ADMIRAL

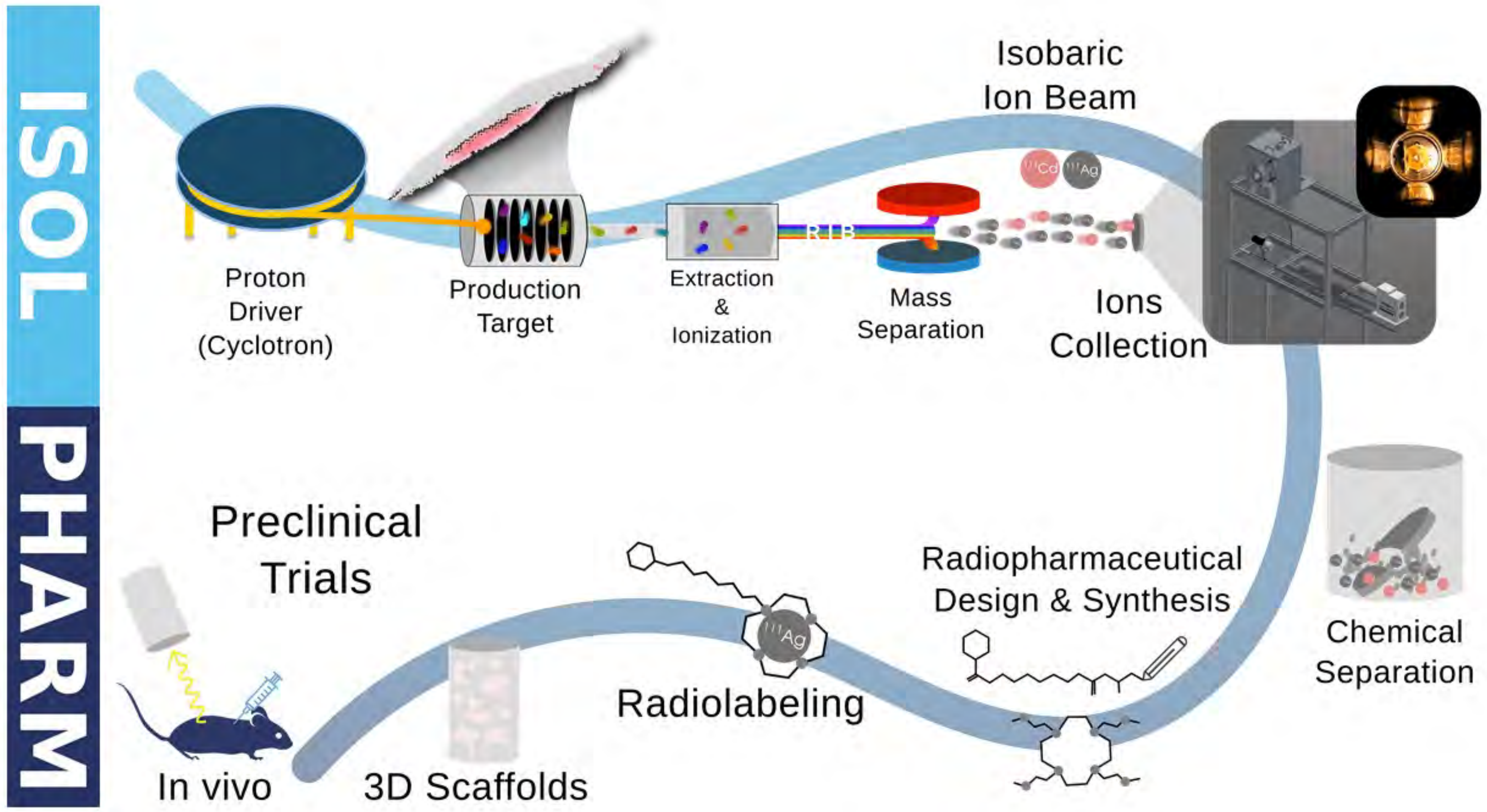
ISOLPHARM

SPES exotic beams for medicine

Advanced **D**osimetry **M**ethods and **I**n-vitro **R**adiobiology of **A**g-111 **L**abeled radiopharmaceuticals

- **Principal Investigator**
  Alberto Andrighetto, INFN-LNL.
- **INFN Research Units**
  LNL, Padova, TIFPA, LNS, Pavia, Bologna.
- **Research Fields**
  Medical Physics, Radiation Detectors, Radiobiology.
- **Duration**
  3 years.

The ISOLPHARM method



ISOLPHARM history

2018 - 2019

Simulations and feasibility evaluation.

2020 - 2022

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

2023 - 2025

Providing new tools for preclinical trials on 3D scaffolds.

Where we are : ISOLPHARM_EIRA

Project structured in 3 main tasks:

^{111}Ag

Task 1: Physics

INFN LNL · INFN PADOVA · INFN PAVIA

- **Simulation and study of ^{111}Ag production via the $^{110}Pd(n,\gamma)^{111}Ag$ reaction.**
- **Quality control of the production of ^{111}Ag trough spectroscopy analysis**
- Laser ionization of Ag

PADOVA mainly involved in task #1 , item #2
collaborating also in task #1, item #1
collaborating also in task #3, item #4 and new #5

Task 2: Radiochemistry

- Development of a library of novel chelators for silver and copper and characterization of their properties.
- Small molecules and linker development
- Radiolabeling of the synthetized compounds prior with ^{64}Cu and then with ^{111}Ag, characterization of their properties (stability, etc.)
- Development of more efficient purification methods from isobaric contaminant

Cancer cell

Task 3: Biology

- In vitro activities: study of affinity and internalization using florescence (eventual studies with ^{64}Cu and ^{111}Ag)
- Development of 3D scaffold and cell cultures for studies in dynamic conditions
- In vivo tests using florescence
- **In vivo imaging using ^{64}Cu and ^{111}Ag radiolabelled compounds**
- **Internal micro-dosimetry calculations using GEANT4/GATE**

Where we are : ISOLPHARM_EIRA

Contribution of the different participants to the ISOLPHARM_EIRA tasks

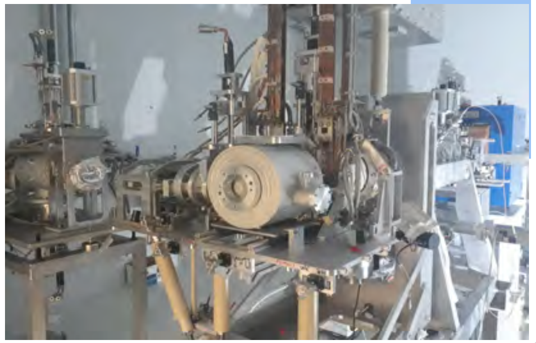
Infrastructures and Laboratories

Physics

^{111}Ag

LENA
Nuclear
Reactor

Radionuclides production



^{111}Ag

SPES ISOL Facility

Radiochemistry

Hot Chemistry Lab, LENA & AUSL

Radiopharmaceutical Development

Sinthesys

Chelators and linker development: DSF and DISC at UNIPD

Biology

Cell line screening and *in-vitro* studies with fluorescence: DSF at UNIPD

Toward In-vitro and In-vivo preclinical trials

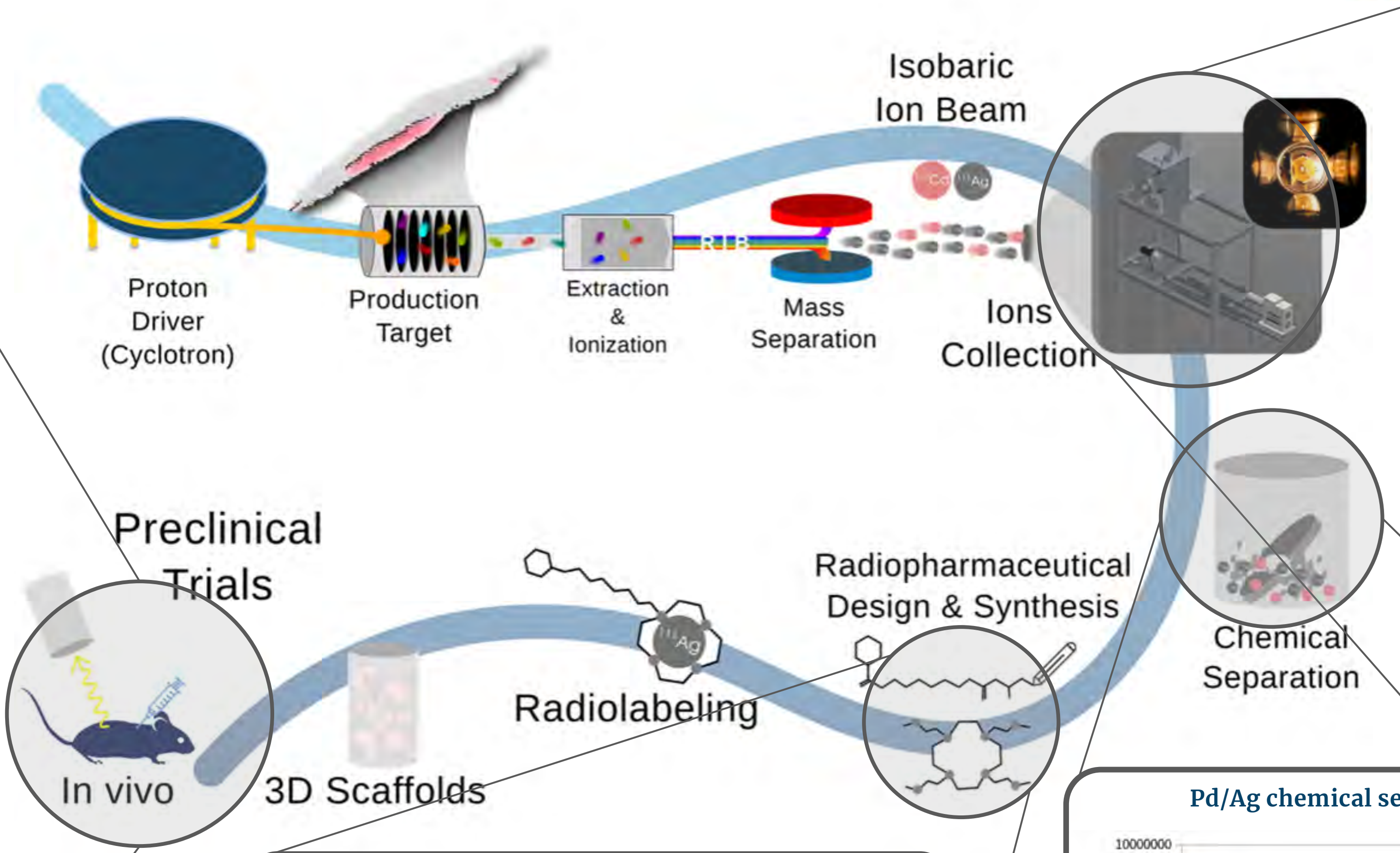
In-vivo tests with fluorescence: CIBIO and Biotech
In/Ex-vivo tests at CAPiR

ISOLPHARM & EIRA Achievements

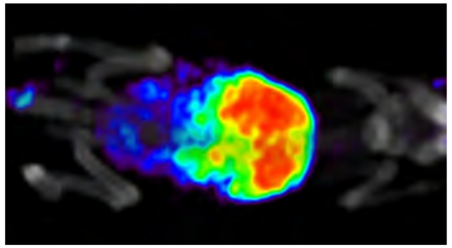
ISOLPHARM SPES exotic beams for medicine

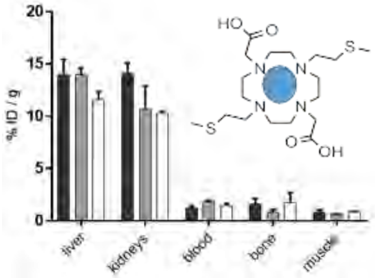
INFN Istituto Nazionale di Fisica Nucleare LABORATORI NAZIONALI DI LEGNARO

Results from ISOLPHARM_EIRA CSNV Experiment

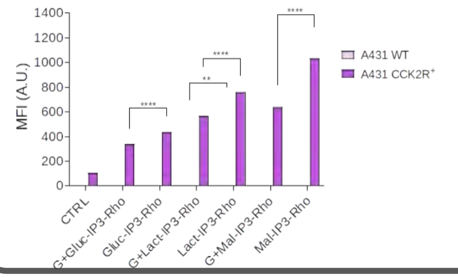


PET/CT fused image after 24 h from the radiolabeled compound injection



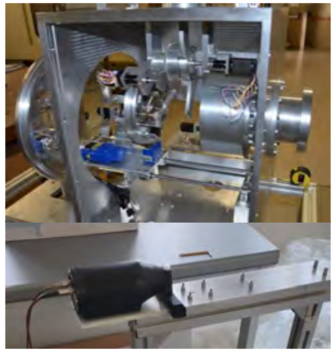


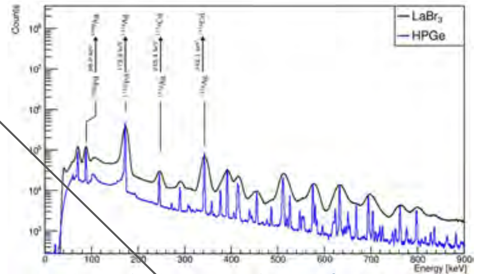
DO2A2S-64Cu ex-vivo biodistributions.



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

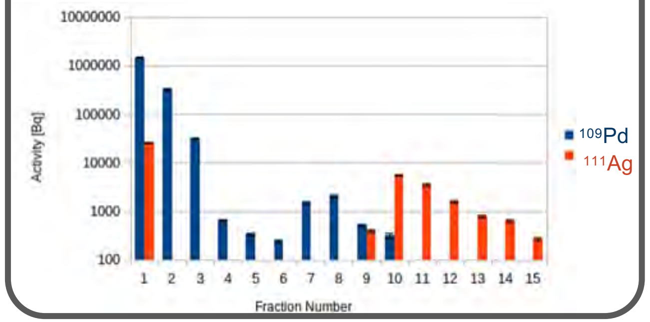
Design & Construction of the IRIS station for radioisotope deposition and spectroscopic characterization





^{110}Pd enriched sample 6 hours after irradiation

Pd/Ag chemical separation



ISOLPHARM - ADMIRAL

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The path of ADMIRAL Collaboration

ISOLPHARM SPES exotic beams for medicine

INFN Istituto Nazionale di Fisica Nucleare LABORATORI NAZIONALI DI LEGNARO

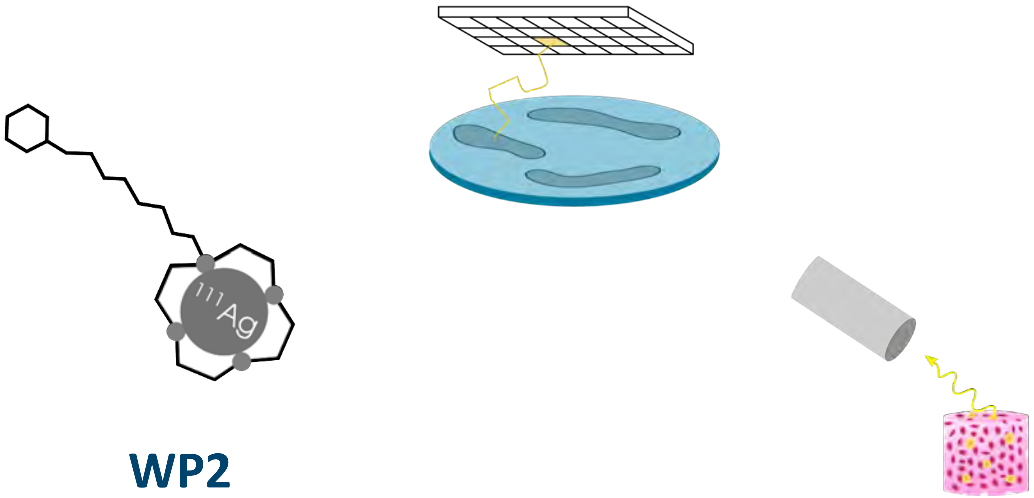
WP3

Dipartimento di Fisica e Astronomia Galileo Galilei

INFN PADOVA Istituto Nazionale di Fisica Nucleare Sezione di Padova

INFN Istituto Nazionale di Fisica Nucleare LABORATORI NAZIONALI DI LEGNARO

Development of a β-imaging system based on solid-state detector



WP1

dsf DiSC

L.E.N.A. INFN PAVIA

UNIVERSITÀ DEGLI STUDI DI BRESCIA

Radiopharmaceutical production

UNIVERSITÀ DI TRENTO

TIFPA Trento Institute for Fundamental Physics and Applications

CIBIO

UNIVERSITÀ DI SIENA 1240

SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA

Azienda Unità Sanitaria Locale di Reggio Emilia

IRCCS Istituto in tecnologie avanzate e modelli assistenziali in oncologia

WP2

Development of a γ-imaging scintigraphic system for ^{111}Ag

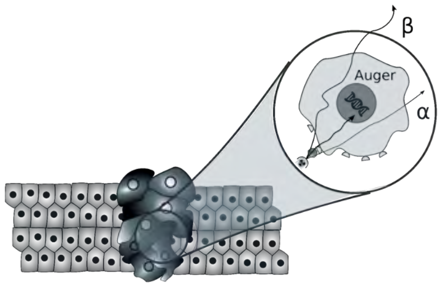
ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA

INFN BOLOGNA Istituto Nazionale di Fisica Nucleare Sezione di Bologna

SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA

POLICLINICO DI SANT'ORSOLA

WP4



Radiobiological characterization of ^{111}Ag radiopharmaceutical

UNIVERSITÀ DI PAVIA

Fondazione Ri.MED

INFN LNS

CAPiR

UNIVERSITÀ degli STUDI di CATANIA

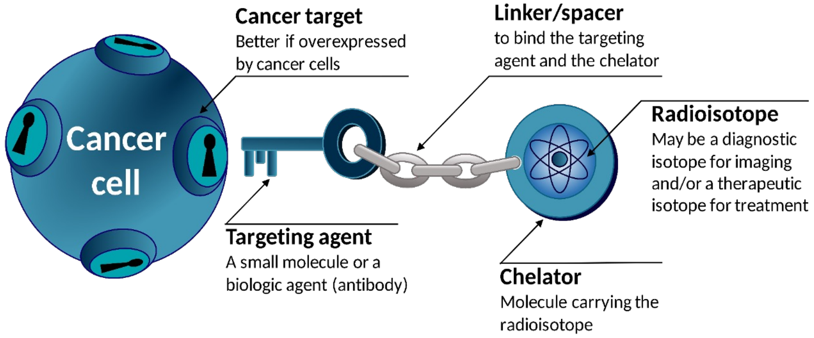
WP 1 & WP 2

WP1

WP Leader: F. Mastrotto (UNIPD)

Work Package Aim

WP1 will sum up all the preexisting activities leading to the **development of the radiopharmaceutical itself**, with the addition of the **tissue-mimicking scaffold production** to generate **more realistic 3D cell cultures** to be employed in the other work packages.

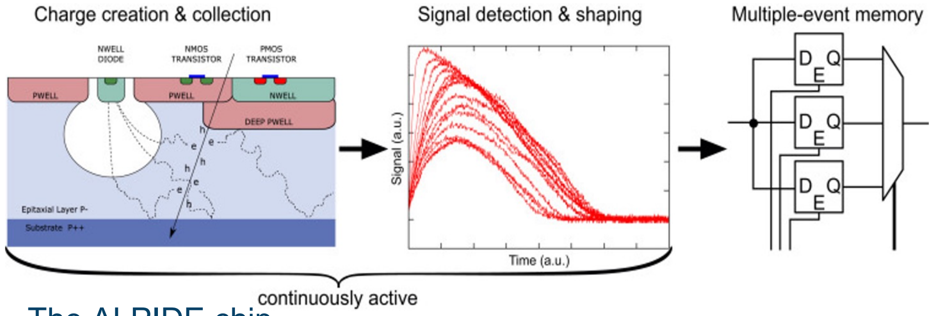


WP2

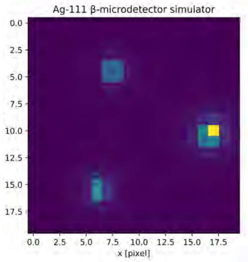
WP Leader: M. Lunardon (UNIPD)

Work Package Aim

This WP will be devoted to the **design**, **construction** and **characterization** of a new large-area detector for 2D β-imaging at high resolution. This new device will take advantage of the monolithic silicon pixel technology developed recently for the ALICE experiment, namely the **ALPIDE**, the Monolithic Active Pixel Sensor of the new Inner Tracking System (ITS).



The ALPIDE chip



preliminary simulation of a cell distribution beta image

WP 3 & WP 4

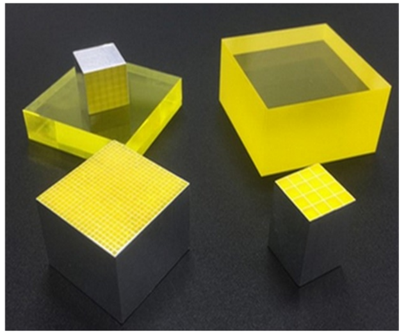
WP3

WP Leader: G. Baldazzi (UNIBO)

Work Package Aim

This WP is aimed at the **design and development** of a planar scintigraphic system optimized for the incoming **γ emission** from the de-excitation of ^{111}Cd after the radioactive decay of **^{111}Ag**. The design and construction of the imaging device will begin considering **all its components**, from **detectors** to **data acquisition software**.

GAGG scintillators in slab and matrix produced by EPIC-Crystals

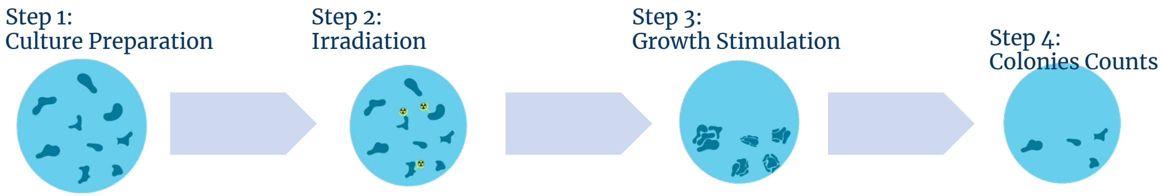


WP4

WP Leader: S. Bortolussi (UNIPV)

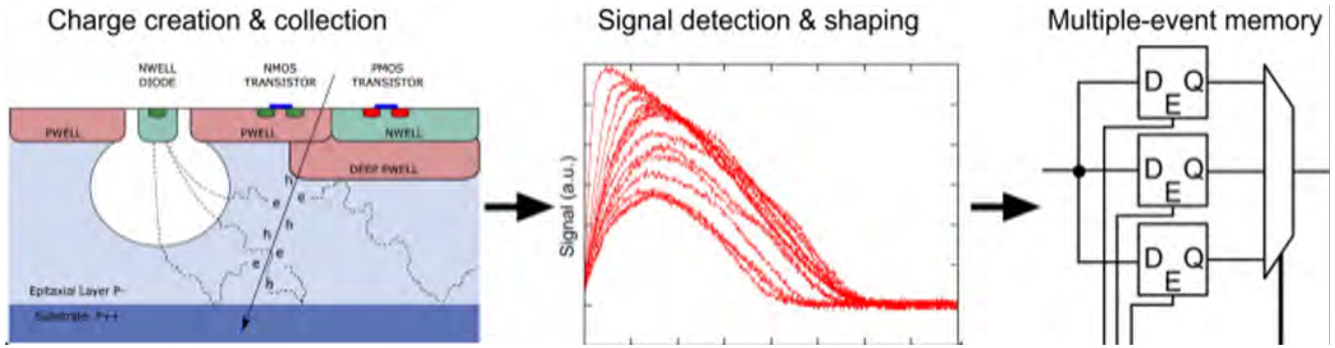
Work Package Aim

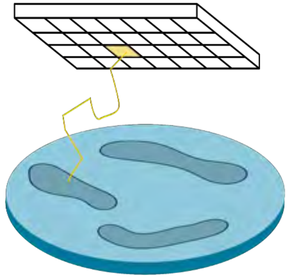
The whole set of experimental activities concerning **radiobiology**. In particular cell survival in 2D and 3D scaffolds will be evaluated. The acquired **radiobiological data** will be related to the absorbed **dose at cell** level, which will be calculated using Monte Carlo method, exploiting the available data about **^{111}Ag uptake** *in vitro* and transporting the emitted radiation in simulated geometries that reproduce the monolayer or the **3D scaffold**.

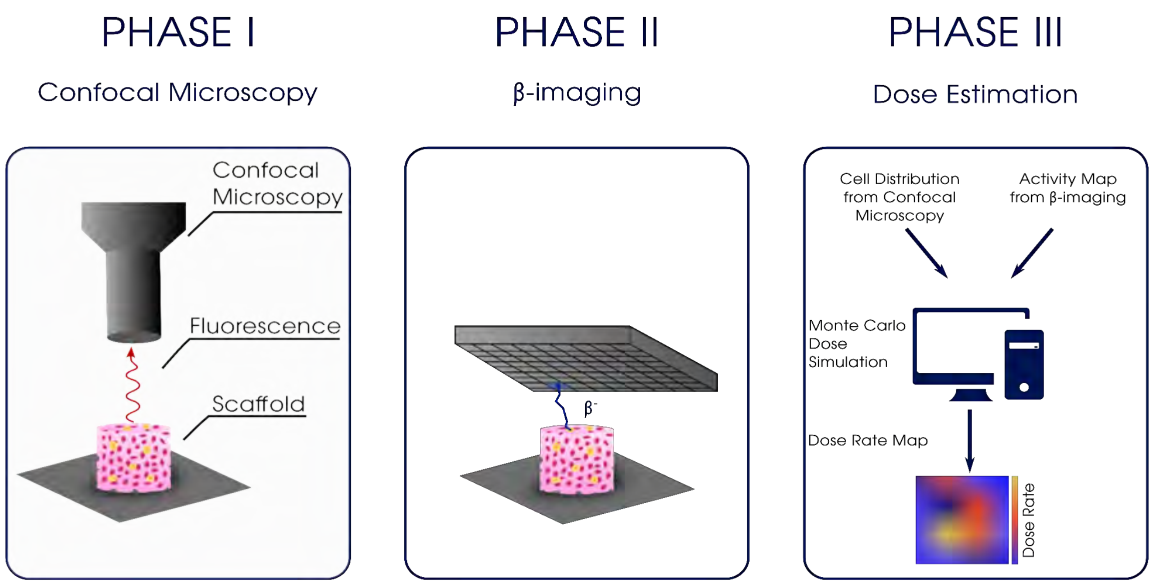


more on WP2: the beta-imaging detector at PD

- **ALPIDE chips**: technology from HEP
- 15 mm x 30 mm active area with 512 x 1024 pixels (typical size about 25 um)
- low-cost readout electronics using commercial FPGA + custom PCB + dedicated Firmware
- modular system, scalable size, compact, easy to use. With 8 chips an active plate of **60 mm x 60 mm** can be easily assembled.



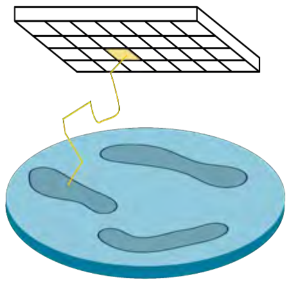




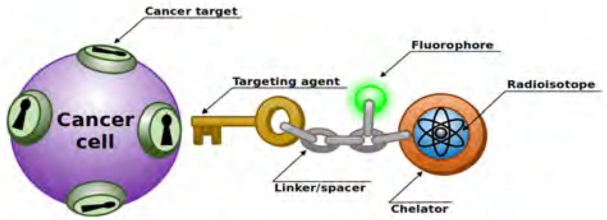
A possible framework for dose estimation in cell survival experiments using confocal and β-imaging.

more on WP2: the beta-imaging detector at PD

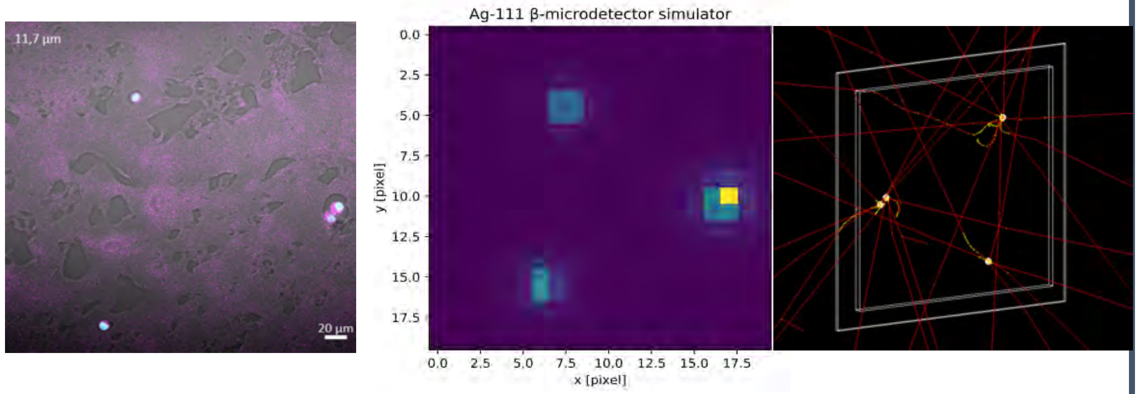
WP2 :
β-imaging



- Mechanics & electronics design
- Monte Carlo simulations for mechanics and detector design
- Detector characterization and tests with fluorescence



Schematic concept of a bivalent fluorescent radiopharmaceutical.



Cell culture in 3D scaffold slice administered with a pharmaceutical: fluorescence confocal microscopy (unlabeled) vs β-microdetector simulation using Geant4 (labeled with ^{111}Ag; pixel size 20 µm, noise 12%, 10^6 CCK2 receptors [26], detector distance 10 µm).

More applications of this technology:

- Direct detection of electrons in the 10 keV – 100 keV range in **Photo Electron Emission Microscopy (PEEMs),** as focal plane detector instead of MCP + phosphor screen => large improvement in spatial resolution and reading speed
- Stack of 10 or more layers for **3D detection of X-rays** up to 1 MeV with single photon and micrometric resolution

ADMIRAL – GANTT

		Year 1				Year 2				Year 3				Notes
		M3	M6	M9	M12	M15	M18	M21	M24	M27	M30	M33	M36	Required for
	WP1 - Radiopharmaceutical production													
MS1.1	Production of Ag-111 at the LENA facilities, purification and quality control	→	o		o		o		o		o		●	MS1.2
MS1.2	Synthesis of the macromolecule for Ag-111 transport and CCK2R-targeted delivery	→	o		o		o		o		o		●	MS1.3, MS2.3, MS3.3, MS4.1, MS4.2
MS1.3	Macromolecules modification with fluorescent with confocal microscopy imaging					→	o		●					MS2.3, MS4.4
MS1.4	Bioengineering of 3D scaffolds for in vitro tissue mimicking	→	o		o		o		o		o		●	MS4.2
	WP2 - β-Imaging													
MS2.1	Electronics and mechanics design	→			o				●					MS2.3
MS2.2	Preliminary Monte Carlo simulations for mechanics and detector design	→		o					●					MS2.3
MS2.3	Detector characterization and test with fluorescence					→			o				●	MS4.4
	WP3 - γ-Imaging													
MS3.1	Preliminary Monte Carlo simulations for detector design	→	o		●									MS3.2
MS3.2	Planar imaging detector construction for Ag-111 γ detection					→	o		●					MS3.3
MS3.3	Characterization and test of the planar system									→			●	
	WP4 - Targeted Radiobiology													
MS4.1	Cell survival tests in 2D Petri dishes					→	o		●					MS4.4
MS4.2	Cell survival tests in 3D scaffold dynamic cultures							→	o		o		●	MS4.4
MS4.3	Comparison between different Monte Carlo codes (Geant4, MCNPX, PHITS)	→			●									MS4.4
MS4.4	Dose computation in cell cultures using MC based on β-imaging/fluorescence					→			o				●	MS4.1, MS4.2

→	Activity started
o	Checkpoint (preliminary/partial results required to start other activities)
●	Milestone reached

ADMIRAL – Personnel and budget

Sezione	Resp. Locale	FTE
LNL	Stefano Corradetti	7.4
PD	Marcello Lunardon	1.4
PV	Aldo Zenoni	2.5
BO	Anselmo Margotti	4.8
TIFPA	Devid Meniglio	2.2
LNS	Giorgio Russo	2.0
Total		~20

	ID		Year 1 [k€]	Year 2 [k€]	Year 3 [k€]	Total [k€]
	ID	WP 1 - Radiopharmaceutical production (LNL, PV, TIFPA)				
CONSUMABLES	1	Reagents - LNL	8	7	8	23
	2	Laboratory material - LNL	8	8	7	23
	3	110Pd - PV	5	5	5	15
	4	Cell cultures - LNL	7	7	7	21
	5	Material for scaffold development - TIFPA	3	3	2	8
SHIPPING	6	Shipping of samples, targets, etc. - LNL	2	2	2	6
	7	Shipping of samples, targets, etc. - PV	2	2	2	6
	8	Shipping of samples, targets, etc. - TIFPA	3	3	3	9
TRAVELS	9	Travels for experimental activity - LNL	3	3	3	9
	10	Travels for experimental activity - PV	1	1	1	3
	11	Travels for experimental activity - TIFPA	3	3	3	9
		TOTAL WP 1	45	44	43	132
		WP 2 - β-Imaging (PD)				
CONSUMABLES	12	Mechanical and ancillary components - PD	9	5	5	19
	13	Electronics - PD	6	5	5	16
SHIPPING	14	Shipping of detectors, etc. - PD	2	2	2	6
TRAVELS	15	Travels for experimental activity - PD	3	4	4	11
		TOTAL WP 2	20	16	16	52
		WP 3 - γ-Imaging (BO)				
EQUIPMENT	16	Detector Collimator - BO	0	10	0	10
CONSUMABLES	17	Laboratory material - BO	1	0	0	1
	18	Electronics - BO	10	0	12	22
	19	Crystals - BO	0	6	0	6
SHIPPING	20	Shipping of detectors, etc. - BO	3	3	3	9
TRAVELS	21	Travels for experimental activity - BO	3	3	3	9
		TOTAL WP 3	17	22	18	57
		WP4 - Targeted Radiobiology (PV, LNS)				
EQUIPMENT	22	Incubator - PV	10	0	0	10
	23	Cell refrigerator - PV	2	0	0	2
CONSUMABLES	24	Biology material - PV	2	5	5	12
	25	Laboratory material - PV	4	3	3	10
	26	Laboratory material - LNS	1	1	1	3
SHIPPING	27	Shipping of samples, targets, etc. - PV	3	3	3	9
	28	Shipping of samples, targets, etc. - LNS	2	2	2	6
TRAVELS	29	Travels for experimental activity - PV	2	2	2	6
	30	Travels for experimental activity - LNS	3	3	3	9
		TOTAL WP 4	29	19	19	67
		TOTAL BUDGET	111	101	96	308

INFN-PD – details for 1st year

		Year 1 [k€]	Year 2 [k€]	Year 3 [k€]
INFN-PD				
Consumables	Mechanical and Ancillary components:			
	- Thorlabs mech. + opt. components for beta-imaging sensor test	3		
	- Thorlabs precision XY movements	5		
	- other components	1	5	5
	Electronics			
	- Xylinx FPGA development kit	3		
	- FPGA boards Trenz Electronic GmbH	1		
	- Power supply Keysight Tech	1		
	- other components	1	5	5
Shipping	Shipping of detectors from PD to test sites in Italy	2	2	2
Travels	Travels for experimental activity	3	4	4
TOTAL INFN-PD		**20**	**16**	**16**

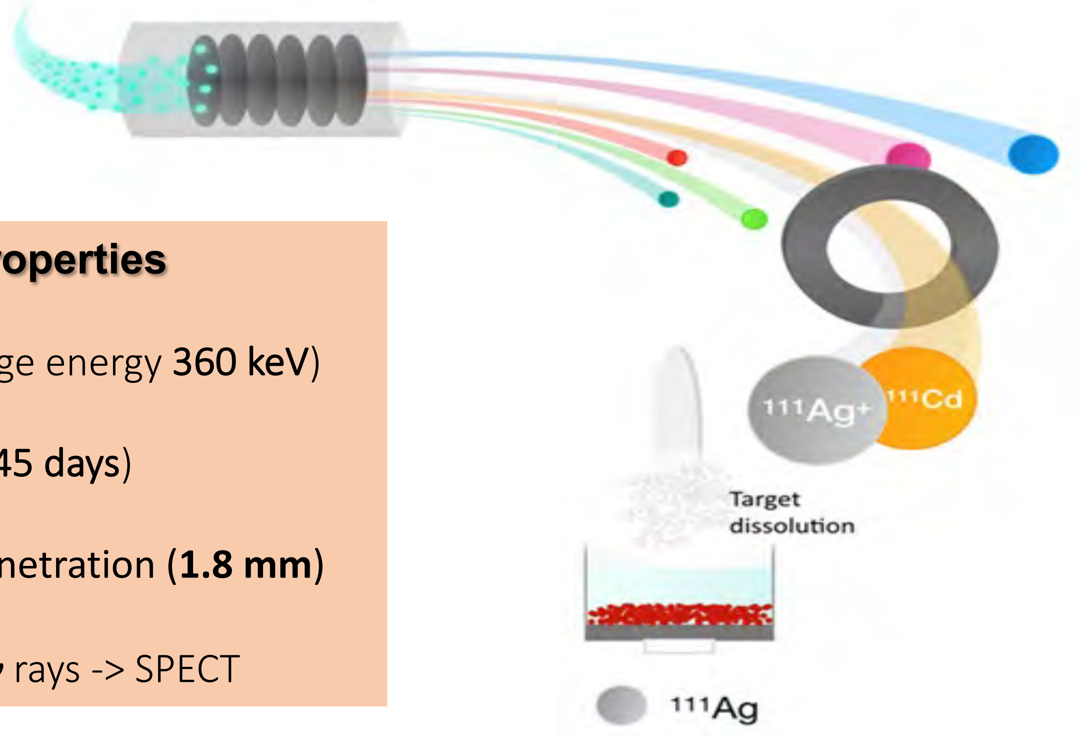
Anagrafica: M. Lunardon **0.3**, S. Moretto **0.1** , P.Lotti **0.3**, L. Zangrando **0.2**, Chiara Bonini **0.5** (new, gruppo di Piero Giubilato) **TOT = 1.4 FTE**

NB: dal 1 novembre ci sarà un assegnista di ricerca al 100% sul progetto (bando PRD 2022 cofinanziato INFN, approvato)

Richieste servizi: 1 M.U. officina meccanica per realizzazione pezzi per supporto e movimentazione del beta-imaging system

Thank you for your attention!

ISOLPHARM: Why ^{111}Silver



^{111}Ag properties

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

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

- ❑ In the market **No radiopharmaceuticals** Silver-based!
- ❑ 111Ag can be produced @ SPES **with high purity** & also with **high production rate.**
- ❑ **No Isobaric radioactive contamination** in the secondary target (also with LASER off)!

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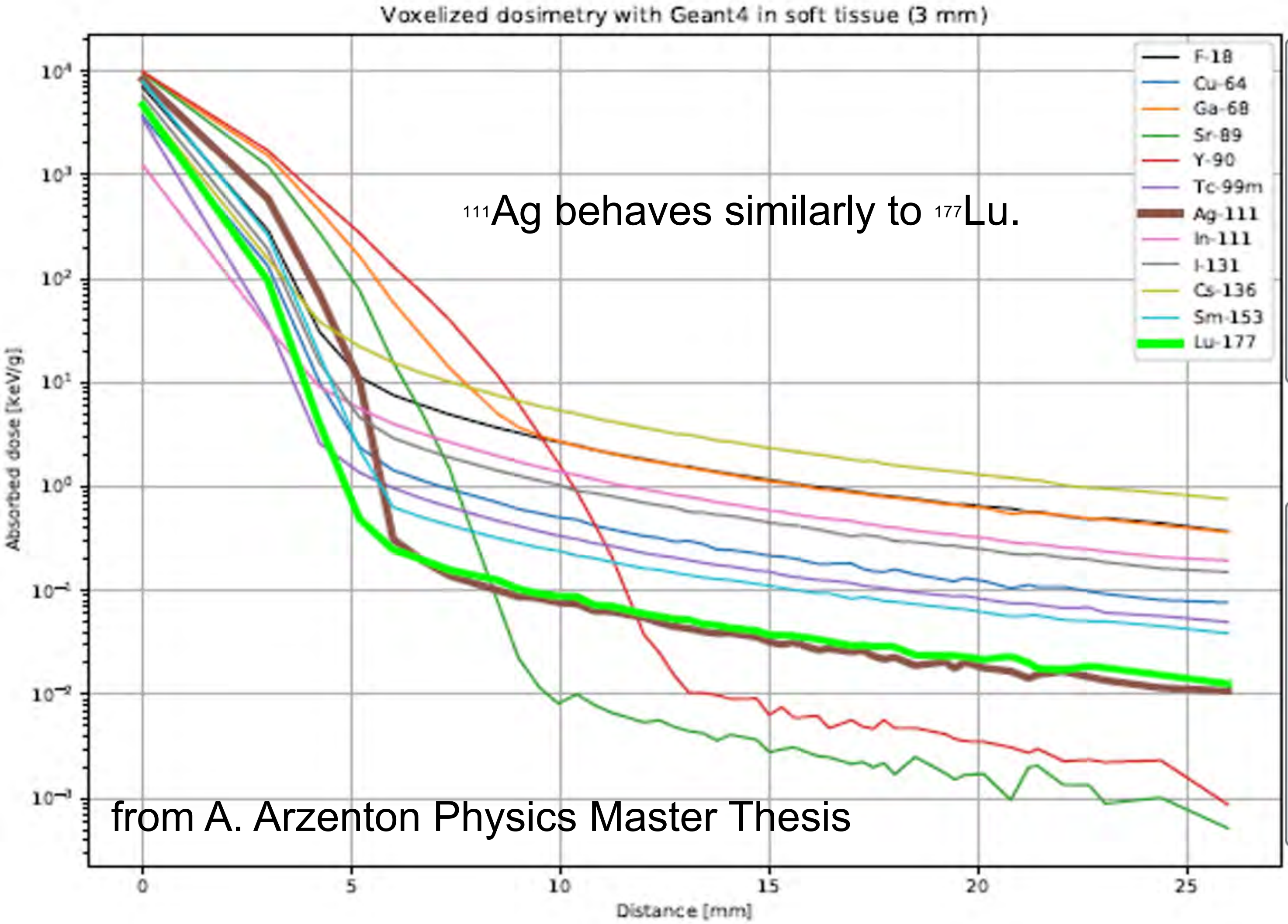
ISOLPHARM: ^{111}Silver versus ^{177}Lutetium



MUTATIS MUTANDIS....