ISOLPHARM
SPES exotic beams for medicine

INFN
Istituto Nazionale di Fisica Nucleare
LABORATORI NAZIONALI DI LEGNARO

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 collaboration

ISOLPHARM
SPES exotic beams for medicine

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Dipartimento di Fisica e Astronomia Galileo Galilei

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dsf DiSC

L.E.N.A.

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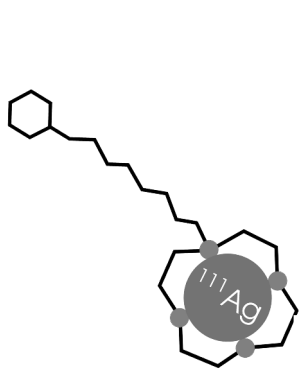
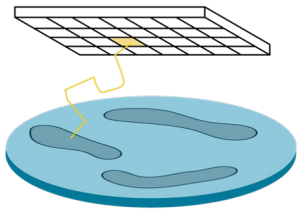
UNIVERSITÀ DEGLI STUDI DI BRESCIA

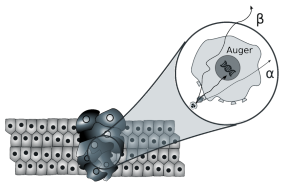
IBFM

Radiopharmaceutical production

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







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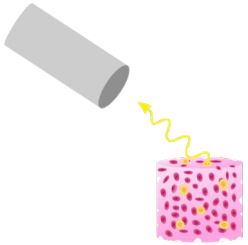
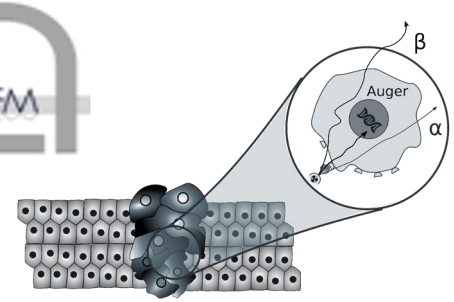


Development of a γ-imaging scintigraphic system



Radiobiological characterization

Fondazione Ri.MED

INFN LNS
Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali del Sud

UNIVERSITÀ DI TRENTO

CAPiR
Center for Advanced Preclinical in vivo Research

UNIVERSITÀ degli STUDI di CATANIA

TIFPA
Trento Institute for Fundamental Physics and Applications

CIBIO
Centre for Integrative Biology

ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA

INFN BOLOGNA
Istituto Nazionale di Fisica Nucleare
Sezione di Bologna

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
IRCCS Istituto di Ricovero e Cura a Carattere Scientifico

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Reggio Emilia
IRCCS Istituto in tecnologie avanzate e modelli assistenziali in oncologia

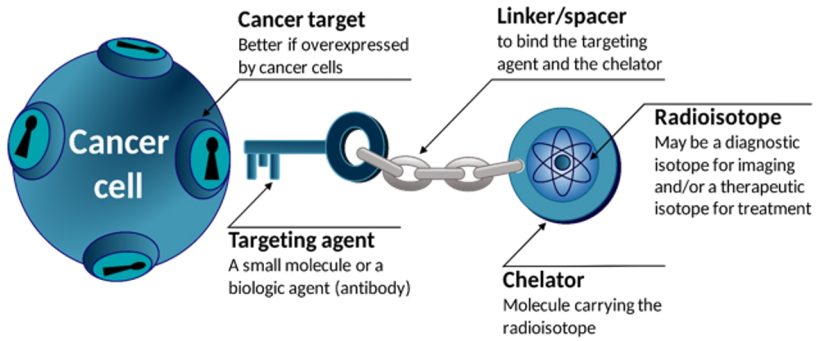
Interdisciplinary WPs: WP1 & WP4

WP1

WP Leader: V. Di Marco (UNIPD) and D. Meniglio (UNITN)

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.

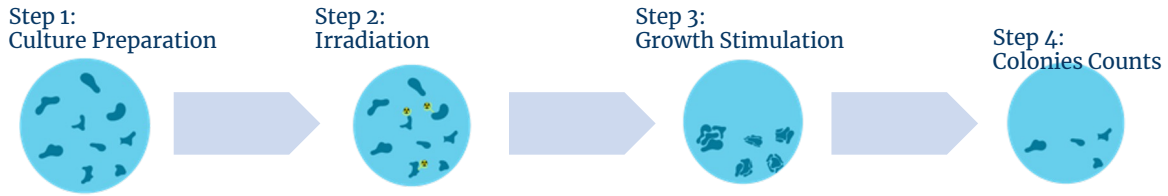


WP4

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**.



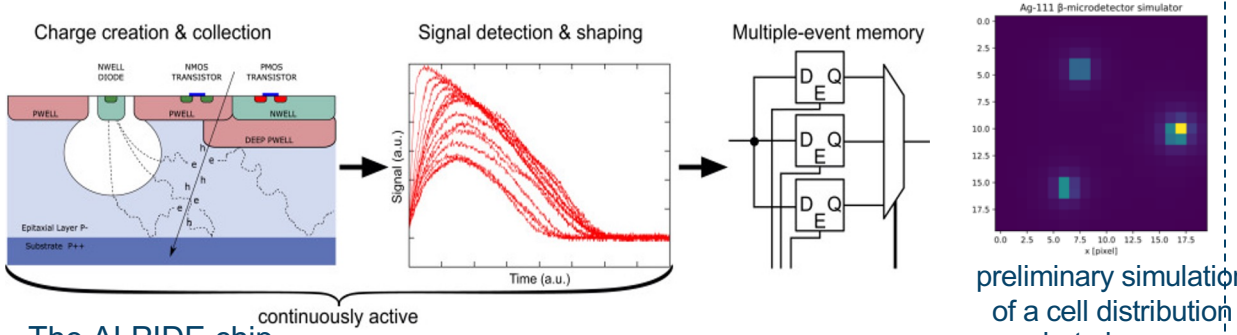
Detector development WPs: WP2 & WP3

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

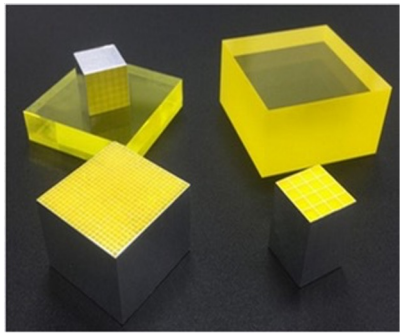
WP3

WP Leader: C. Sbarra (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



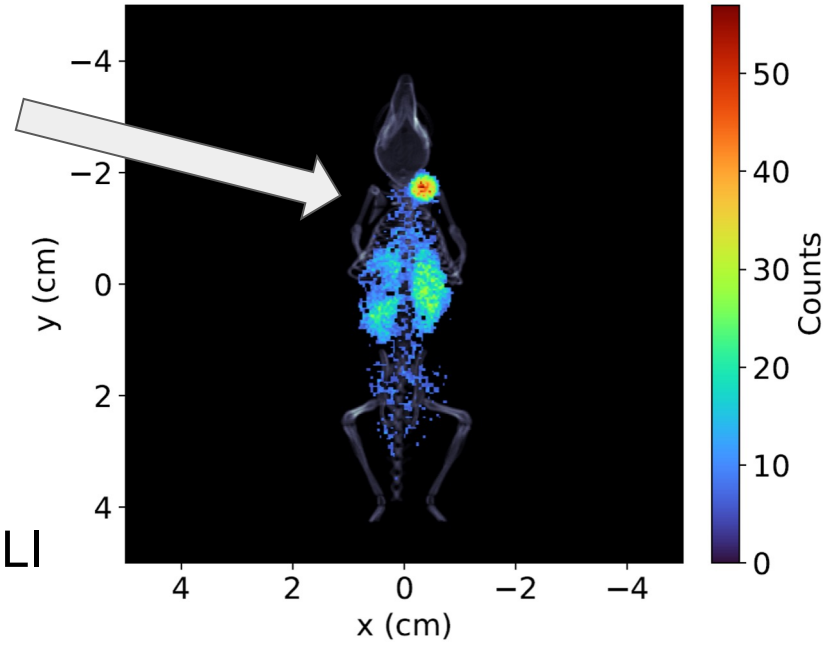
WP1 – Simulation of ^{111}Ag imaging

Targeting of the radiolabeled macromolecule

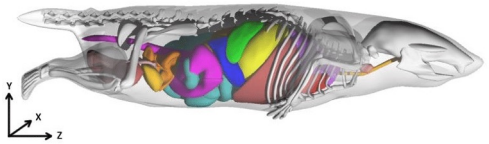
Ga-68
experimental
biodistribution

Ag-111
Ga-68

Ag-111
simulated
biodistribution



- Superimposition of:
  - **CLI** image
  - **CT** image



MOBY phantom for the geometry

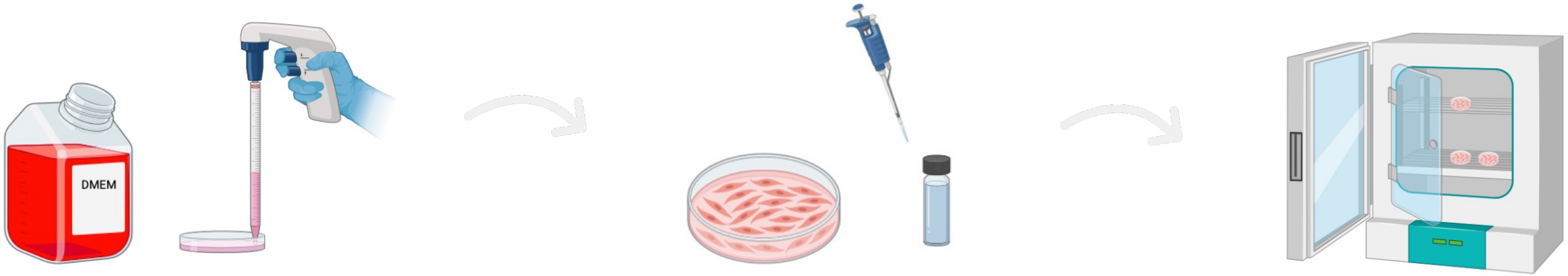
Geant4 toolkit for CLI

- Lesions in *in-vivo* experiments can be imaged with Ag-111 and Xtreme

WP4 – First cell survival test with ^{111}Ag

- 48 ore prima dell'esposizione ad Ag111, sono state allestite **3 capsule Petri** seminate con 10.000 cellule per ogni condizione da testare;

- Ciascuna delle Petri è stata così trattata:
  - Sostituzione del terreno di coltura con terreno fresco;
  - Aggiunta di Ag111 al terreno di coltura per esporre le cellule alla prestabilita attività di Ag111;
  - Incubare fino al time-point prestabilito.



WP4 – First cell survival test with ^{111}Ag

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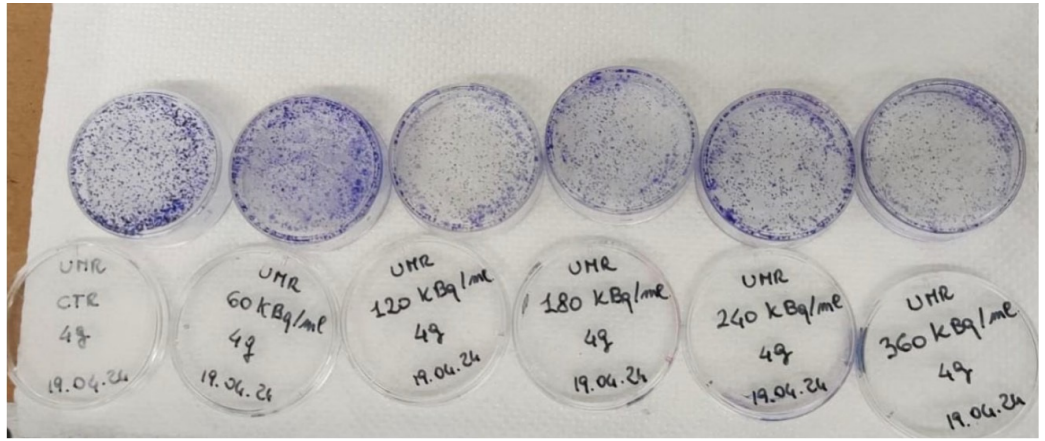
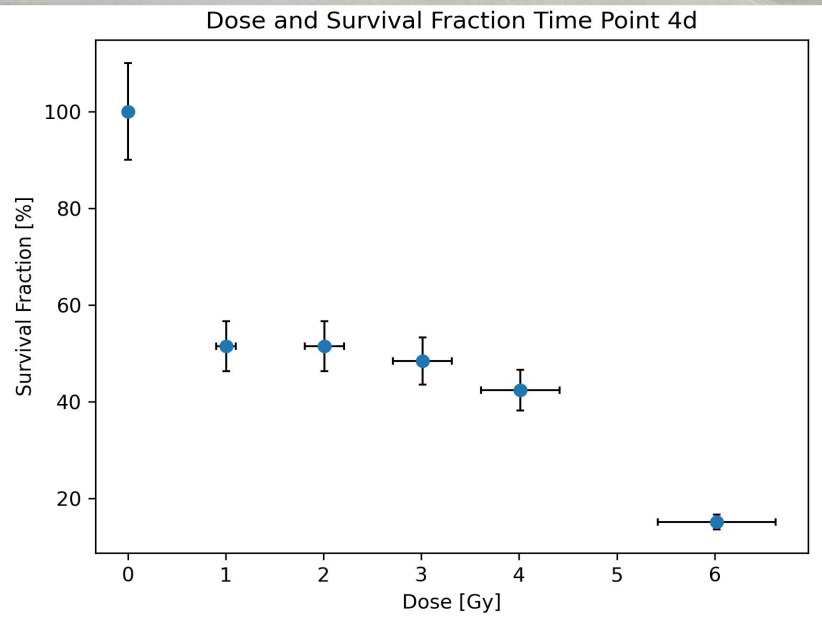


Time Point 4d

Dose [Gy]	Survival Fraction [%]
-	100 ± 10
1.0 ± 0.1	52 ± 5
2.0 ± 0.2	52 ± 5
3.0 ± 0.3	48 ± 5
4.0 ± 0.4	42 ± 4
6.0 ± 0.6	15 ± 2



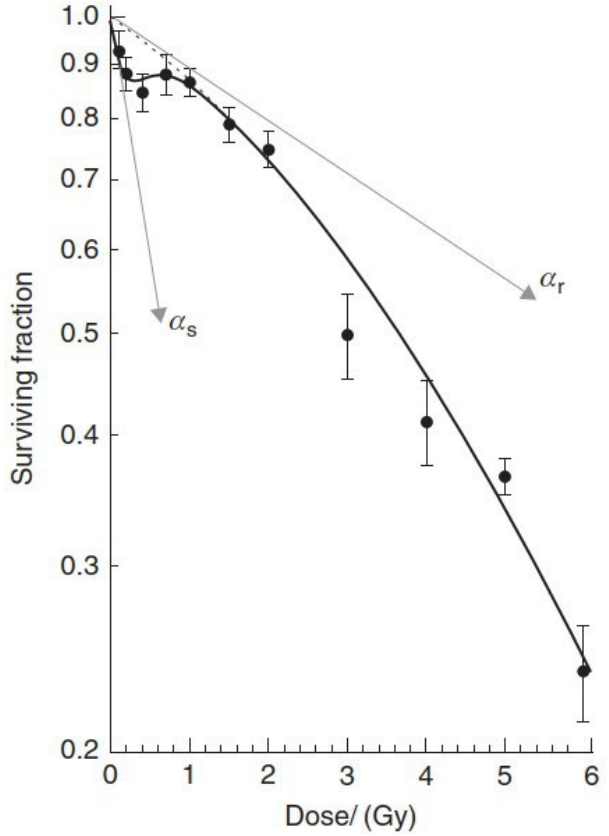
Dose and Survival Fraction Time Point 4d

WP4 – First cell survival test with ^{111}Ag

Low-Dose Hyper-Radiosensitivity

The LQ model describes cellular response to radiation above about 1 Gy. Below about 10 cGy, the cells show HRS, a phe- nomenon by which cells die from exces- sive sensitivity to low doses, due to rapid cell cycle arrest of irradiated cells in the G2 phase of the cycle. It can be char- acterized by a slope (α_s) that is consid- erably steeper than the slope expected by extrapolating back the response from high-dose measurements (α_r).[1]

The induced-repair model



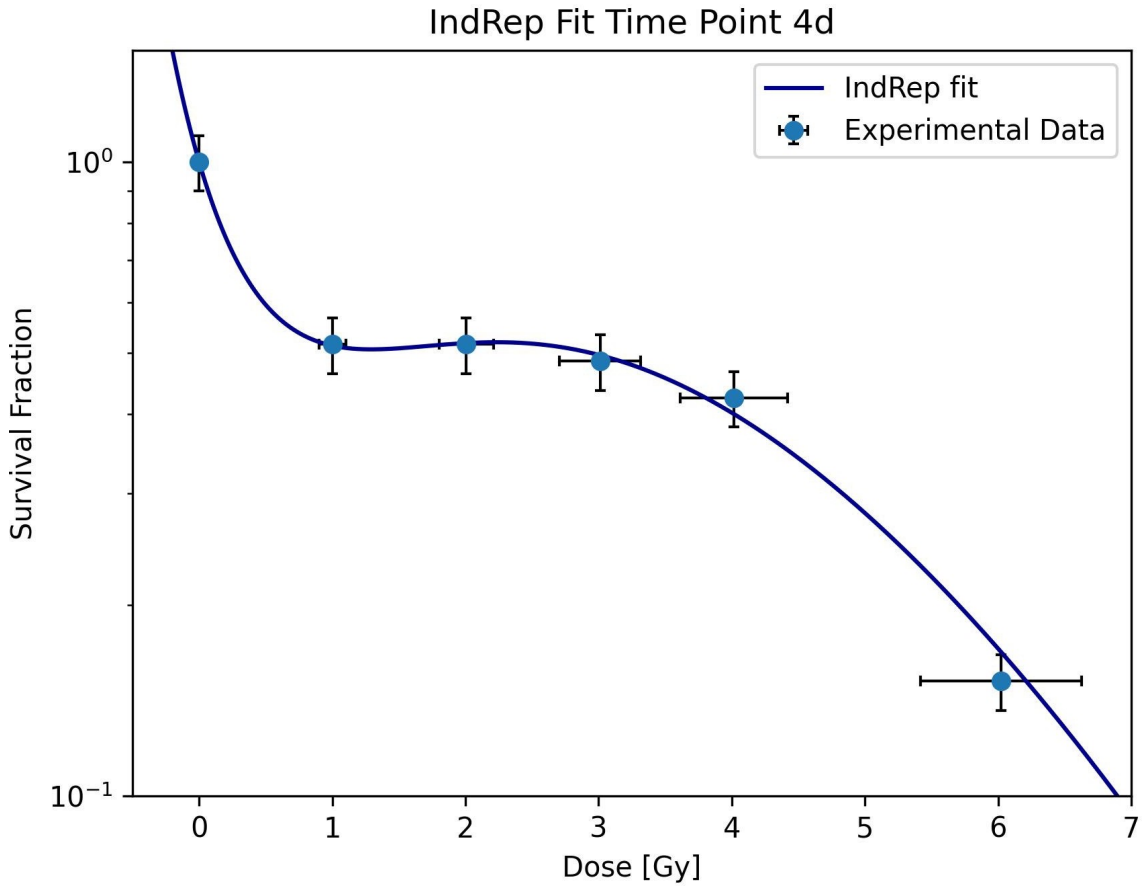
The IndRep model thus comprises two LQ models with different α sensitivities dependent on the dose given, merged into a single equation:

$$S(D) = exp\left(-\alpha_r \cdot D \cdot \left(1 + \left(\frac{\alpha_s}{\alpha_r} - 1\right) e^{-\frac{D}{D_c}}\right) - \beta \cdot D^2\right)$$

[1]Joiner, M. & Van der Kogel, A. (2009). *Basic Clinical Radiobiology*, Great Britain, Hodder Arnold, 1993, pp.53-54.

WP4 – First cell survival test with ^{111}Ag

Induced-repair model Fit

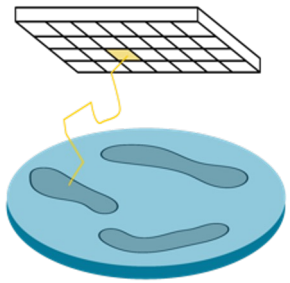


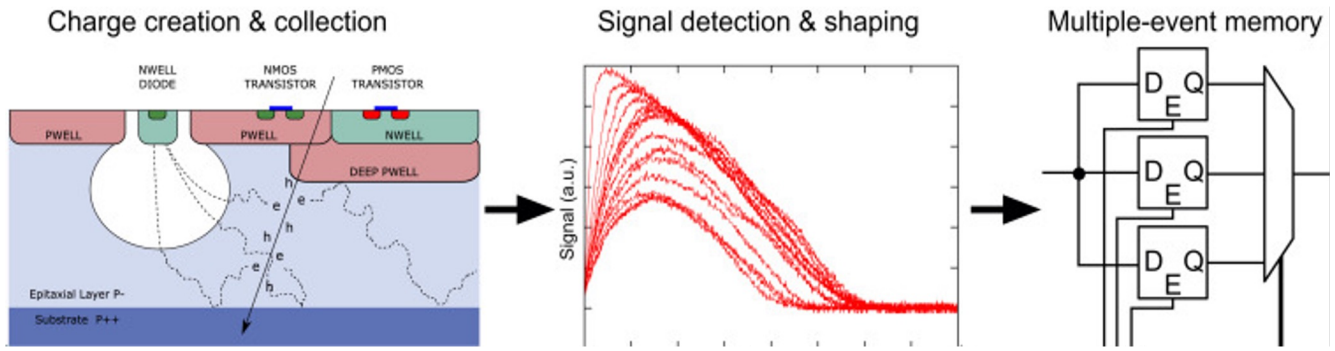
Fit parameters:

- $\alpha_r = 0.01 \pm 0.11 \ \frac{1}{\text{Gy}}$
- $\alpha_s = 1.7 \pm 0.4 \ \frac{1}{\text{Gy}}$
- $D_c = 1.0 \pm 0.3$ Gy
- $\beta = 0.05 \pm 0.02 \ \frac{1}{\text{Gy}^2}$

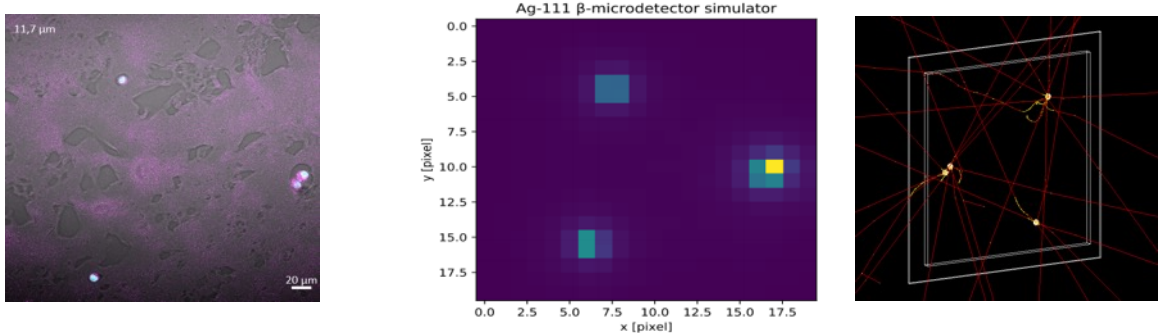
the beta-imaging detector at PD

- **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.





Schematic concept of a bivalent fluorescent radiopharmaceutical.

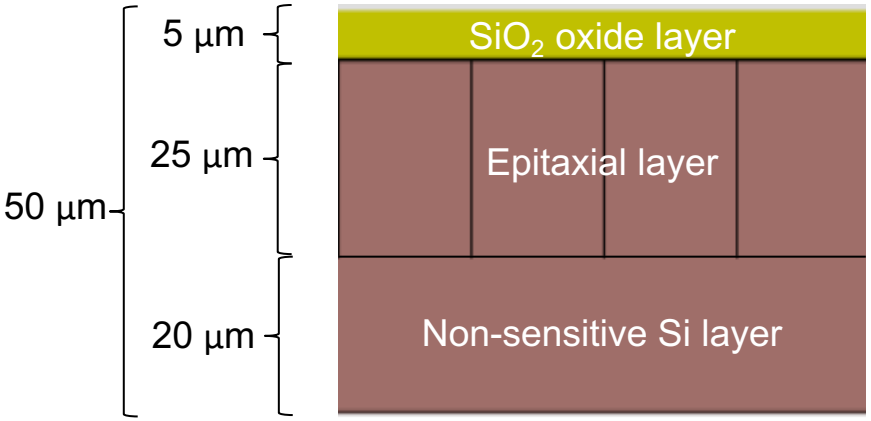


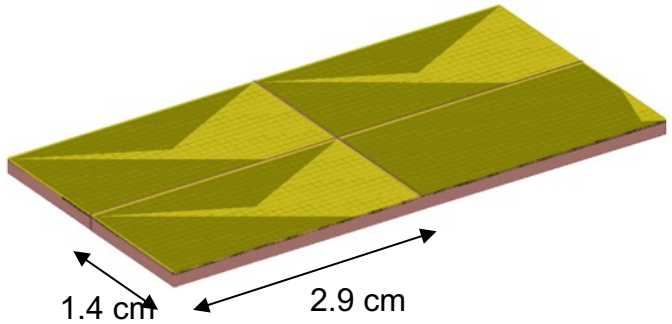
Cell culture in 3D scaffold slice administered with a pharmaceutical: fluorescence confocal microscopy (unlabeled) vs β-microdetector simulation using Geant4 (labeled with ^{111}Ag; pixel size 20 µm, noise 12%, 10^6 CCK2 receptors [26], detector distance 10 µm).

the beta-imaging detector at PD

ALPIDE Modelling

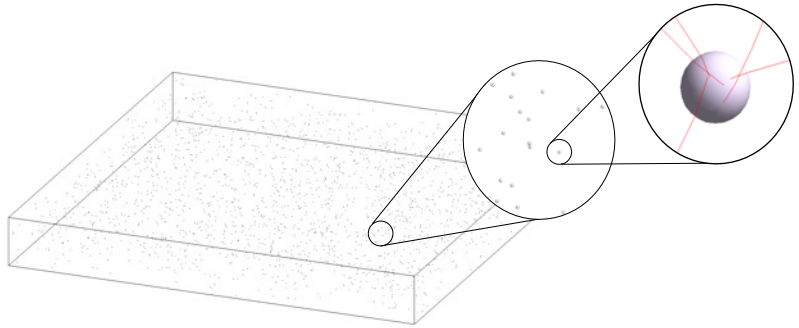
ALPIDE: silicon detector *developed for* ***particle tracking*** *in ALICE (CERN). It is made of 1024x512 sensitive pixels of size (28x28) μm².*

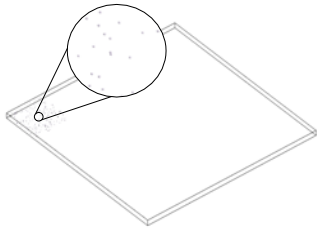


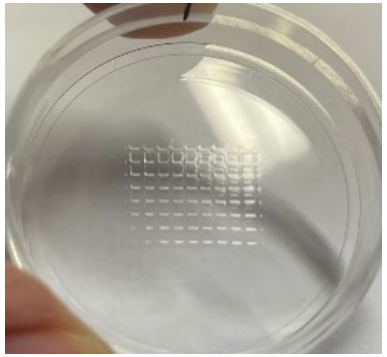


Source Modelling

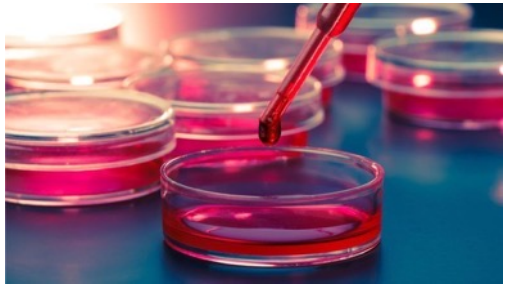
Radiation source: Scaffold → Aqueous spherical cells *(**10 μm** radius) dispersed in hydrogel matrix. Inside the cell volume,* ***^{111}Ag*** *undergoes β decay.*







→ **Scaffold**
- different geometries
- different substrates

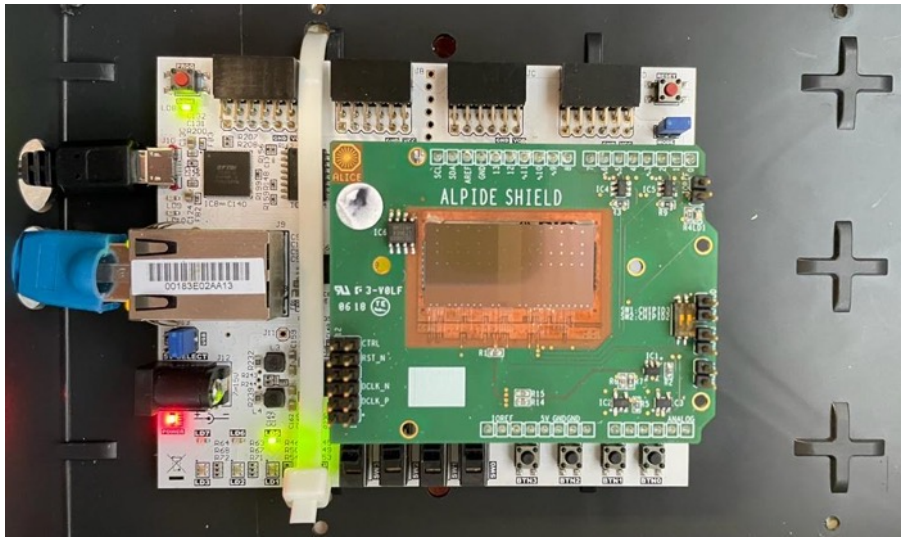


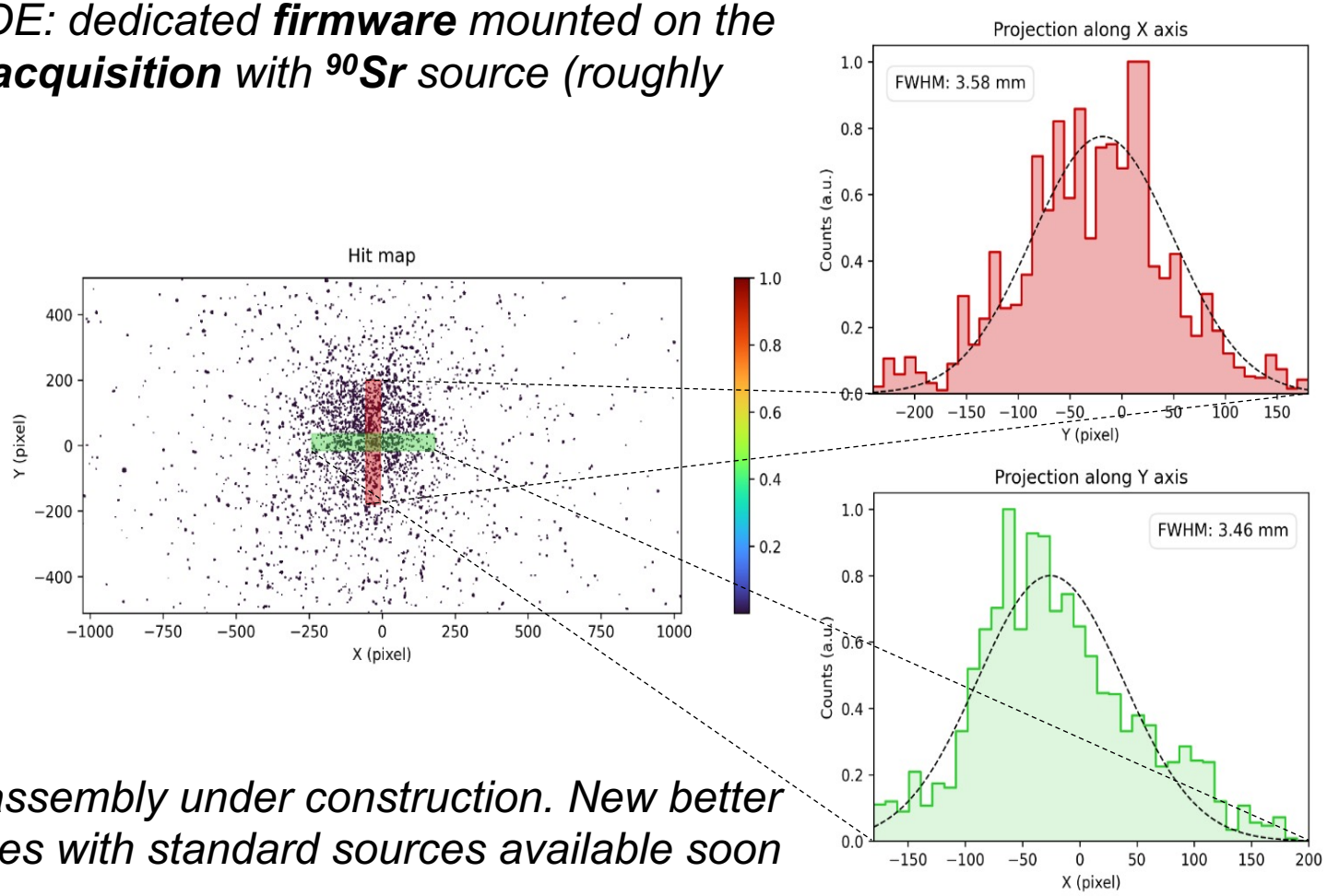
→ **Traditional cell culture**
- Petri dish
- Mylar (or other materials) substrate

the beta-imaging detector at PD

first measurements with ALPIDE (2023)

*First measurements conducted with ALPIDE: dedicated **firmware** mounted on the detector and carried out preliminary **data acquisition** with ^{90}**Sr** source (roughly collimated).*



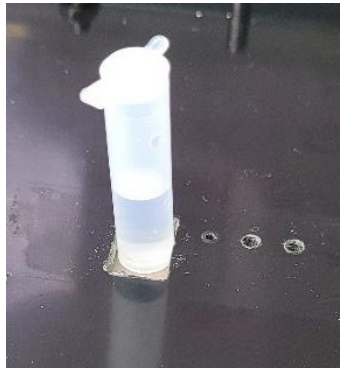


New more precise assembly under construction. New better images with standard sources available soon

ALPIDE measurements in Pavia (4/2024)

Measurement performed with different quantities of ^{111}Ag and different test vial at LENA (Pavia) April 2024.

- 1kBq + Glass vial(d=0.96cm) (very low rate).
- 247kBq +Plastic vial(d=1.2cm) + solvent (0.4 ml) (low rate)
- 222kBq + Plastic vial(d=0.6cm) + solvent (0.4 ml) (low rate)
- 27.5MBq + Plastic vial(d=1.2cm) + solvent (0.4 ml) (high rate – measurement crashed)
- **3.5MBq + Plastic vial (d=1.2cm) + solvent (0.3 ml) (measurement crashed after two minutes). Vial used for the rest of the measurements.**



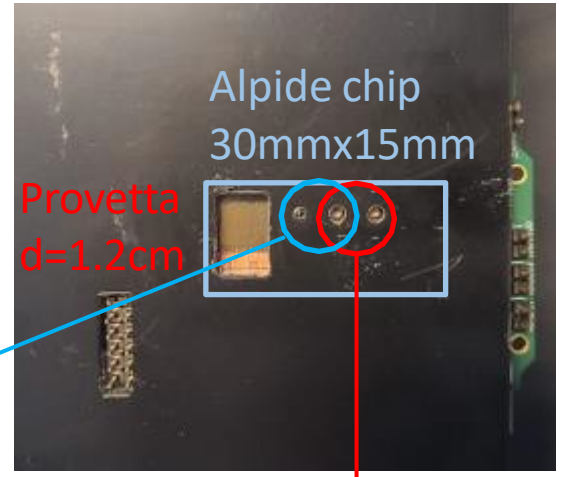
d=0.96cm

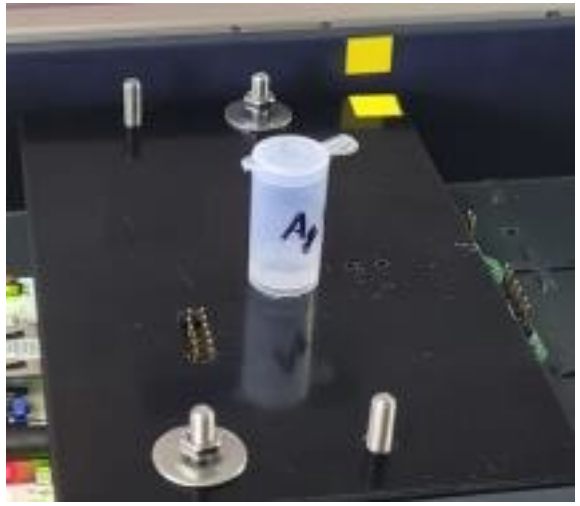
d=0.6cm

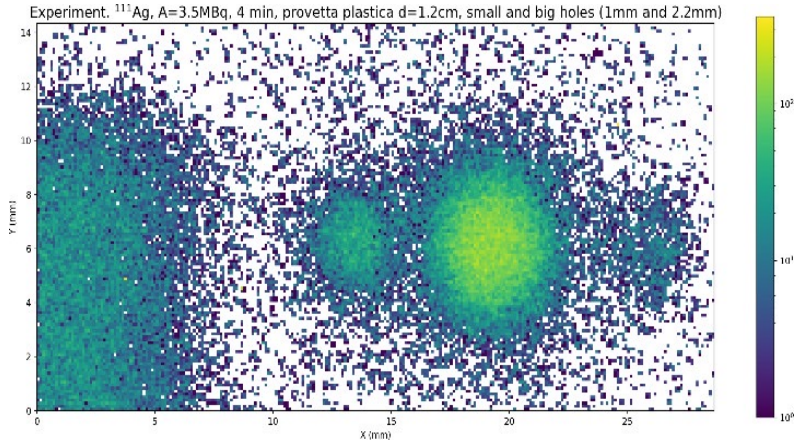
d=1.2cm

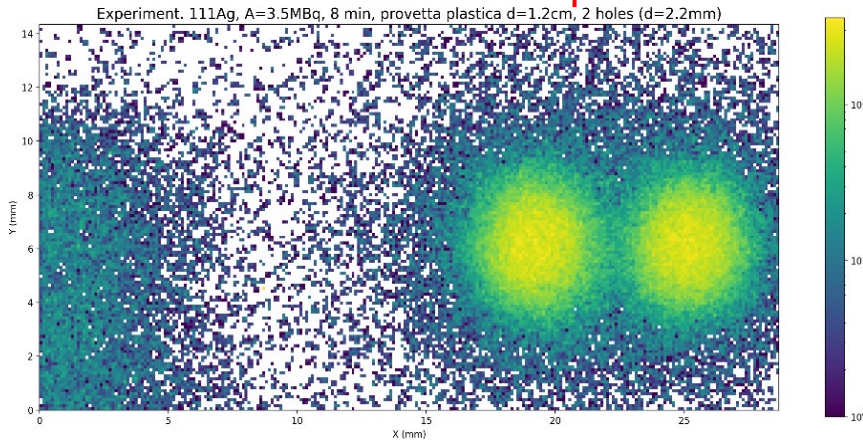
ALPIDE Measurements in Pavia

- Measurement performed with ^{111}Ag A=3.5 MBq, inside a plastic vial with d=1.2cm, and solvent solution 0.3ml.
- PVC was cut in order to have an idea of the spatial resolution of the detector:
  1. Two holes d=2.2mm
  2. Large slot 7.8mm x 12.2mm, almost half of the chip exposed
  3. Small and big holes, d=1mm and d=2.2mm



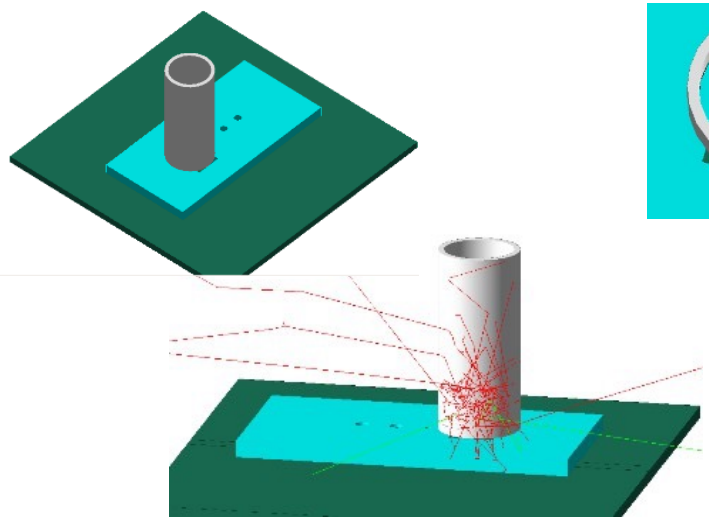


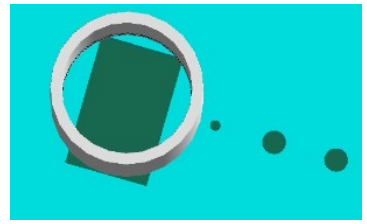




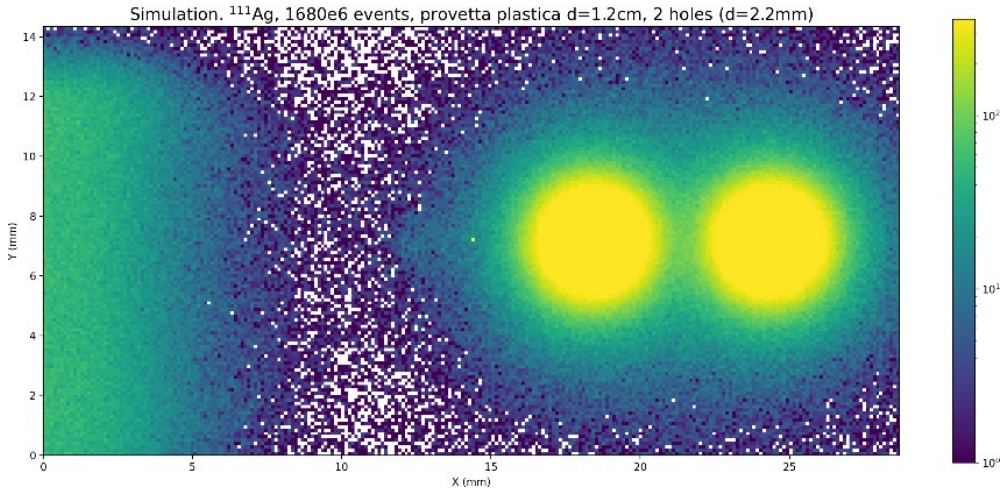
ALPIDE Measurements in Pavia

- Simulations on the same condition of the experimental measurements.
- Simulation of the beta spectrum emitted by the ^{111}Ag.
- Number of events simulated equivalent to the number of decays during the measurement

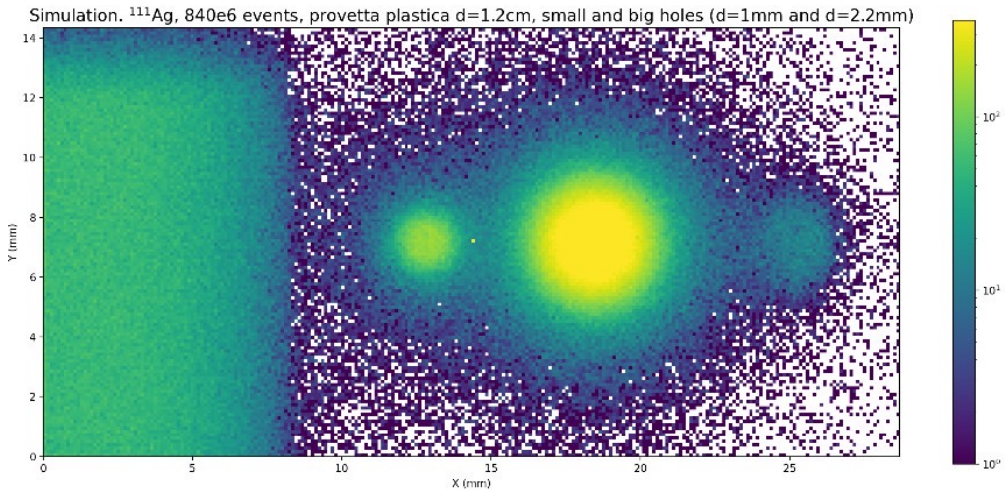




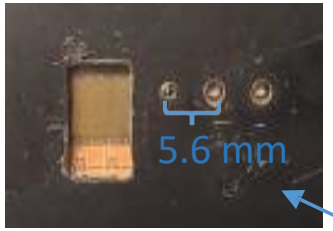
Two holes (d=2.2mm)



Small and big holes (d=1mm and d=2.2mm)

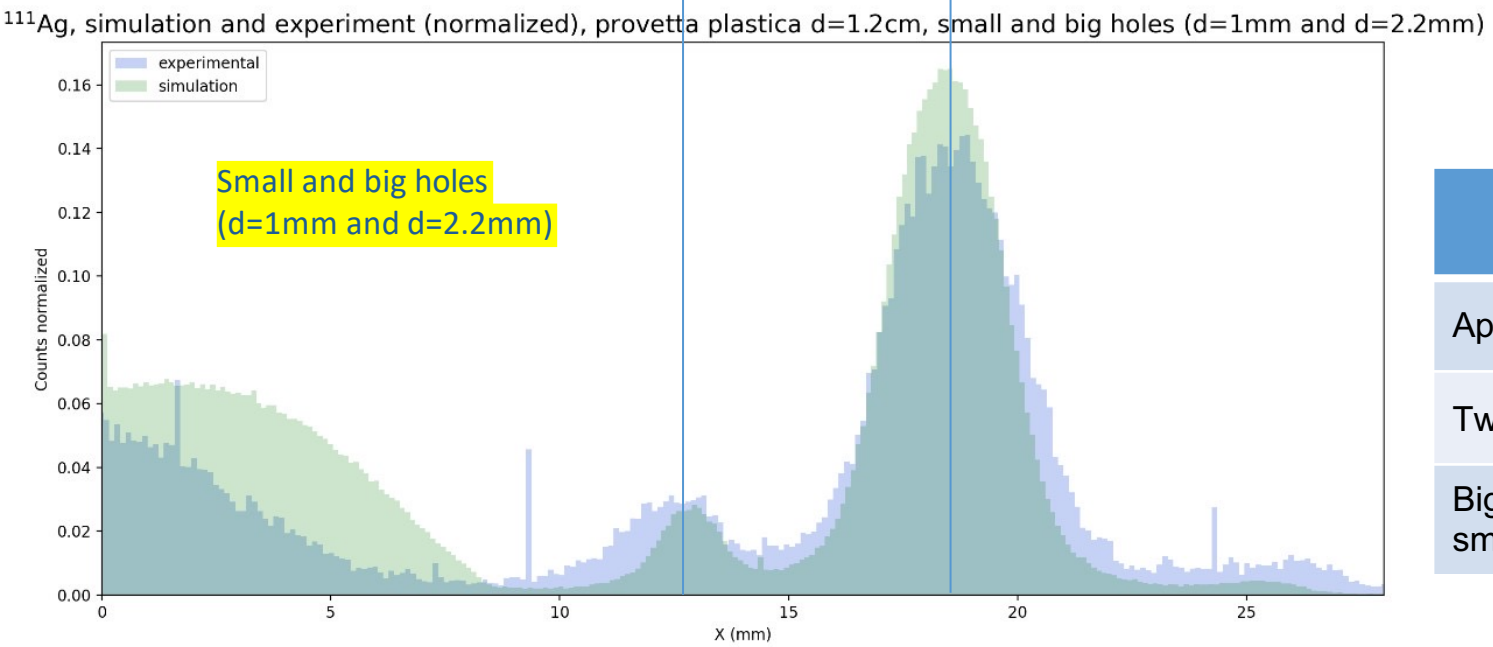


Exp. and Sim. comparison



Good agreement of the spatial distribution between the experimental and simulations results.

Δx≈6 mm



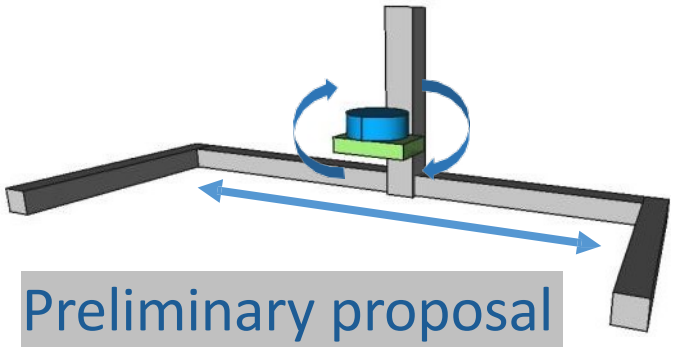
	Exp (counts)	Sim (counts)	Eff (%)
Aperture	6768623	39037992	17.33
Two holes	688339	1990557	34.58
Big and small holes	294995	842104	35.03

Higher rate

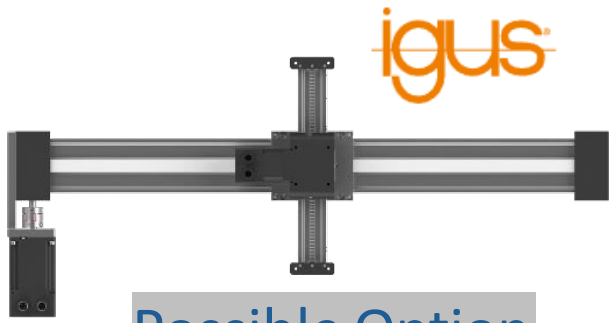
Lower rate

Mechanical design

- Useful help from Roberto Michinelli, from the Mechanical Design Service at INFN Bologna.
- Some administrative difficulty for buying ready-to-use parts (mainly from China)
- Possible option: linear gantry two-dimensional movement, parameters can be customized by the user. Produced by IGUS and FESTO (German companies).
- Waiting for the budget proposal.



Preliminary proposal



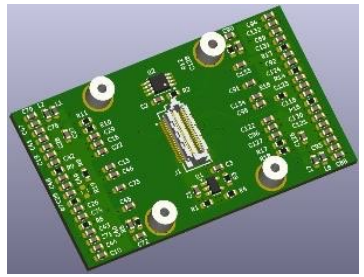
Possible Option

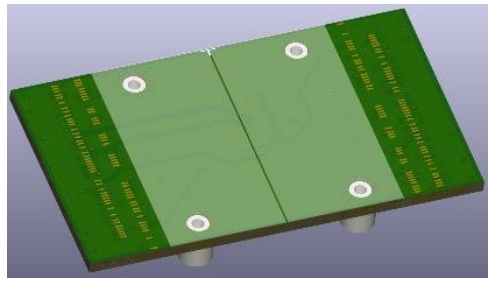
Possible Option

Design of the PCB for the chips

- Chip mounting PCB hosting two ALPIDE chips (basic module): design ready.
- Design of the mezzanine board still pending (to be defined next weeks).
- The bottom layer hosts the FPGA. A Raspberry Pi temporary option is also being evaluated

PCB design





PCB for chip mounting

mezzanine board

FPGA board

connection from commercial FPGA (standard connectors) to custom PCB with ALPIDE chips

Raspberry Pi Pico

ADMIRAL – GANTT

we are here

ADMIRAL WP2

		Year 1				Year 2				Year 3				Notes
		M3	M6	M9	M12	M15	M18	M21	M24	M27	M30	M33	M36	Required for
	WP2 - β-Imaging													
MS2.0	Development of the detector control firmware prototype	→			●									MS2.3
MS2.1	Electronics and mechanics design	→			○		○		●					MS2.3
MS2.2	Preliminary Monte Carlo simulations for mechanics and detector design	→		○					●					MS2.3
MS2.3	Detector characterization and test with fluorescence							→	○				●	MS4.4

Milestone MS2.1 :

- work ongoing, design for electronic board and mechanics expected on time

Milestone MS2.2:

- MC code already implemented and working. To be updated according with final E+M design

Milestone MS2.3 (2025):

- some first experimental test already done!

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ADMIRAL WP2

we are here

		Year 1				Year 2				Year 3				Notes
		M3	M6	M9	M12	M15	M18	M21	M24	M27	M30	M33	M36	Required for
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MS2.2	Preliminary Monte Carlo simulations for mechanics and detector design	→		○					●					MS2.3
MS2.3	Detector characterization and test with fluorescence							→	○				●	MS4.4

Activity planned for second semester 2024:

- finalize the design of board and FW for a 2 chips module (30 mm x 30 mm) and start the realization. This module can be easily duplicated to allow for a 2 x N chip configuration
- finalize the design of the final mechanics and start the realization
- finalize the MC tool
- more experimental test with the currently working prototype

Activity proposed for 2025:

- complete the realization of the prototype detector and the mechanics
- test and characterization of the prototype

INFN-PD – budget for 3nd year

		Requested [k€]	Granted [k€]
Consumables	**Mechanics**	1	-
	Electronics	4	-
Shipping	Shipping of detectors from PD to test sites in Italy	2	-
Travels	Travels for experimental activity	4	-
TOTAL INFN-PD		**16**	**-**

Anagrafica 2024: M. Lunardon **0.6**, S. Moretto **0.1** , P.Lotti **0.3**, L. Zangrando **0.2**, Chiara Bonini (PhD) **0.5,** Daiyuan Chen (PhD) **1.0**, Jessica Delgado Alvarez (Assegno) **1.0**

TOT = 3.7 FTE

Anagrafica 2025: M. Lunardon **0.5** (0.2 in SPES_MED), S. Moretto **0.1** (0.5 in SPES_MED) , Jessica Delgado Alvarez (Assegno) **1.0 +** possibile percentuale parziale di dottorando elettronica nel corso del 2025

TOT = 1.6 FTE

Collaborano inoltre: Piero Giubilato, Michele Giorato

Richieste servizi: 2/3 M.U. officina elettronica per realizzazione scheda, chip bonding e altre operazioni (TBD next con Marino)

ISOLPHARM
SPES exotic beams for medicine

INFN
Istituto Nazionale di Fisica Nucleare
LABORATORI NAZIONALI DI LEGNARO

Thank you for your attention!