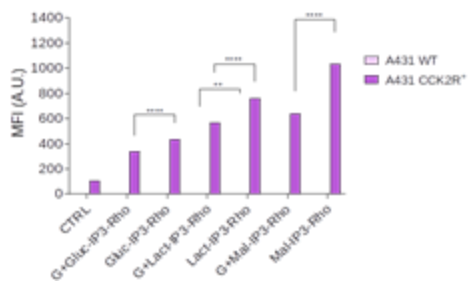




DO2A2S-^{64}Cu ex-vivo biodistributions

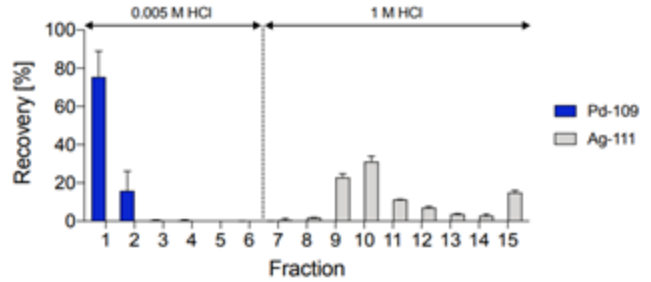


Results from ISOLPHARM CSN5 experiments



Development of 2nd gen. ligands: increased uptake and total competition with more hydrophilic linkers

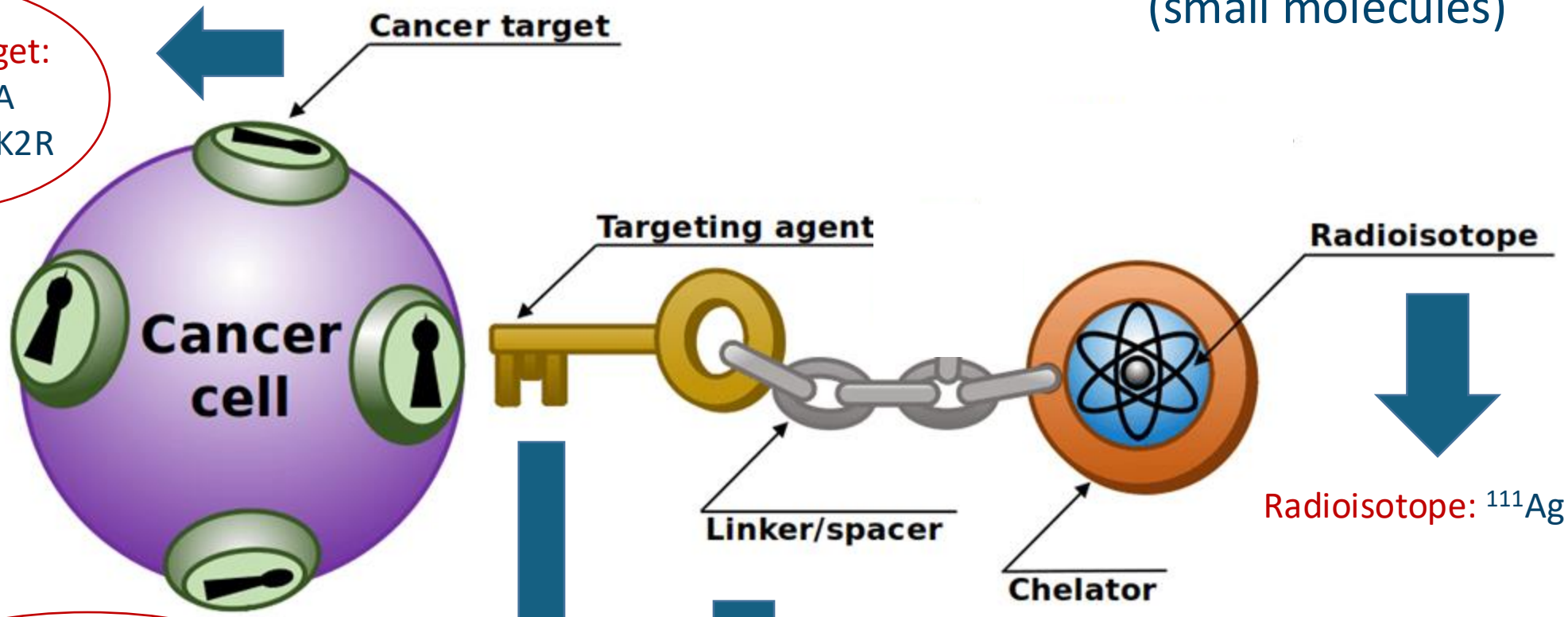
Pd/Ag chemical separation



Radiopharmaceutical frame

(small molecules)

Cancer target:
Now: PSMA
Before: CCK2R



Targeting agent:
Now: PSMA-617
Before: Z360 (for CCK2R)

Linker: Bifunctional

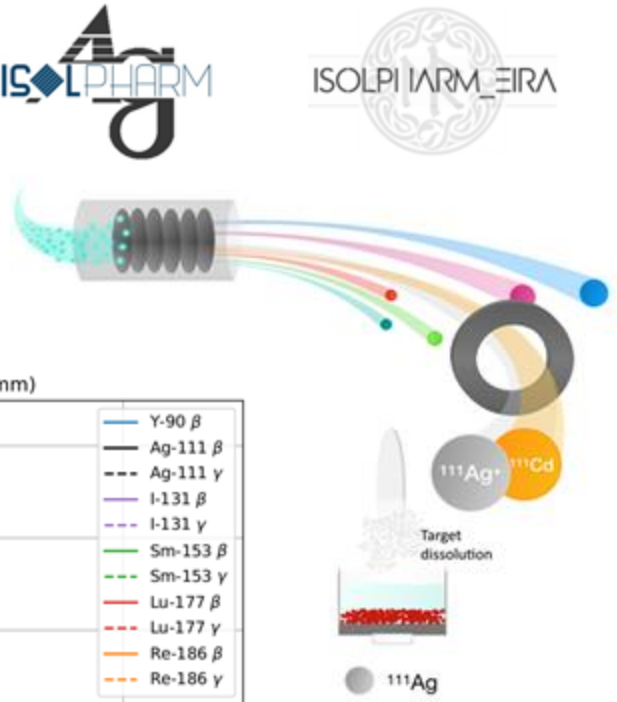
Chelator: DO4S

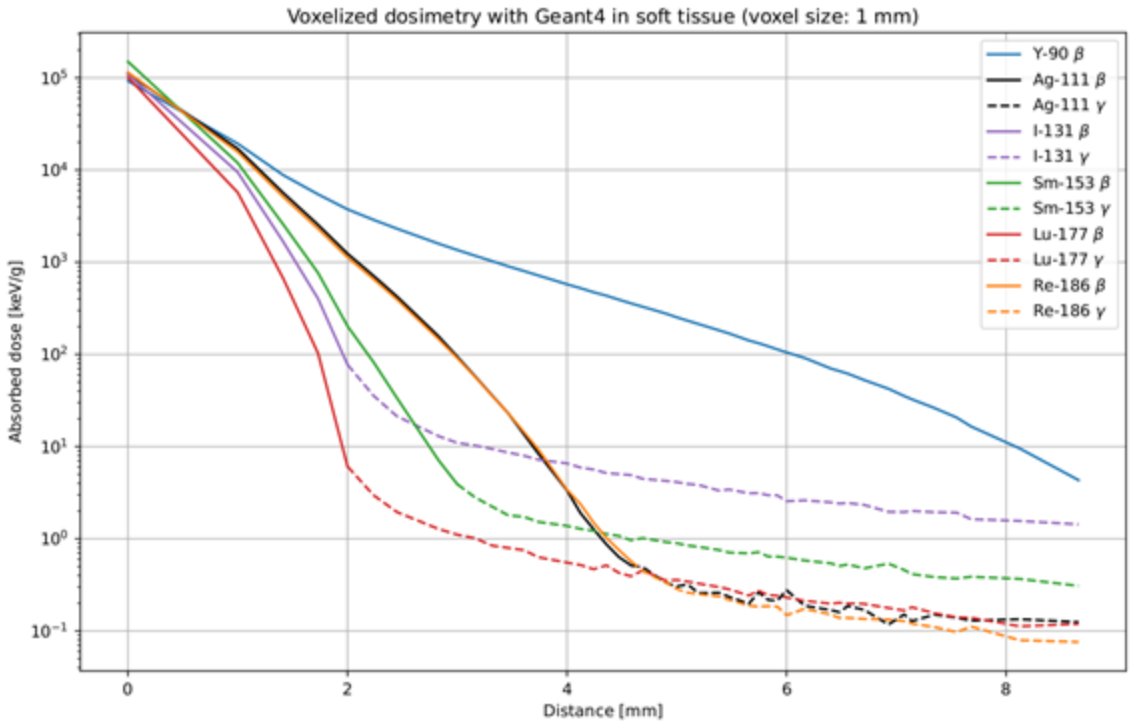
Radioisotope: ^{111}Ag

Experiments: why ^{111}Ag?

^{111}Ag properties

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





→ In the market no radiopharmaceuticals radiolabeled with silver-111

→ Silver-111 can be produced @ SPES with high purity & high production rate

→ No isobaric radioactive contamination in the implantation foil (also with LASER off!)

→ ^{111}Ag exhibits theranostic properties similar to ^{177}Lu which was recently approved by FDA

→ ^{111}Ag behaves similarly to ^{186}Re, recently studied in phase I/II clinical trials

111 Isobaric chain	Half-Life $T_{½}$	Decay	Target Yield
Cadmium-111	Stable		Low yield production
Silver-111	7.45 days	β^-	Good yield production
Palladium-111	23.4 min	β^-	Bad release, short $T_{1/2}$
Rhodium-111	11 sec.	β^-	No release, very short $T_{1/2}$

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

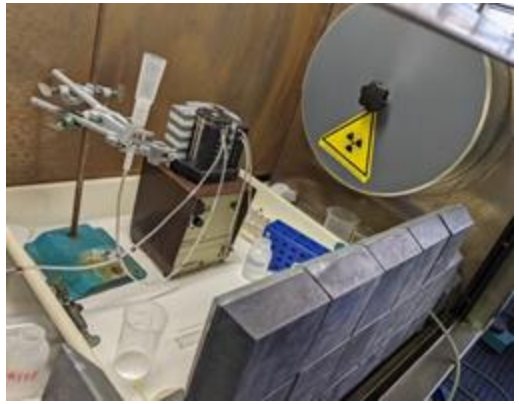
Characterizing the 2D/3D *in-vitro* therapeutic effect of ^{111}Ag and its imaging capabilities

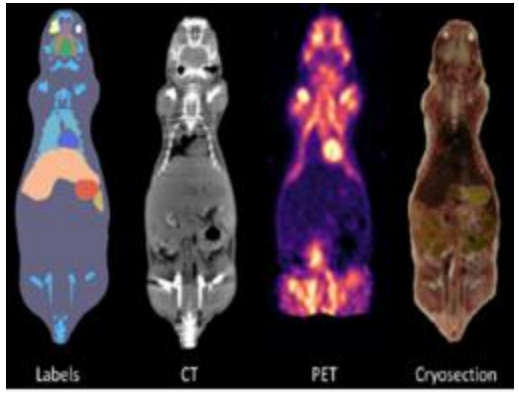
2025 – 2027

First nuclear measurements of radionuclide production at SPES

2024 – 2025

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





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 ^{111}Ag

WP3 - γ imaging

- ^{111}Ag γ camera prototype development
- Characterization tests with ^{111}Ag

WP4 - Targeted radiobiology

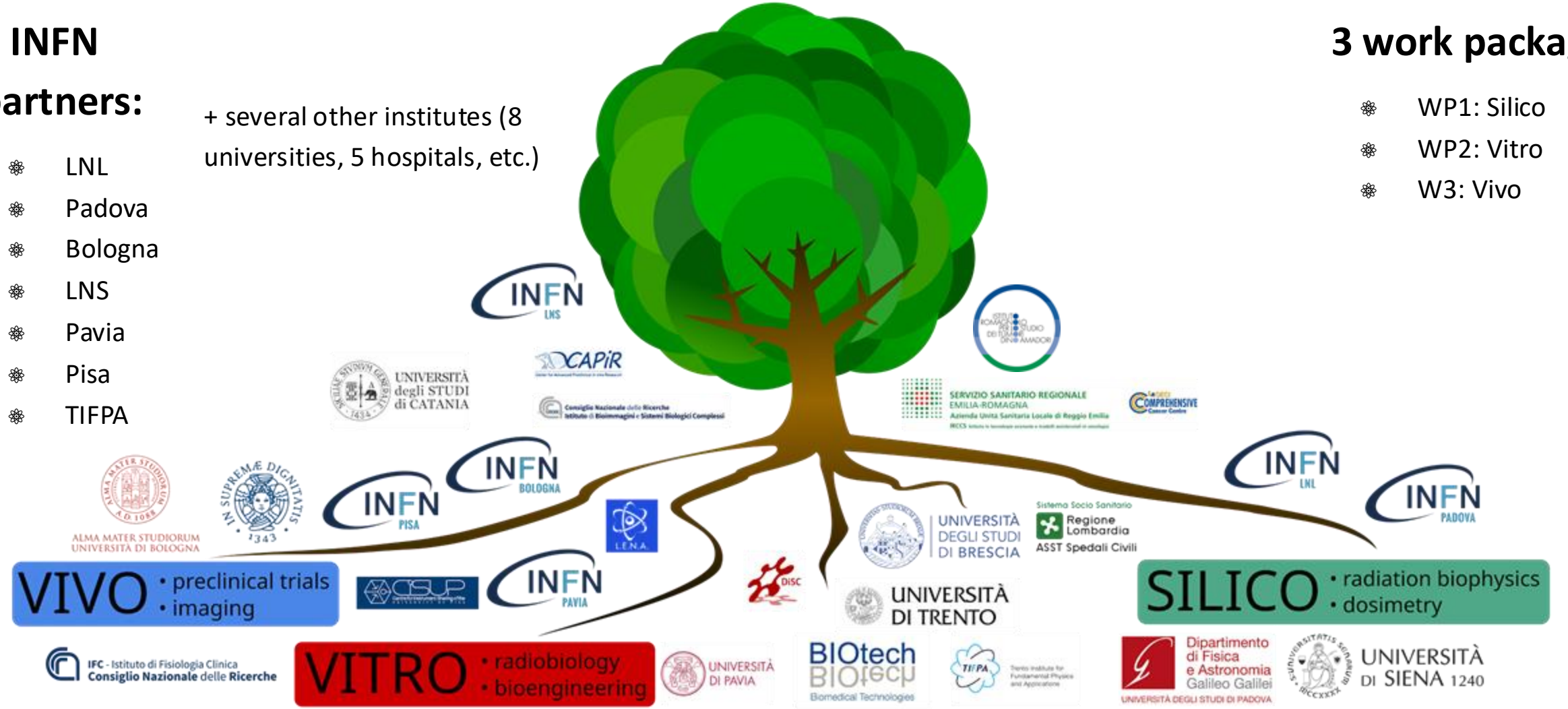
- 2D survival of different cell lines treated with free ^{111}Ag
- Protocol for experiments in 3D scaffolds
- Cell dosimetry and DNA damage/repair models

Project organization

7 INFN partners:

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

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

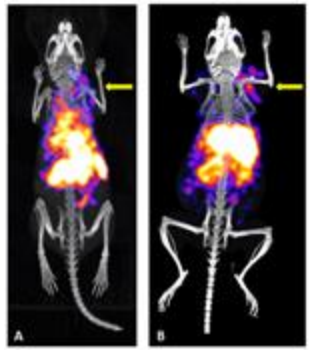


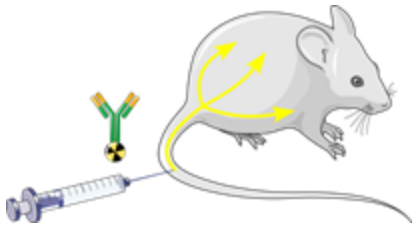
3 work packages:

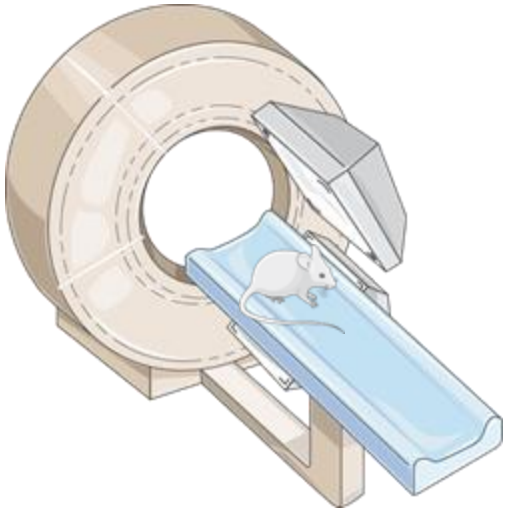
- WP1: Silico
- WP2: Vitro
- W3: Vivo

WP2 – INVITRO and WP3 – VIVO

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







INFN LNS
Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali del Sud

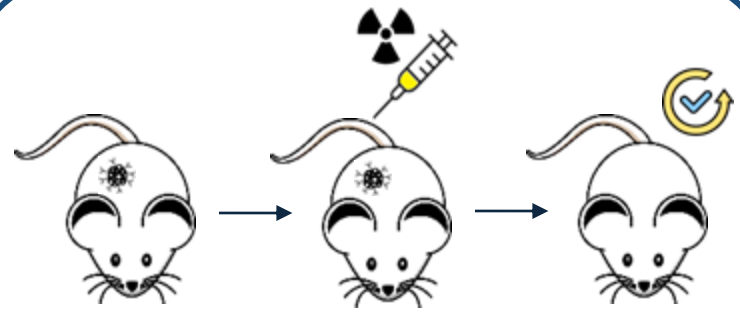
INFN PISA

INFN BOLOGNA

WP3 methodology

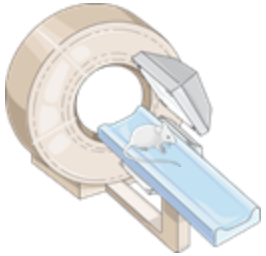
Preclinical experiments: biodistribution and animal trials

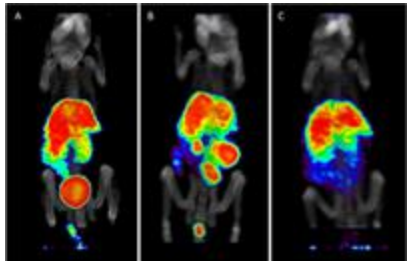
The **ex-vivo biodistribution** is preliminarily evaluated with free ^{111}Ag, chelated ^{111}Ag and ^{111}Ag-PSMA-617 in healthy mice and in mice **transfected with tumors** expressing or not expressing the target receptor.



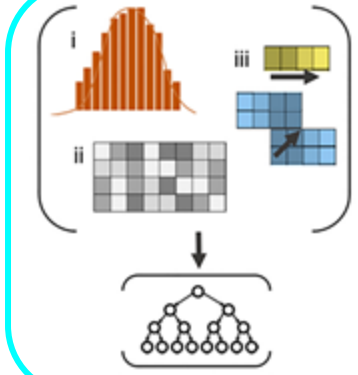
If the targeting is good, the **therapeutic effect** is finally assessed evaluating the **recovery** of treated mice.

Imaging and radiomics





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



PET/CT or SPECT/CT imaging can also be used for **pattern recognition** (extraction of **radiomic features**).

LNS prospect

LNS							
Type	ID	Item	WP	Year 1 [k€]	Year 2 [k€]	Year 3 [k€]	Total
Consumables	13	Laboratory material	3	1	1	1	3
	14	Mice for in-vivo experiments	3	6	6	6	18
Shipping	15	Shipping of detector, drugs, samples	3	4	4	4	12
Travels	16	Travels for experimental activity	3	2	2	2	6
Total LNS				13	13	13	39

FTE

Alessandro Stefano	Apex	0,3
Francesco Cammarata	Apex	1
Giorgio Russo	Apex	0,3
Giusi Irma Forte	Apex	0,8