S. Corradetti on behalf of the ISOLPHARM collaboration

ISOLPHARM

Study of new radiopharmaceuticals at the SPES facility

ISOLPHARM
SPES exotic beams for medicine

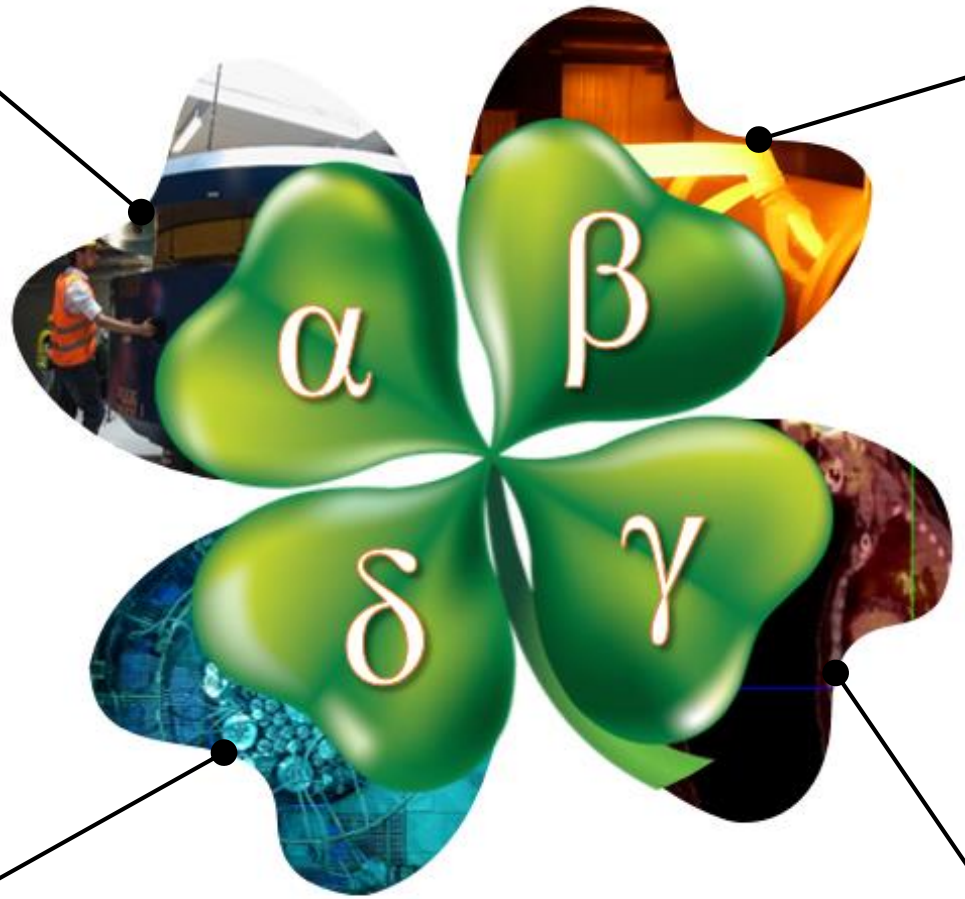
Outline

- The innovative ISOLPHARM method @ SPES ISOL facility
- ISOLPHARM early experimental feasibility studies
- ISOLPHARM_Ag, a CSNV experiment
- ISOLPHARM_EIRA, a CSNV experiment
- Conclusions

ISOLPHARM framework: the SPES project

SPES-α

at the heart of SPES: the cyclotron and related infrastructure.



SPES-β

the ISOL facility and the acceleration of neutron-rich unstable nuclei.

ISOLPHARM
SPES exotic beams for medicine

SPES-δ

multidisciplinary neutron sources.

SPES-γ

production of radionuclides for applications.

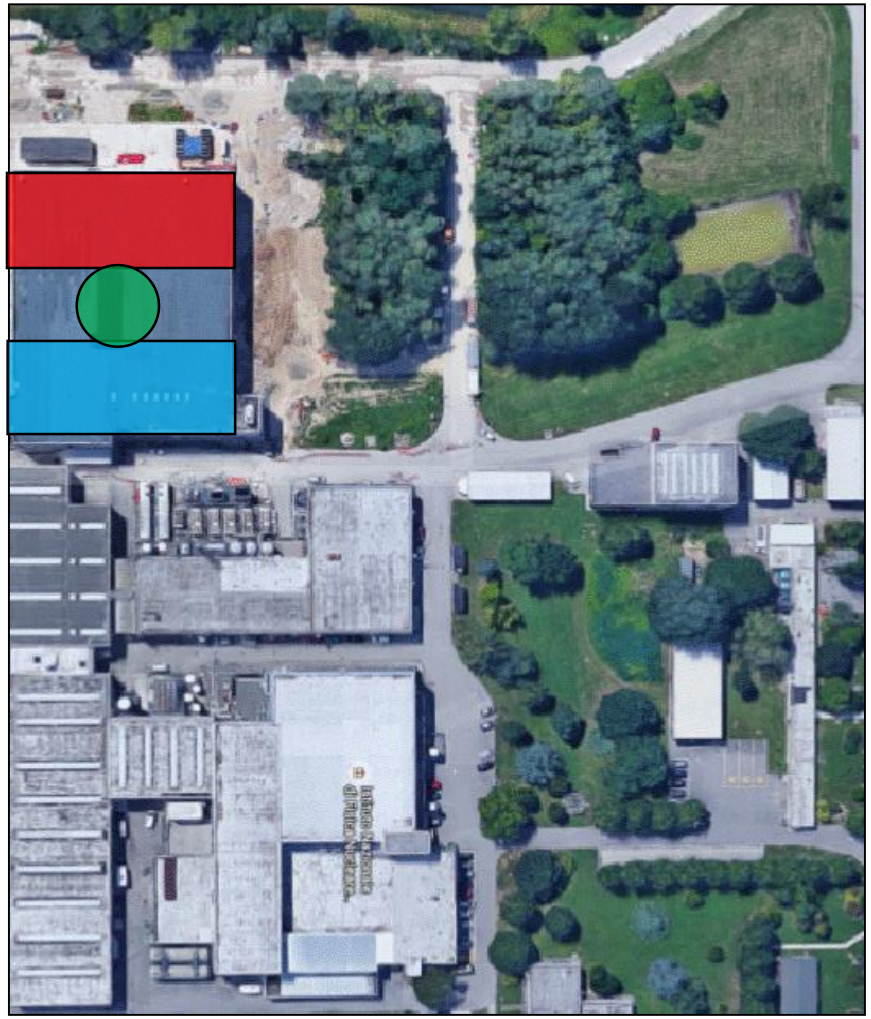
ISOLPHARM framework: the SPES facility

Exotic beam team SPES project is:

1. A second generation **ISOL RIB Facility** (for neutron-rich radioactive ion beams)
2. An interdisciplinary **Application Facility** (for p,n applications)

New infrastructure for:

- **Cyclotron**
- **RIB Facility**
- **Application Facility**

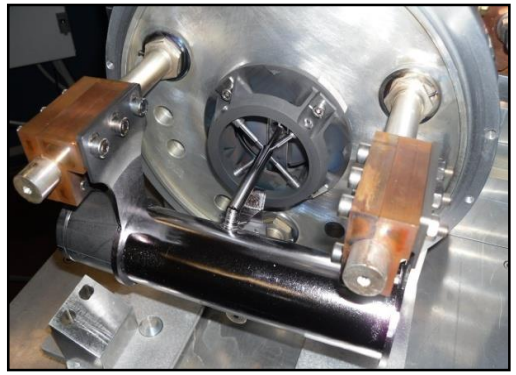


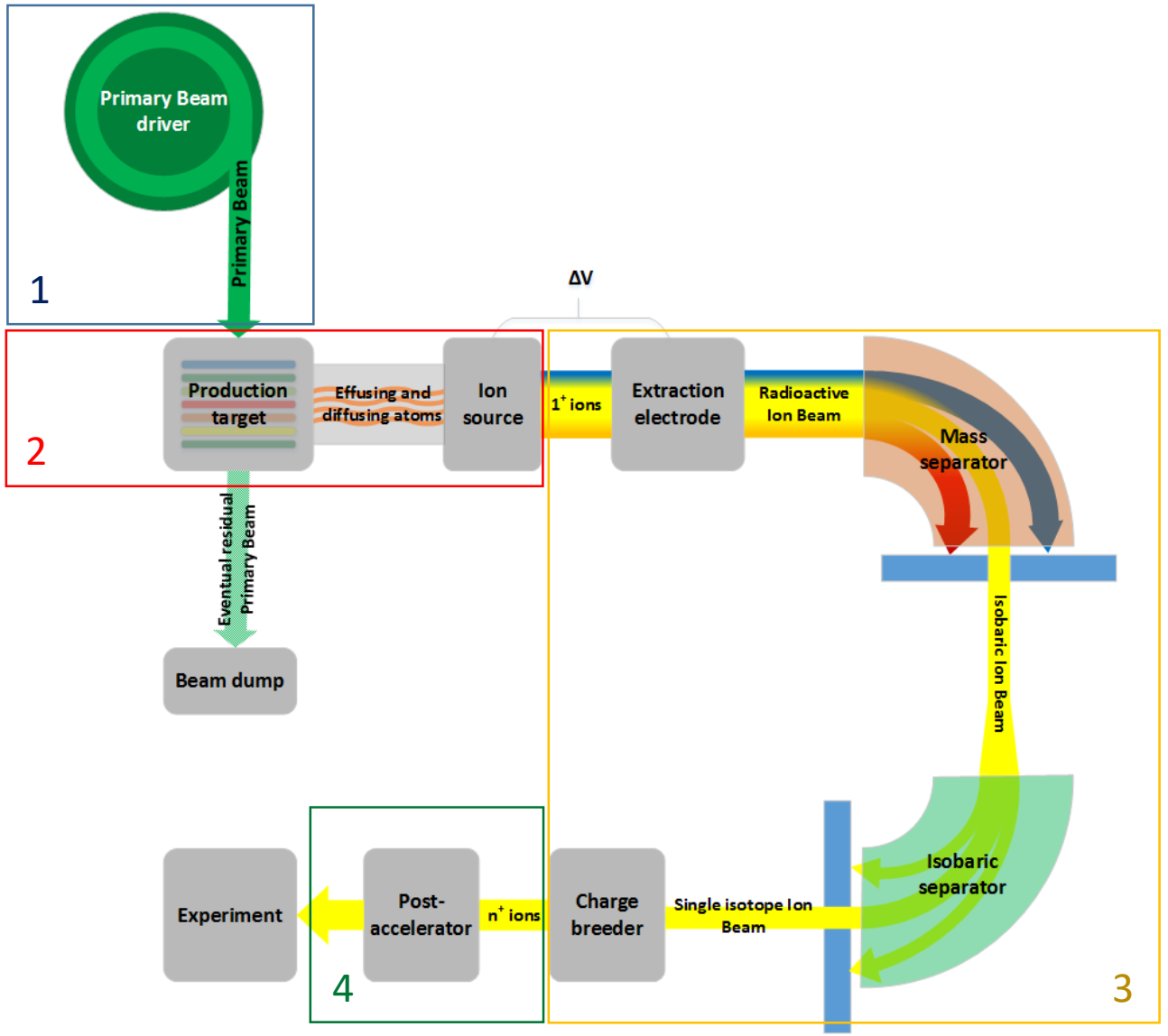
ISOLPHARM framework: the SPES ISOL facility

1 - Driver

70 MeV commercial cyclotron

2 – Target-Ion Source unit





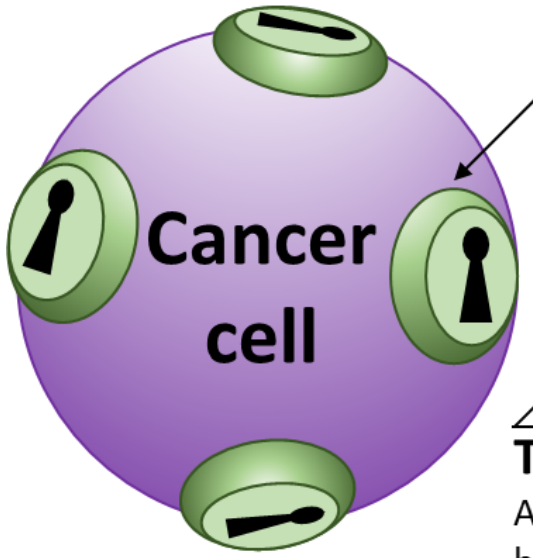
3- RIB manipulation

- Mass Separator (WF)
- Beam Cooler
- HRMS
- ECR Charge Breeder
- RFQ

4 - Post Accelerator:

ALPI existing complex

Radiopharmaceuticals



Cancer target
Better if overexpressed by cancer cells

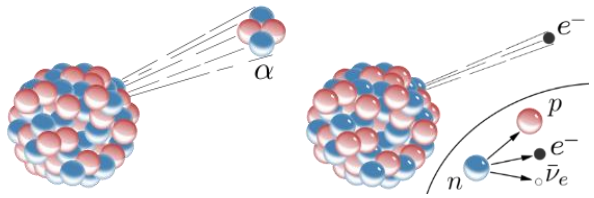
Linker/spacer
to bind the targeting agent and the chelator

Radioisotope
May be a diagnostic isotope for imaging and/or a therapeutic isotope for treatment

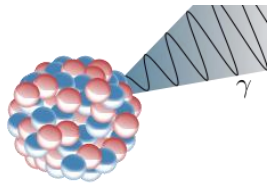
Targeting agent
A small molecule or a biologic agent (antibody)

Chelator
Molecule carrying the radioisotope

Therapeutic agents



Diagnostic agents



Specific activity → $\frac{\text{activity of the radioisotope (MBq)}}{\text{mass of the element (mg).}}$

Radionuclidic purity → $\frac{\text{activity of the desired nuclei}}{\text{overall activity of the compound}}$

Radionuclides properties:

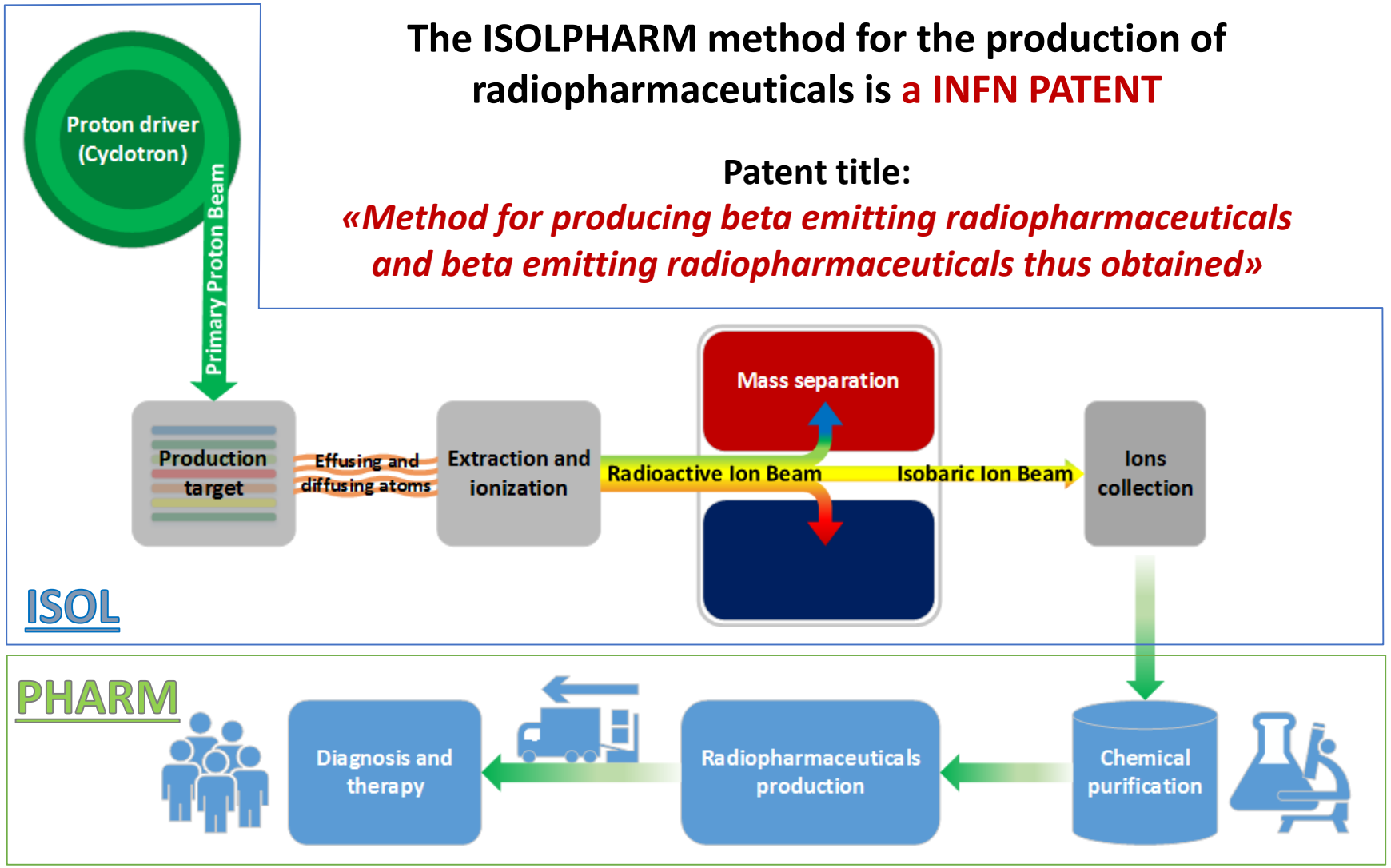
- Decay properties
- Half-life
- Chemical properties
- Production Feasibility

The ISOLPHARM method

The ISOLPHARM method for the production of radiopharmaceuticals is a INFN PATENT

Patent title:

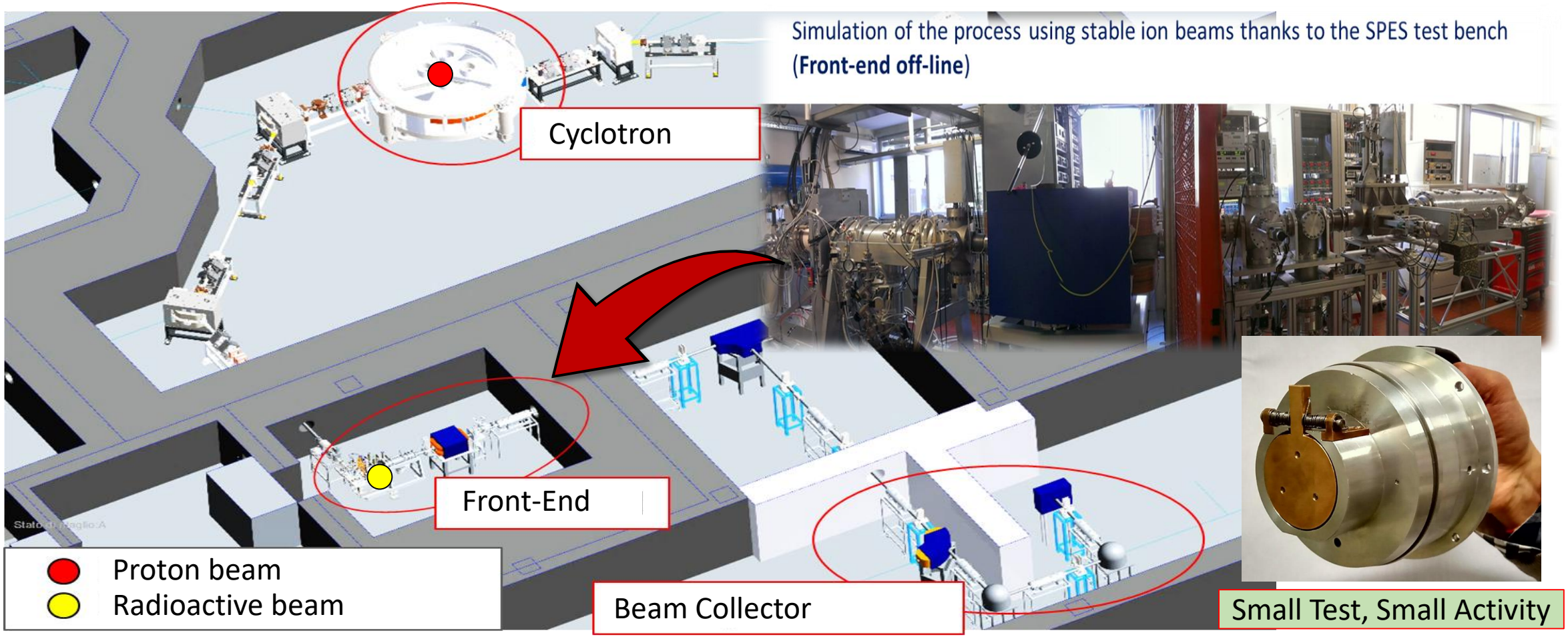
«Method for producing beta emitting radiopharmaceuticals and beta emitting radiopharmaceuticals thus obtained»



Flexible production, high specific activity & radionuclidic purity

The ISOLPHARM set-up (test facility)

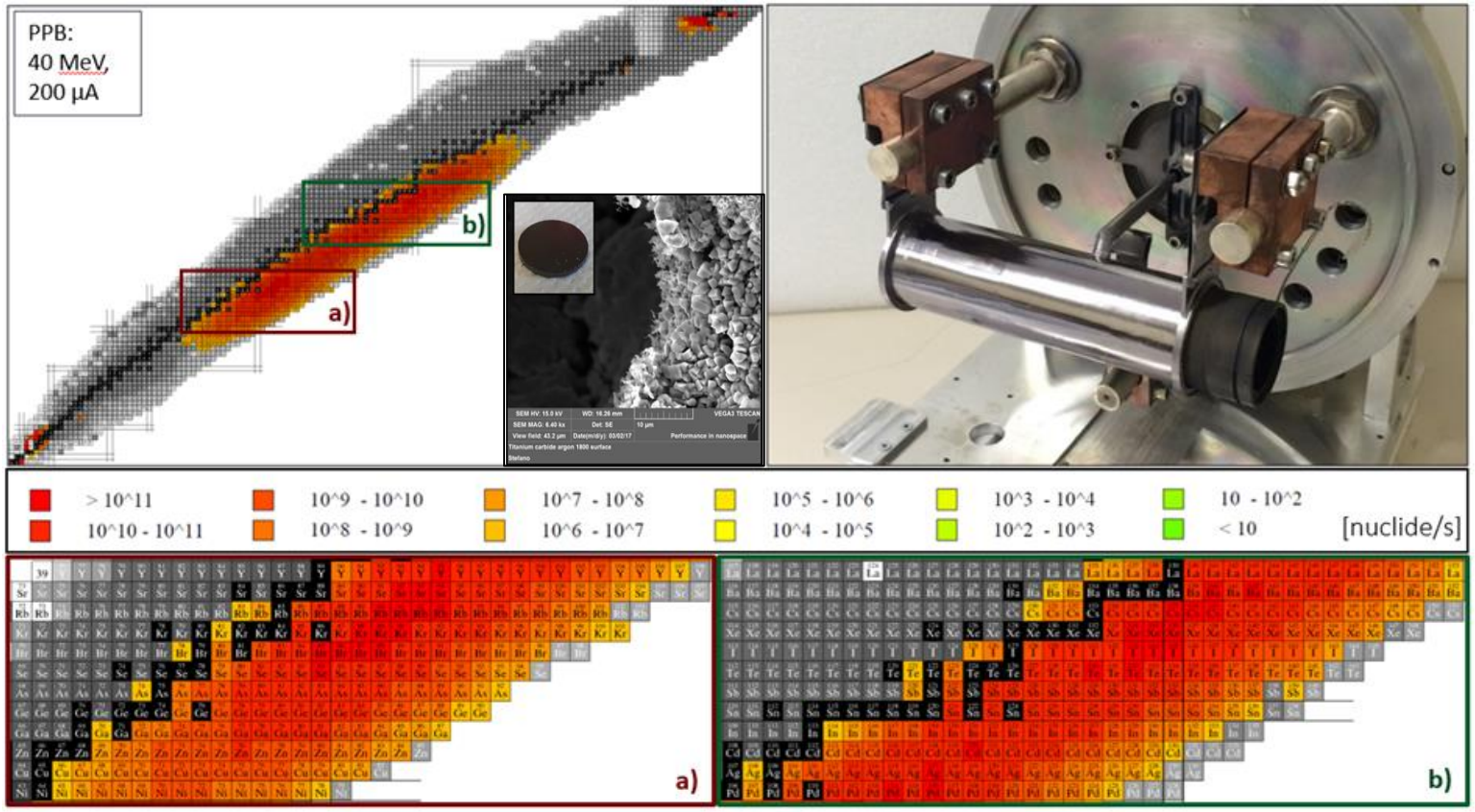
Starting Point: Some tens of mCi are sufficient to start a R&D on radiopharmaceuticals



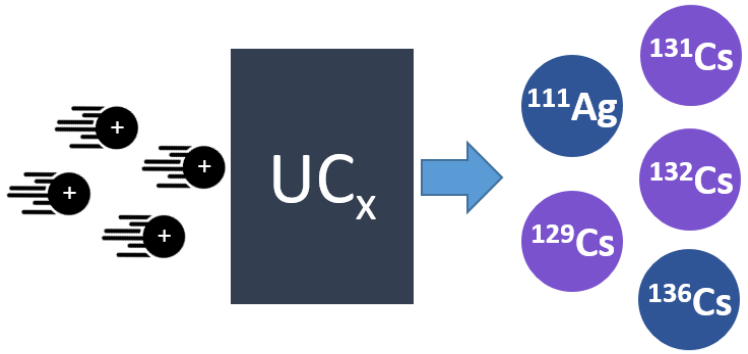
low costs, easy set-up, possibility to be users of SPES…

ISOLPHARM Medical radionuclides production

From Fissile (UC_x) target



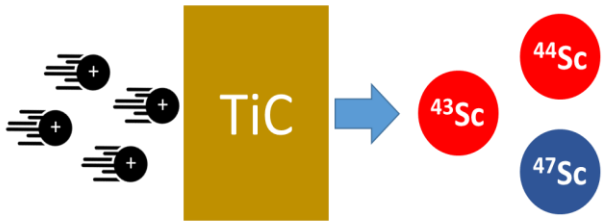
- UC_x target already **developed** and **tested on-line**
- One material, **many radioactive ion beams** (fission)
- **Neutron-rich nuclides**

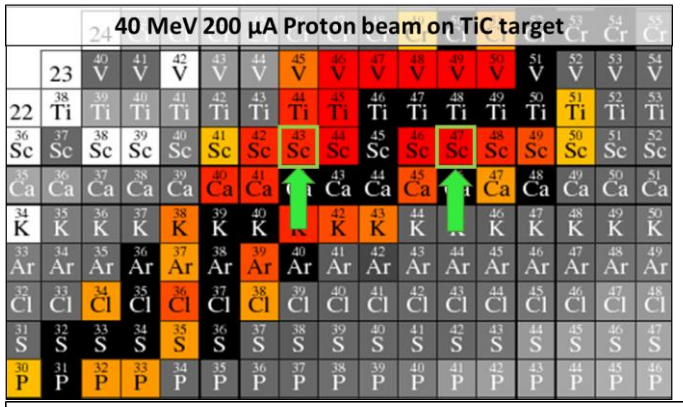


ISOLPHARM Medical radionuclides production

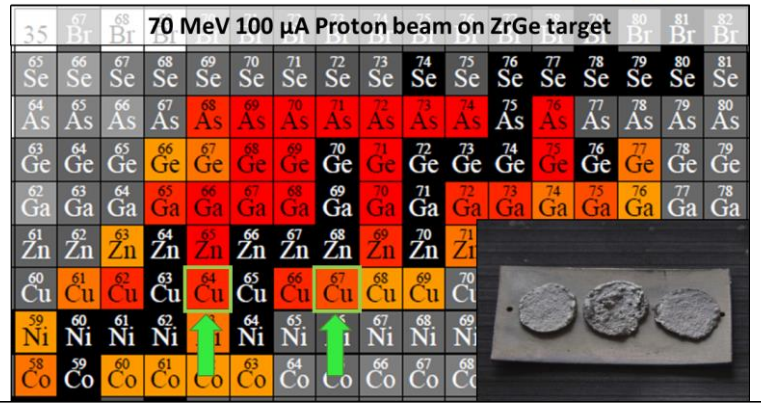
From non fissile targets

Titanium carbide

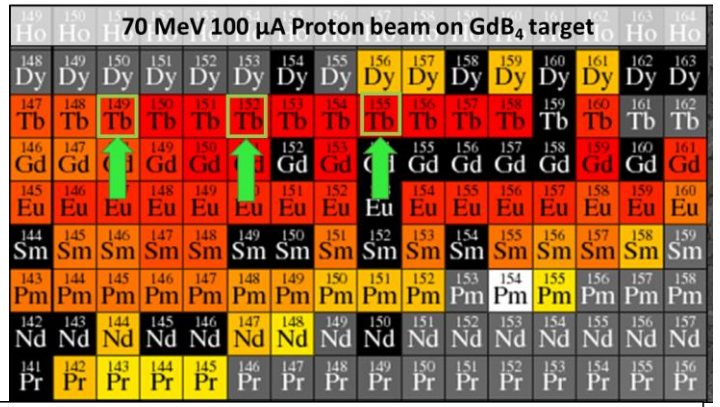




Zirconium germanide



Gadolinium Boride

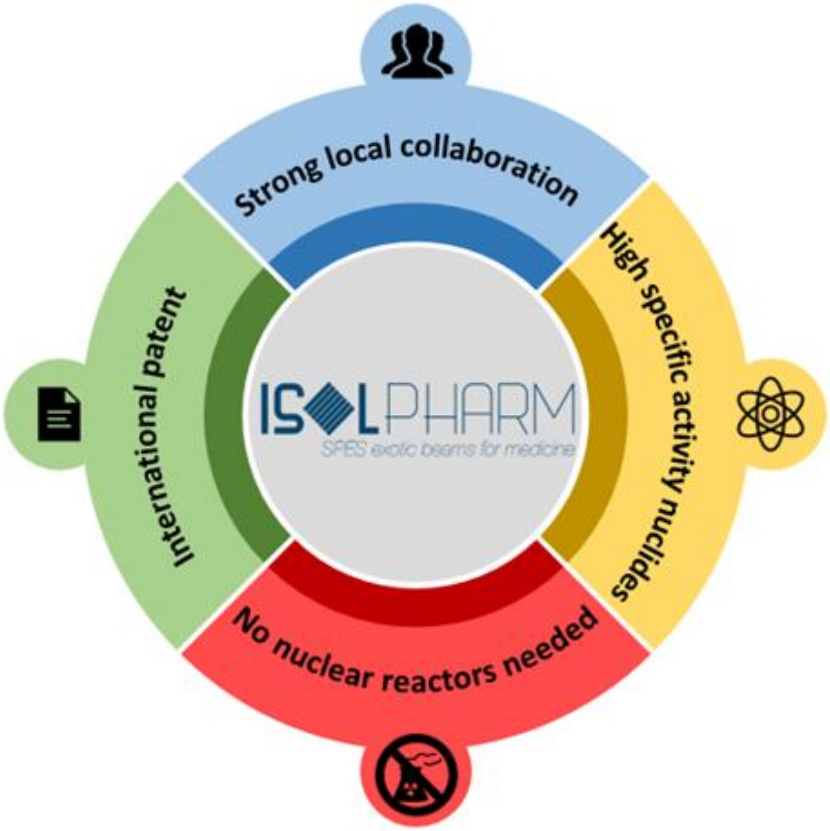


> 10^11	10^9 - 10^10	10^7 - 10^8	10^5 - 10^6	10^3 - 10^4	10 - 10^2
10^10 - 10^11	10^8 - 10^9	10^6 - 10^7	10^4 - 10^5	10^2 - 10^3	< 10

[nuclide/s]

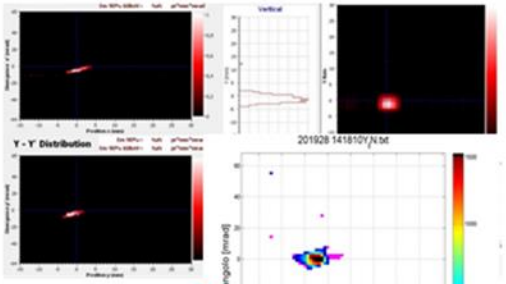
Summary: main features of ISOLPHARM

- Production of a large set of radionuclides **carrier-free** & with large **radionuclide purity** → **(versatility)**
- Many **unconventional radioisotopes** (short $T_{1/2}$) difficult to produce with traditional techniques → **(innovativity)**
- On-line mass selection by tuning the separator; **easy production** of different radionuclides → **(flexibility)**
- Production of **less nuclear wastes** respect to nuclear reactors → **(green technology)**



ISOLPHARM experimental activity overview

Ionized element	Desired radionuclide	Ionization source	Efficiency
Sr	^{89}Sr, ^{90}Sr/^{90}Y	SIS	~ 20 %
Y	^{90}Y	PIS	~ 1 %
I	^{125}I, ^{126}I and ^{131}I	PIS	~ 20 %
Cu	^{64}Cu, ^{67}Cu	PIS	~ 10 %
Ag	^{111}Ag	PIS	~ 15 %



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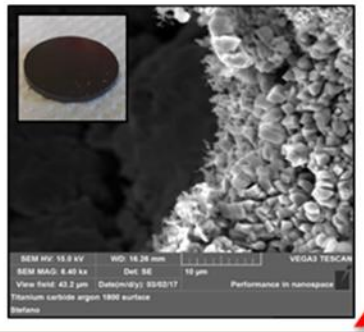
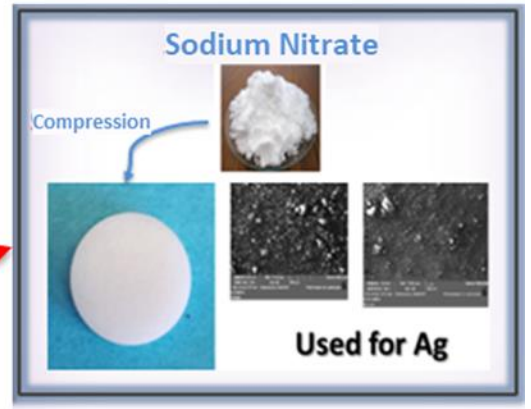
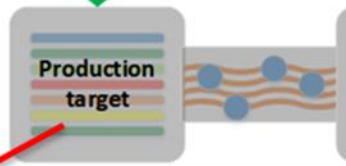
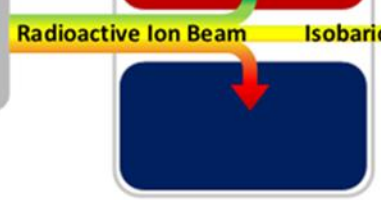


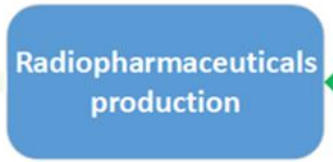


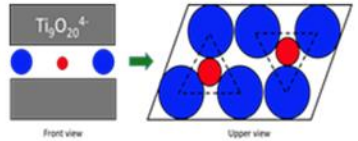


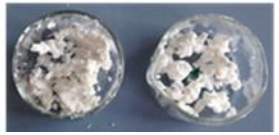


SPES UC$_x$ target production, 40 MeV

	^{111}Ag		^{129}Cs		^{131}Cs	
Time	Produced activity		Produced activity		Produced activity	
[days]	[Bq]	[Ci]	[Bq]	[mCi]	[Bq]	[mCi]
0.5	9.46E+09	0.26	1.14E+06	0.03	4.30E+06	0.12
1	1.92E+10	0.52	2.02E+06	0.05	8.45E+06	0.23
1.5	2.85E+10	0.77	2.70E+06	0.07	1.24E+07	0.34
2	3.74E+10	1.01	3.22E+06	0.09	1.63E+07	0.44
3	5.40E+10	1.46	3.94E+06	0.11	2.36E+07	0.64
4	6.92E+10	1.87	4.37E+06	0.12	3.04E+07	0.82
5	8.29E+10	2.24	4.62E+06	0.12	3.68E+07	0.99

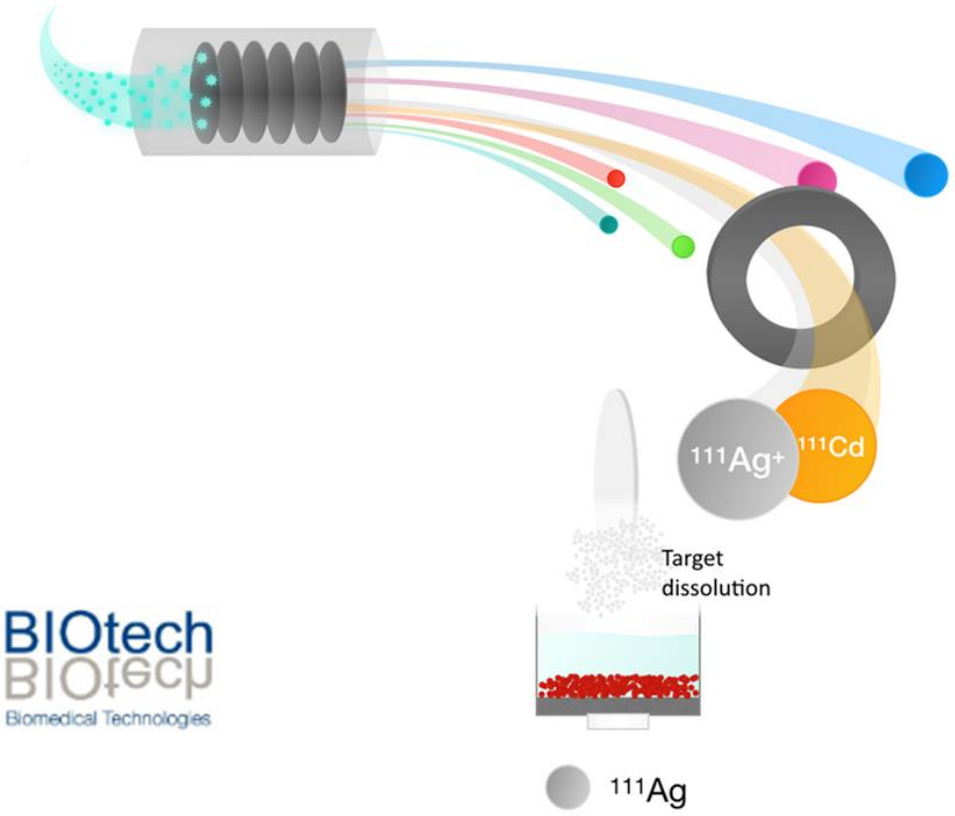




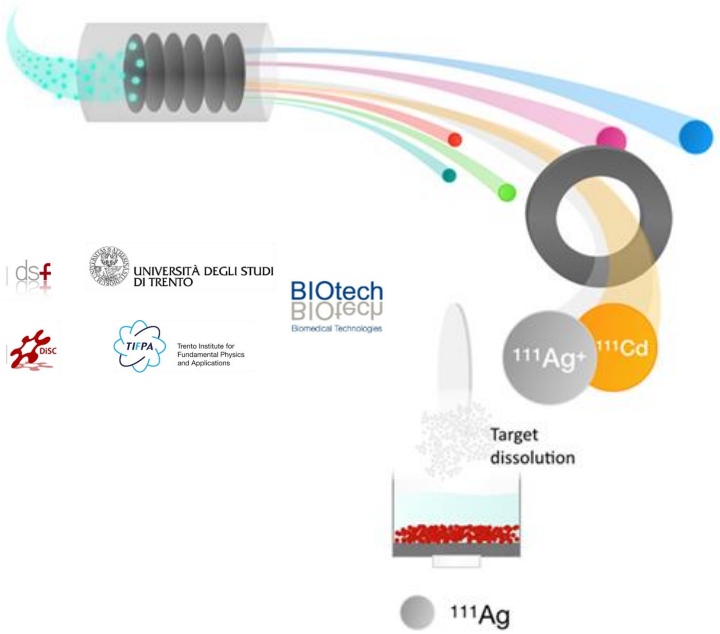


ISOLPHARM_Ag

A CSNV experiment (2018-19)



ISOLPHARM_Ag: a case study on ^{111}Ag



Experiment financed by INFN CSN V

^{111}Ag properties

- ***β*$^-$ emitter** (average energy **360 keV**)
- Medium half-life (**7.45 days**)
- Medium tissue penetration (**1.8 mm**)
- Low energy γ rays SPECT

111 Isobaric chain	$t_{½}$	Decay	Target Yield
^{111}Cd	Stable		Low yield production
^{111}Ag	7.45 days	β^-	Good yield production
^{111}Pd	23.4 min	β^-	Bad release, Low prod
^{111}Rh	11 sec.	β^-	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.**

ISOLPHARM_Ag project organization

- **Task 1**: Investigation of the production and release capabilities of ^{111}Ag from the SPES fission target, exploiting production, diffusion and effusion complex Monte Carlo codes on a dedicated grid computing infrastructure
- **Task 2**: Study of the Ag chemistry in order both to develop suitable purification techniques from contaminants and to synthesize new chelators for Ag^{+} with controlled thermodynamic and kinetic
- **Task 3**: Development of targeting agents to transport ^{111}Ag to defined tumor cells

Feasibility study of ^{111}Ag production at ISOLPHARM

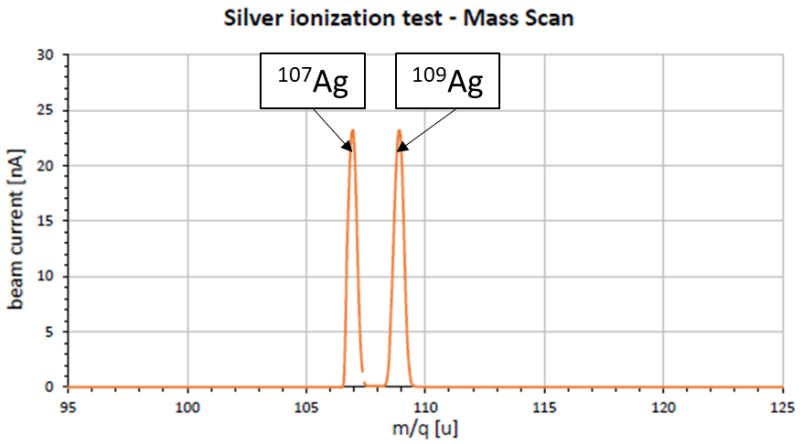
MC calculations of the 111Ag production

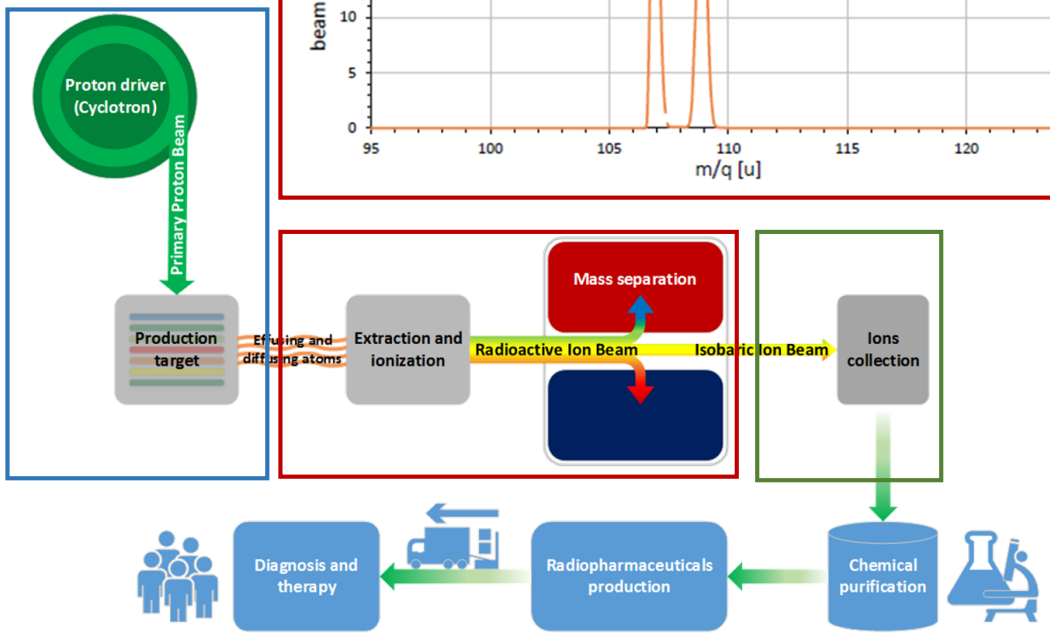
^{111}Ag production (SPES UC_X target, 40 MeV, 200 μA)		
Time	Produced activity	
[days]	[GBq]	[Ci]
0,5	9,46	0,26
1	19,17	0,52
1,5	28,48	0,77
2	37,39	1,01
3	54,01	1,46
4	69,15	1,87
5	82,95	2,24

cloudveneto

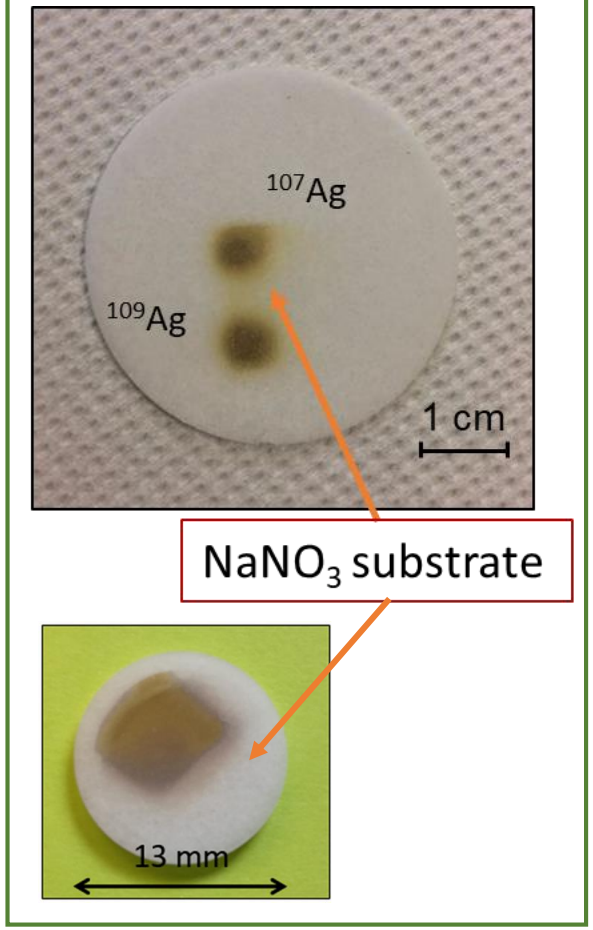
For such calculations a dedicated IT infrastructure was designed in CloudVeneto

Stable Ag ionization tests

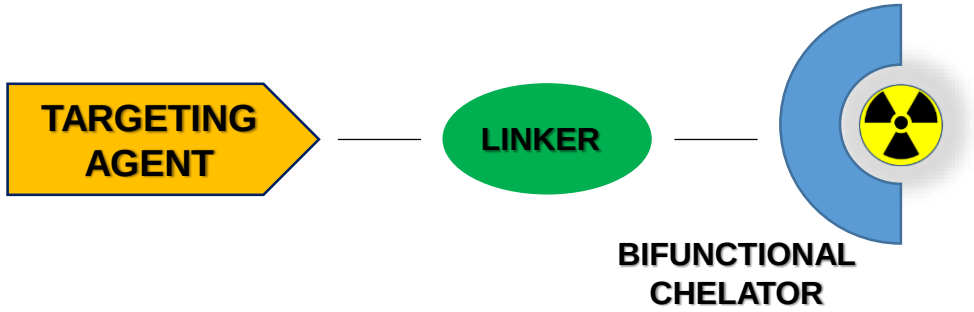




Stable Ag deposition tests



Experimental activity on radiopharmaceuticals



1) Beam delivery & Target productions

2) Ionization and Ion transport/collections

3) Molecular synthesis

4) Purification after molecular synthesis

5) Cold Characterization

6) Radiolabeling of new synthesized ligands

7) Hot Characterization : Stability in PBS buffer and blood solution

INFN Istituto Nazionale di Fisica Nucleare Laboratori Nazionali di Legnaro

Università degli Studi di Padova

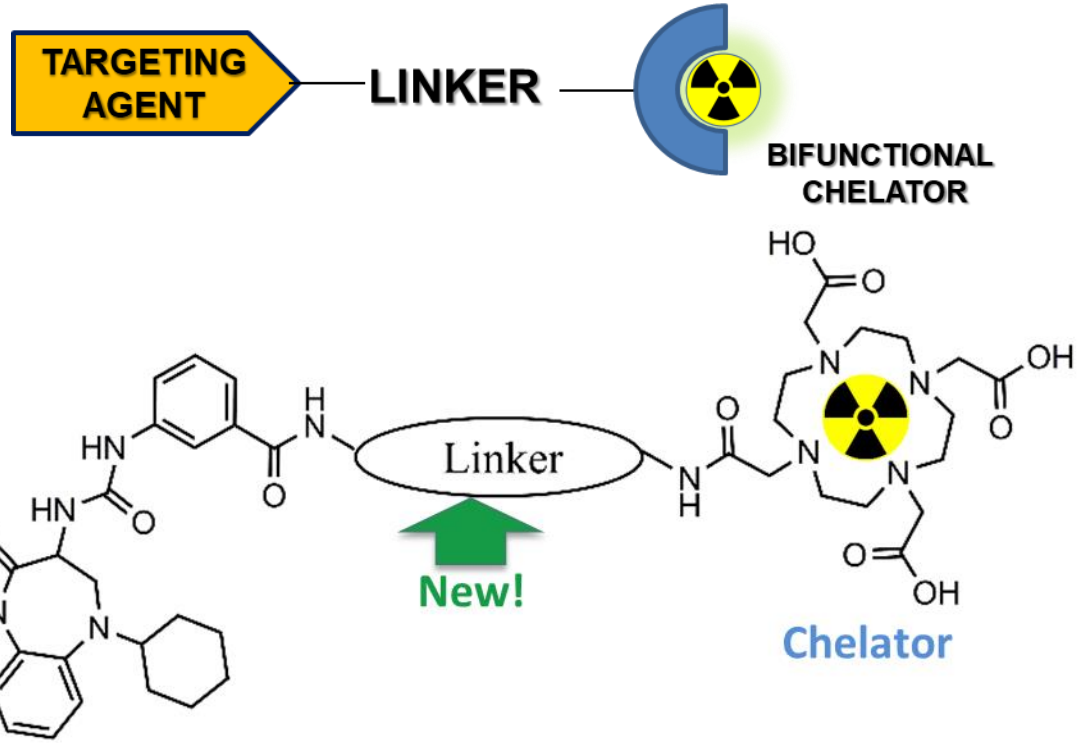
SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA

Azienda Unità Sanitaria Locale di Reggio Emilia

Azienda Ospedaliera di Reggio Emilia
Arcispedale S. Maria Nuova

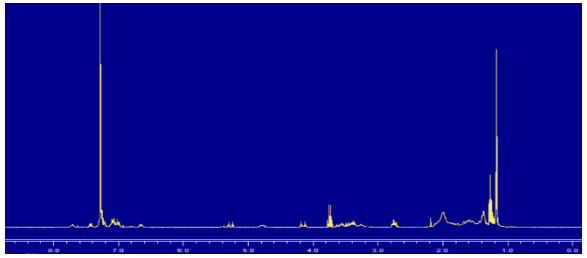
Istituto in tecnologie avanzate e modelli assistenziali in oncologia
Istituto di ricovero e cura a carattere scientifico

Final result: first radiopharmaceutical prototype

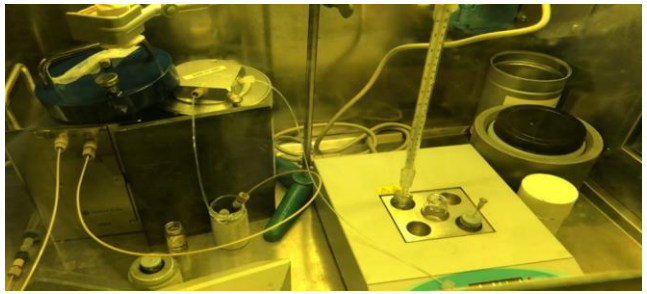


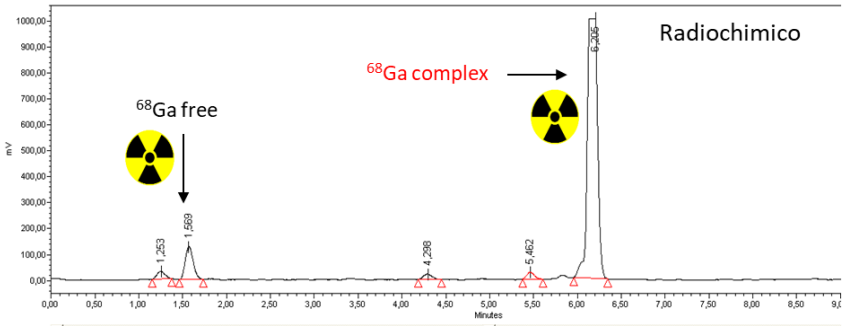
New ligands for targeting of **CCK2R**

1) Synthesis completed

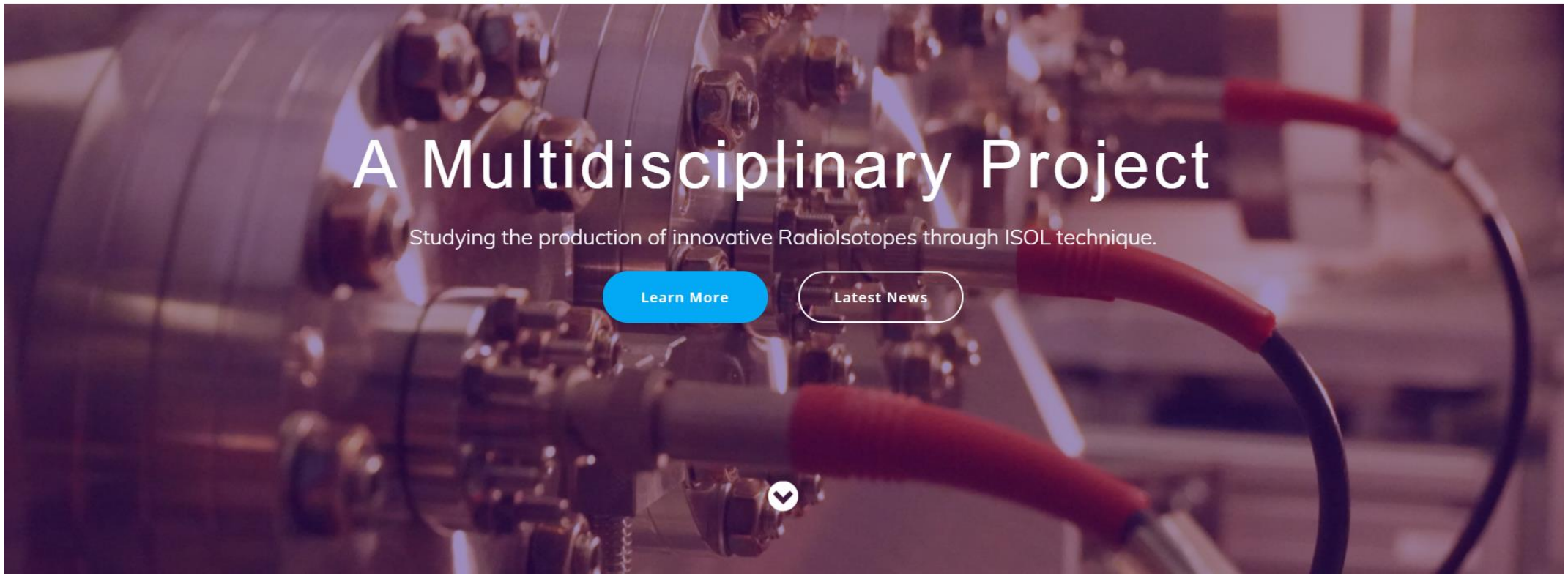


2) Radiolabeling with ^{68}Ga at Reggio Emilia Hospital





The ISOLPHARM website



https://isolpharm.pd.infn.it/web/

ISOLPHARM_EIRA

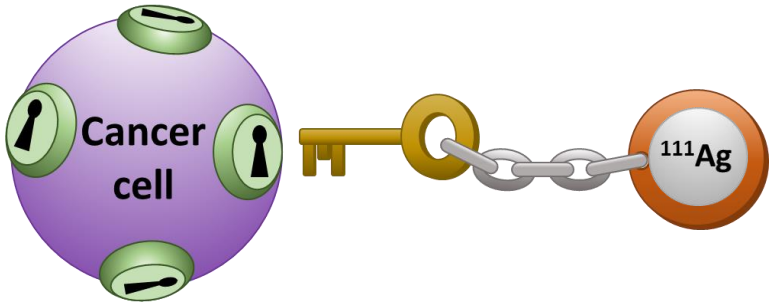
(CSNV 2020-22)

Main goal of ISOLPHARM_EIRA

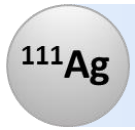
To **go beyond the results of ISOLPHARM_Ag** and further promote the research on a ^{111}Ag based radiopharmaceutical by:

1. Producing the first batches of radioactive ^{111}Ag via neutron irradiation at the existing TRIGA Mark II research reactor at LENA.

2. Testing *in-vitro* and *in-vivo* the first ^{111}Ag radiolabeled compounds



Project organization

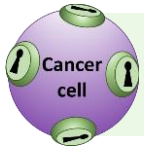


Task 1: Physics

- Simulation and study of ^{111}Ag production via the ^{110}Pd(n,γ)^{111}Ag reaction.
- Quality control of the production of ^{111}Ag trough 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

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

ISOLPHARM collaboration network

The National Network

The International Network

The SPES-ISOLPHARM team