*CSNV proposal*

# ISOLPHARM_EIRA

## Experiment on Interdisciplinary research on Radioactive Ag

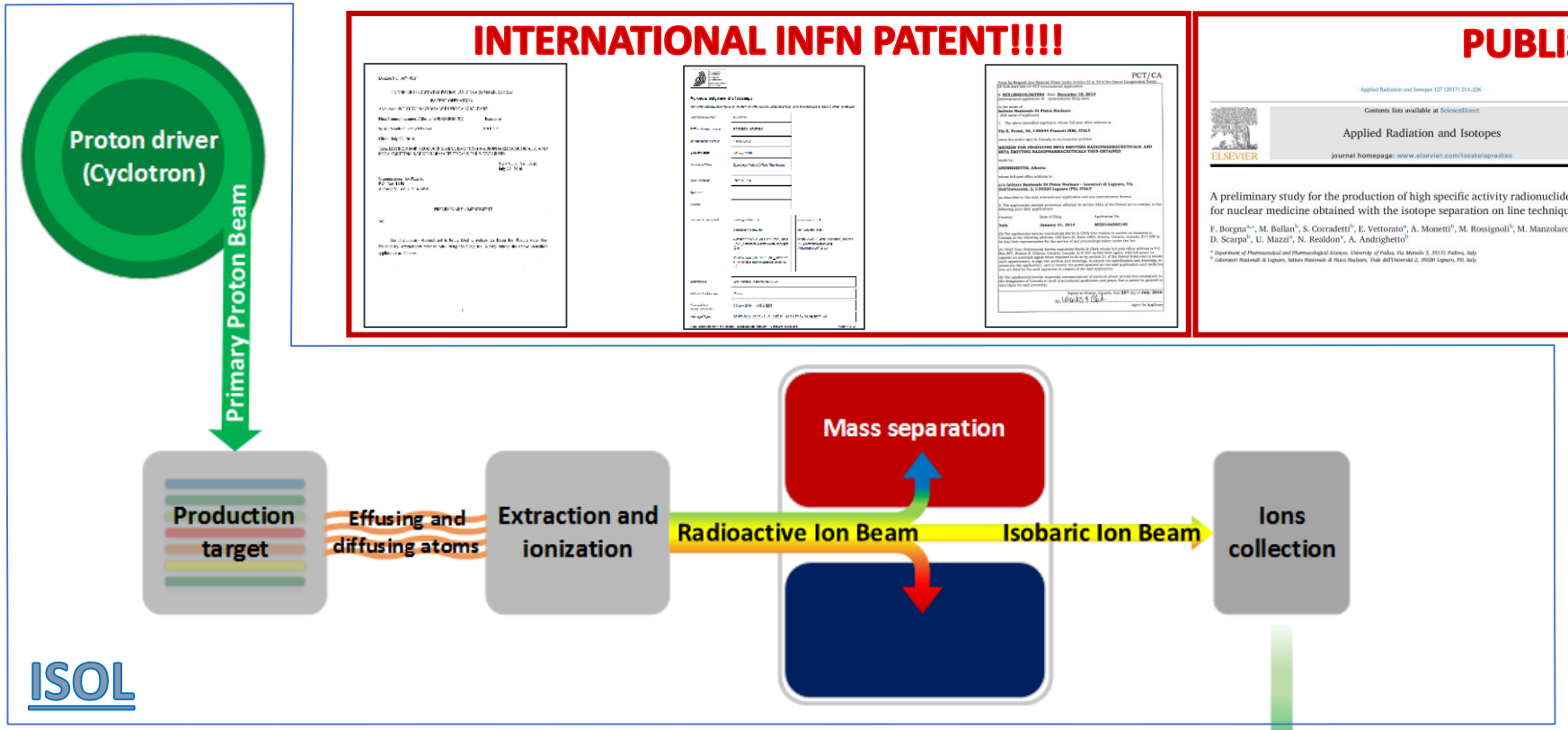
ISOLPHARM
SPES exotic beams for medicine

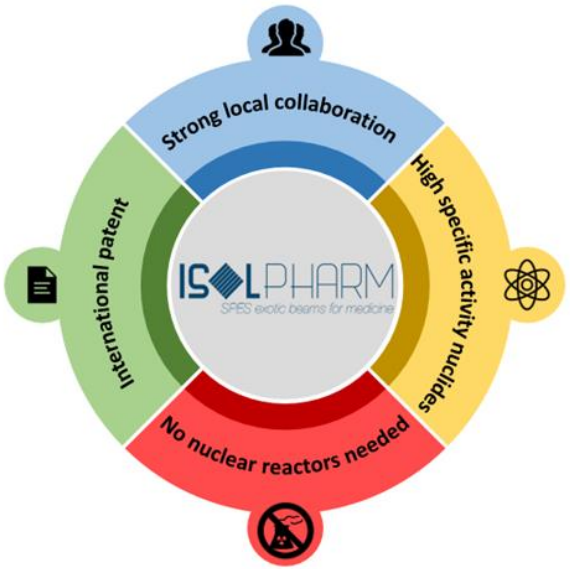
# The ISOLPHARM method

## INTERNATIONAL INFN PATENT!!!!



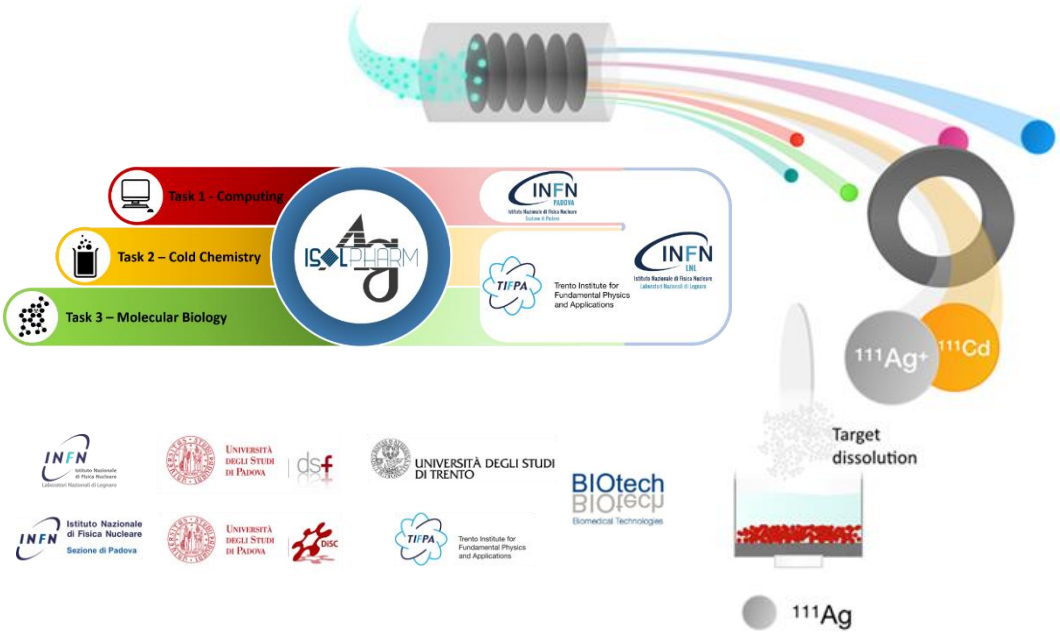
## PUBLISHED PAPERS


**Flexible production, high specific activity & radionuclidic purity**

# ISOLPHARM_Ag: a case study on $^{111}$Ag




Experiment financed by INFN CSN V

## $^{111}$Ag properties

- ❑ $\beta^-$ emitter (average energy 360 keV)
- ❑ Medium half-life (7.45 days)
- ❑ Medium tissue penetration (**1.8 mm**)
- ❑ Low energy $\gamma$ rays SPECT

| 111 Isobaric chain | $t_{½}$ | Decay | Target Yield |
|---|---|---|---|
| **$^{111}$Cd** | Stable | | Low yield production |
| **$^{111}$Ag** | 7.45 days | $\beta^-$ | Good yield production |
| **$^{111}$Pd** | 23.4 min | $\beta^-$ | Bad release, Low prod |
| **$^{111}$Rh** | 11 sec. | $\beta^-$ | No release |

- ❑ $^{111}$Ag can be produced not only at **high purity**, but also with **high production rate:** up to 2 Ci in target after 5 days (8kW $UC_x$ target)
- ❑ All **Ag isotopic contaminants will be removed** using the **on-line mass separation.**
- ❑ Only **$^{111}$Ag** and low amounts of its **stable daughter $^{111}$Cd** (mostly produced by the decay of silver) will be **collected on the secondary target.**

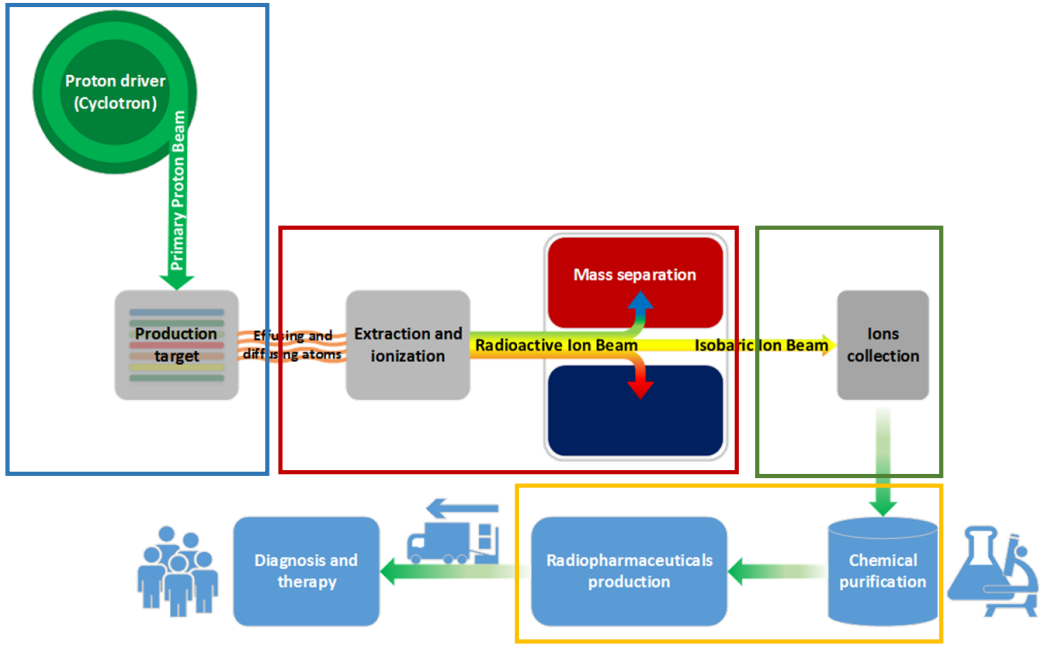
# Feasibility study of $^{111}$Ag production at ISOLPHARM

## MC calculations of the 111Ag production

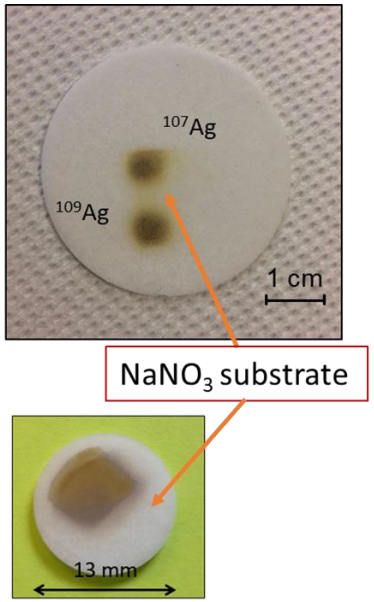
| $^{111}$Ag production (SPES $UC_X$ target, 40 MeV, 200 μA) | | |
|---|---|---|
| Time | Produced activity | |
| [days] | [GBq] | [Ci] |
| 0,5 | 9,46 | 0,26 |
| 1 | 19,17 | 0,52 |
| 1,5 | 28,48 | 0,77 |
| 2 | 37,39 | 1,01 |
| 3 | 54,01 | 1,46 |
| 4 | 69,15 | 1,87 |
| 5 | 82,95 | 2,24 |

For such calculations a dedicated IT infrastructure was designed in CloudVeneto

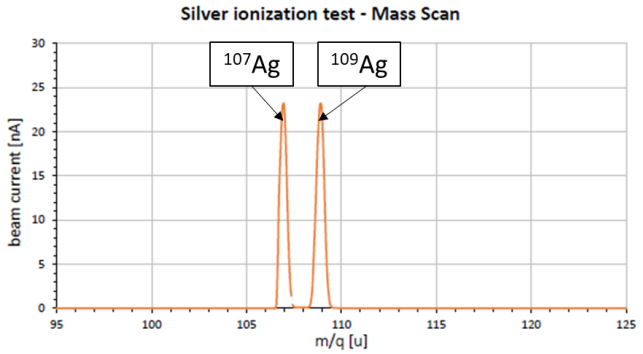
cloudveneto




## Stable Ag deposition tests

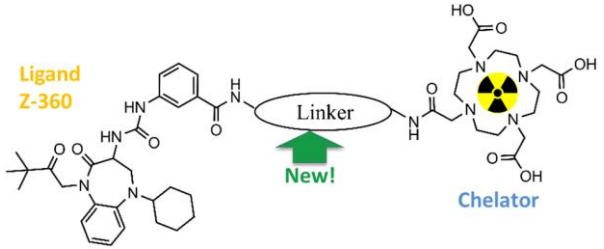



## Stable Ag ionization tests

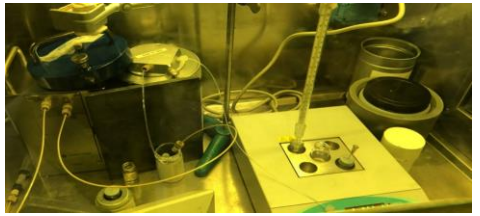



## First radiopharmaceutical prototype


**New ligands** for targeting of **CCK2R**




Radiolabeling with $^{68}$Ga at Reggio Emilia Hospital



ISOLPHARM
SPES exotic beams for medicine

# Proposal of a CSN5 experiment

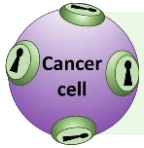
**Goal:** **First in-vitro and in-vivo test of a $^{111}$Ag based radiopharmaceutical produced by INFN**


## Task 1: Physics

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

## 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




## Task 3: Biology

Trento Institute for Fundamental Physics and Applications

- 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

SPES exotic beams for medicine

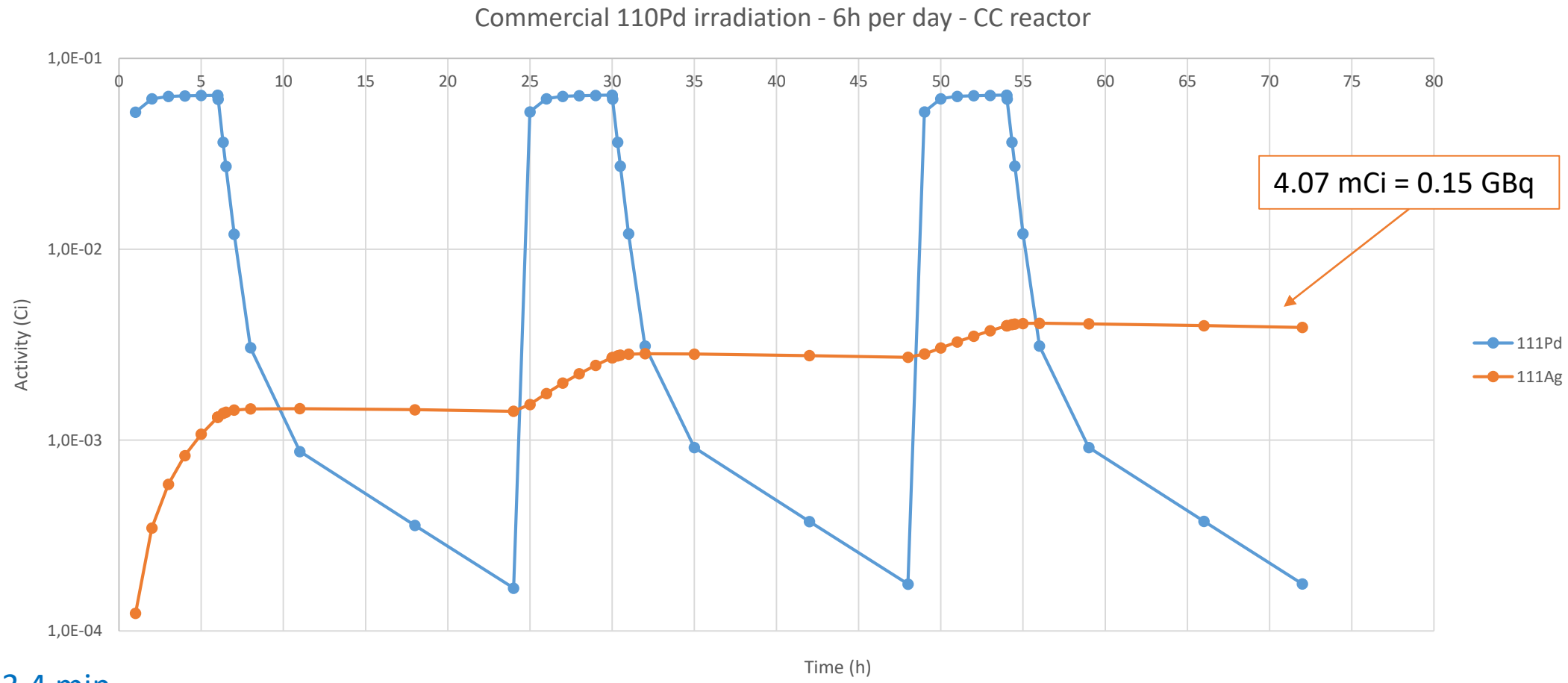
# Project schedule

| | | Year 1 | | | | Year 2 | | | | Year 3 | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | M3 | M6 | M9 | M12 | M15 | M18 | M21 | M24 | M27 | M30 | M33 | M36 | Required for |
| | **Task 1 - Physics** | | | | | | | | | | | | | |
| MS1.1 | Design and production of $^{110}$Pd based targets | → | | | ● | | | | | | | | | MS1.2 |
| MS1.2 | Irradiation of $^{110}$Pd target and extraction of $^{111}$Ag at LENA | | | | | → | ○ | | | | ● | | | MS2.10 |
| MS1.3 | Design and offline test of proper ionizing radiation detectors | → | | | ● | | | | | | | | | MS1.4 |
| MS1.4 | Spectroscopic analyses of irradiated targets for quality controls and yield measurements at LENA | | | | | → | ○ | | | | ● | | | |
| MS1.5 | Porting of MC codes in CloudVeneto | → | | | ● | | | | | | | | | MS1.6 |
| MS1.6 | MC code development and simulations in CloudVeneto for $^{111}$Ag production estimation and dose evaluation | → | | | ○ | | ● | | | | | | | MS1.3 |
| MS1.7 | Laser ionization of Ag | | | | | | | → | | | | | ● | |
| | **Task 2 - Radiochemistry** | | | | | | | | | | | | | |
| MS2.1 | Development of purification methods for Ag from Pd and recovery of Pd | → | | | ○ | | ● | | | | | | | MS1.2 |
| MS2.2 | Development of a more efficient purification methods for Ag from Cd | | | | | | | → | | | | | ● | |
| MS2.3 | Development and characterization of a first library of chelators for Ag and Cu (DOTETE and analogues) | → | | ● | | | | | | | | | | MS2.4 |
| MS2.4 | Radiolabeling and stability studies for the first library of chelators | | | | → | | | | ● | | | | | |
| MS2.5 | Development and characterization of a second library of optimized chelators for Ag and Cu | | | | | → | | ○ | | | ● | | | MS2.6 |
| MS2.6 | Radiolabeling and stability studies for the second library of chelators | | | | | | | | → | | | | ● | |
| MS2.7 | Synthesis and radiolabeling Z360 targeting vectors and analogues (1$^{st}$ gen.) | → | ○ | | ● | | | | | | | | | MS3.2 |
| MS2.8 | Synthesis and characterization of fluorescent targeting vectors (2$^{nd}$ gen.) | | | → | ○ | | ○ | | ● | | | | | MS3.3, MS3.5 |
| MS2.9 | Synthesis of optimized targeting vectors for $^{64}$Cu and $^{111}$Ag (3$^{rd}$ gen.) | | | | | | | → | ○ | | ● | | | MS2.10 |
| MS2.10 | Radiolabeling with $^{64}$Cu and $^{111}$Ag and characterization of the optimized targeting vectors (3$^{rd}$ gen.) | | | | | | | | | → | | | ● | MS3.7, MS3.8 |
| | **Task 3 - Biology** | | | | | | | | | | | | | |
| MS3.1 | Selection of a cell line for CCK2R+ and characterization | → | ○ | | ● | | | | | | | | | MS3.2 |
| MS3.2 | *In-vitro* and *in-vivo* study of DOTA-Z360 targeting vectors analogues (1$^{st}$ gen.) | | | → | | | ● | | | | | | | |
| MS3.3 | *In-vitro* studies of targeting vectors with flourescent targeting agents (2$^{nd}$ gen.) | | | | | → | ○ | | ● | | | | | MS3.6 |
| MS3.4 | Design of suitable 3D scaffold for in vitro tissue mimicking | → | | | | | ● | | | | | | | MS3.5 |
| MS3.5 | *In-vitro* uptake studies (3D scaffolds) with fluorescent compounds (2$^{nd}$ gen.) | | | | | | | → | | | ● | | | |
| MS3.6 | Biodistribition studies, pharmacokinetics and *in-vivo* imaging with fluorescent compounds (2$^{nd}$ gen.) | | | | | | | → | | | ○ | | ● | MS3.8 |
| MS3.7 | *In-vitro* studies of optimized targeting vectorsrediolabelled with $^{64}$Cu and $^{111}$Ag (3$^{rd}$ gen.) | | | | | | | | | → | ○ | | ● | MS3.8 |
| MS3.8 | Biodistribition studies, pharmacokinetics and *in-vivo* imaging with $^{64}$Cu and $^{111}$Ag radiolabelled compounds (3$^{rd}$ gen.) | | | | | | | | | | | → | ● | |

| | |
|---|---|
| → | Activity started |
| ○ | Preliminary results required to start other subsequent activities |
| ● | Milestone reached |

# $^{110}$Pd irradiation at LENA - 3 days

$^{110}$Pd 99.4%
100 mg




$^{111}$Pd $t_{1/2}$ = 23.4 min
$^{111}$Ag $t_{1/2}$ = 7.45 day

# Economic request for ISOLPHARM-EIRA

| | Year 1 [€] | Year 2 [€] | Year 3 [€] |
|---|---|---|---|
| **INFN-LNL** | | | |
| **Inventoriables** | 1500 | 6000 | |
| **Consumables** | 16000 | 14400 | 12200 |
| **Travels** | 8000 | 8000 | 8000 |
| **TOTAL INFN-LNL** | **25500** | **28400** | **20200** |
| **INFN-PD** | | | |
| **Inventoriables** | 14500 | | |
| **Consumables** | 500 | 500 | 500 |
| **Travels** | 5500 | 6500 | 7000 |
| **TOTAL INFN-PD** | **20500** | **7000** | **7500** |
| **INFN-PV** | | | |
| **Inventoriables** | 2000 | 3000 | 1000 |
| **Consumables** | 1000 | 8000 | 8000 |
| **Travels** | 5000 | 5000 | 5000 |
| **TOTAL INFN-PV** | **8000** | **16000** | **14000** |
| **INFN-TIFPA** | | | |
| **Inventoriables** | 0 | 0 | 0 |
| **Consumables** | 7160 | 1900 | 7900 |
| **Travels** | 2000 | 2000 | 2000 |
| **TOTAL INFN-TIFPA** | **9160** | **3900** | **9900** |
| **INFN-LNS** | | | |
| **Inventoriables** | 0 | 0 | 0 |
| **Consumables** | | | 6700 |
| **Travels** | 2000 | 2000 | 5000 |
| **TOTAL INFN-LNS** | **2000** | **2000** | **11700** |
| **TOTAL PROJECT** | **65160** | **57300** | **63300** |

| | | Year 1 [€] | Year 2 [€] | Year 3 [€] |
|---|---|---|---|---|
| **INFN-PV** | | | | |
| **Inventoriables** | Set-up for the analysis of irradiated samples | | 1000 | 1000 |
| | Set-up for a radiochemistry hood at LENA | 2000 | 2000 | |
| | **TOTAL** | **2000** | **3000** | **1000** |
| **Consumables** | Irradiations of 110Pd targets at LENA | | 5000 | 5000 |
| | Consumables for the radiochemistry laboratory at LENA | 1000 | 2000 | 2000 |
| | Transport of irradiated samples | | 1000 | 1000 |
| | **TOTAL** | **1000** | **8000** | **8000** |
| **Travels** | Travels for meetings | 5000 | 5000 | 5000 |
| **TOTAL INFN-PV** | | **8000** | **16000** | **14000** |

# Personnel involved

| LNL | | | |
|---|---|---|---|
| **Name** | **Expertise – Activity in the project** | **Task** | **FTE** |
| Alberto Andrighetto (National resp.) | Project coordination | 1,2,3 | 0.5 |
| Stefano Corradetti (LNL local resp.) | Local coordination and Ag release-ionization tests | 2 | 0.5 |
| Michele Ballan | MC codes and simulations, Ag ionization | 1,2 | 0.5 |
| Marianna Tosato | Purification and chelators development | 2 | 1 |
| Marco Verona | Synthesis and characterization of ligands | 2,3 | 1 |
| Michele Caeran | *In-vitro* studies | 3 | 1 |
| Giovanni Marzaro | Synthesis and characterization of ligands | 2 | 1 |
| Valerio Di Marco | Purification and chelators development | 2 | 1 |
| Francesca Mastrotto | *In-vitro* studies | 3 | 1 |
| Mattia Asti | *In-vitro* and *in-vivo* studies | 3 | 1 |
| **Total LNL FTE** | | | **8.5** |

| PD | | |
|---|---|---|
| **Name** | **Task** | **FTE** |
| Marcello Lunardon (PD local resp.) | 1 | 0.2 |
| Sandra Moretto | 1 | 0.1 |
| Cristiano Fontana | 1 | 0.2 |
| Luca Stevanato | 1 | 0.2 |
| Paolo Lotti | 1 | 0.3 |
| Lisa Zangrando | 1 | 0.2 |
| **Total PD FTE** | | **1.2** |

| PV | | |
|---|---|---|
| **Name** | **Task** | **FTE** |
| Aldo Zenoni (PV local resp.) | 1 | 0.6 |
| Antonietta Donzella | 1 | 0.5 |
| Andrea Salvini | 1 | 0.3 |
| Lucilla Strada | 1 | 0.3 |
| Massimo Oddone | 1 | 0.2 |
| Barbara Smilgis | 1 | 0.2 |
| Michele Prata | 1 | 0.2 |
| **Total PV FTE** | | **2.3** |

| TIFPA | | |
|---|---|---|
| **Name** | **Task** | **FTE** |
| Devid Maniglio (TIFPA local resp.) | 3 | 1 |
| Antonella Motta | 3 | 1 |
| Alberto Quaranta | 2 | 0.3 |
| Alessandra Bisio | 3 | 0.5 |
| **Total TIFPA FTE** | | **2.8** |

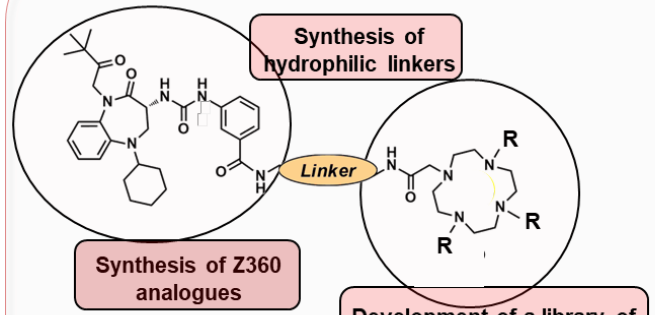
| LNS | | |
|---|---|---|
| **Name** | **Task** | **FTE** |
| Giorgio Russo (LNS local resp.) | 3 | 0.2 |
| Francesco P Cammarata | 3 | 0.5 |
| Rosalba Parenti | 3 | 0.5 |
| Massimo Gulisano | 3 | 0.2 |
| **Total LNS FTE** | | **1.4** |

## Personnel:

31 researchers involved in the project. Total **16.2 INFN - FTE**

# ISOLPHARM_EIRA overview

## Radiopharmaceutical Development

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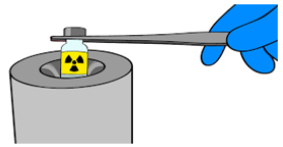


Radiolabeling with $^{111}Ag$ and $^{64}Cu$

SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
Azienda Ospedaliera di Reggio Emilia
Arcispedale S. Maria Nuova

Purification process

## $^{111}Ag$ production and quality control

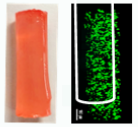
$^{110}Pd$ enriched powder


$^{111}Ag$

$^{110}Pd$

Production at LENA reactor (Pavia)

## Pre-screening with fluorescent probe

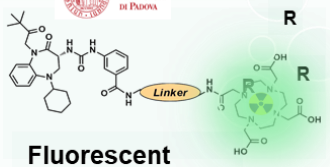


3D cellular scaffolds

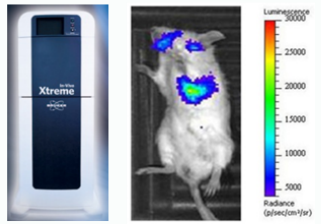
TIFPA Trento Institute for Fundamental Physics and Applications

BIOtech Biomedical Technologies

In vivo studies

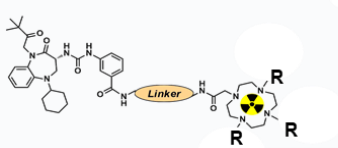


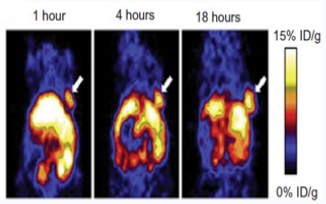

Fluorescent ligand

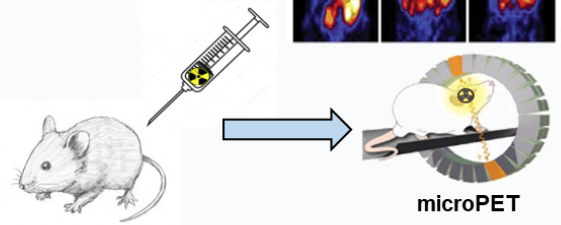



In vivo Xtreme

## *In vivo* studies



microPET

# The path of ISOLPHARM_EIRA

MC cloud calculations of yields and doses

Chelators development

Linkers development

Targeting agents development

$^{111}$Ag Production of $^{111}$Ag in nuclear reactor

Radiopharmaceutical synthesis

Cell line for CCK2R development and *in-vitro* and *in-vivo* testing

Cancer cell

$^{111}$Ag

**First *in-vivo* test of a $^{111}$Ag based radiopharmaceutical**