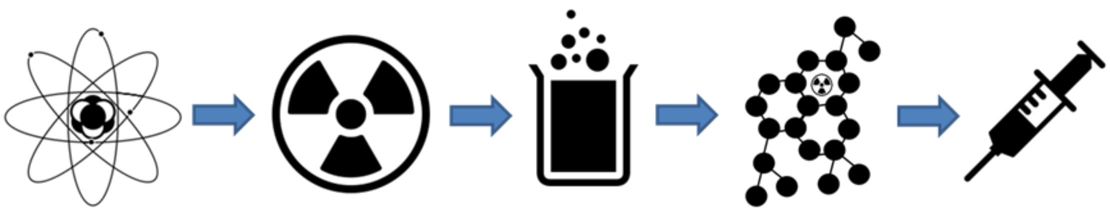
Radioisotope production: The ISOLPHARM project at LNL



Stefano Corradetti

Istituto Nazionale di Fisica Nucleare – Laboratori Nazionali di Legnaro

On behalf of the SPES target, ISOLPHARM and ISOLPHARM_Ag groups

Eurisol Town Meeting – Pisa, 2nd July 2018

Radioisotope production
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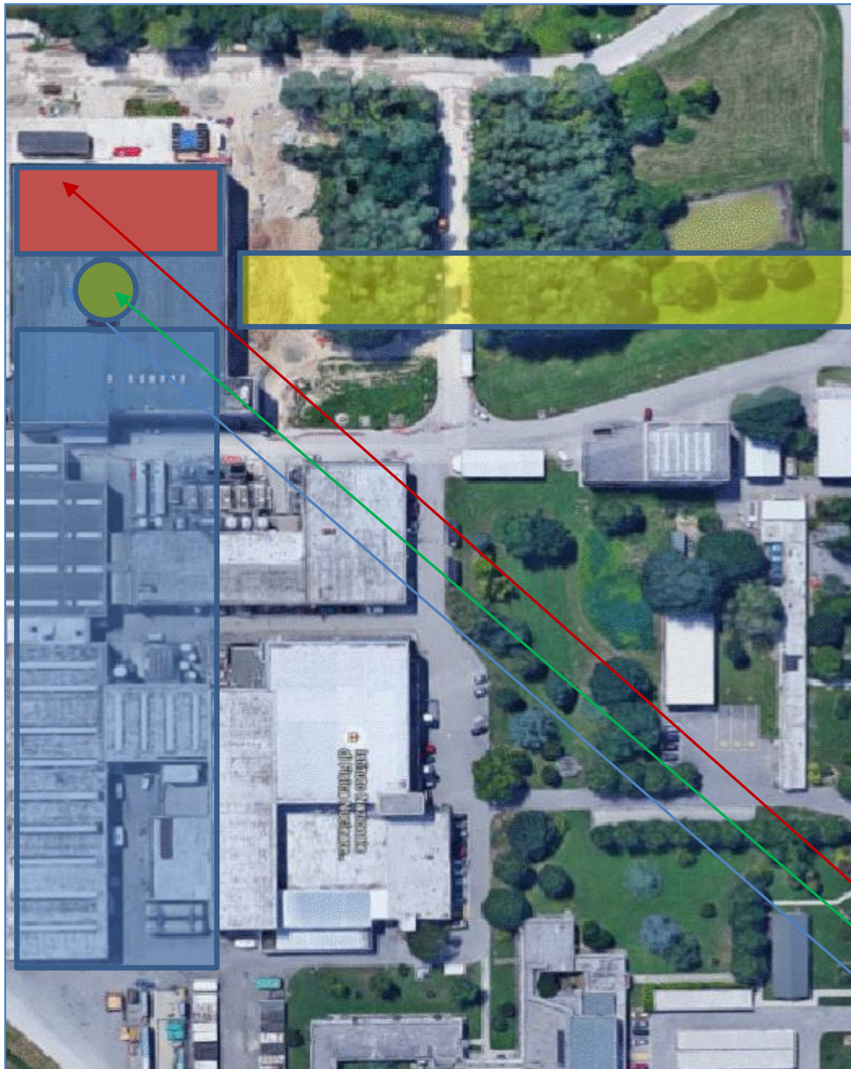


Project financed by INFN

New infrastructure for:

- Application Facility
- Cyclotron
- RIB facility (2th generation ISOL)

ISOLPHARM:

Between the β and γ phase of the SPES project

α

Cyclotron installation & commissioning:
E=70 MeV proton beam, I= 750 μA

δ

Accelerator based neutron source
(**Proton and Neutron Facility for Applied Physics**)

β

Production and reacceleration of exotic beams,
from p-induced Fission on UC_x

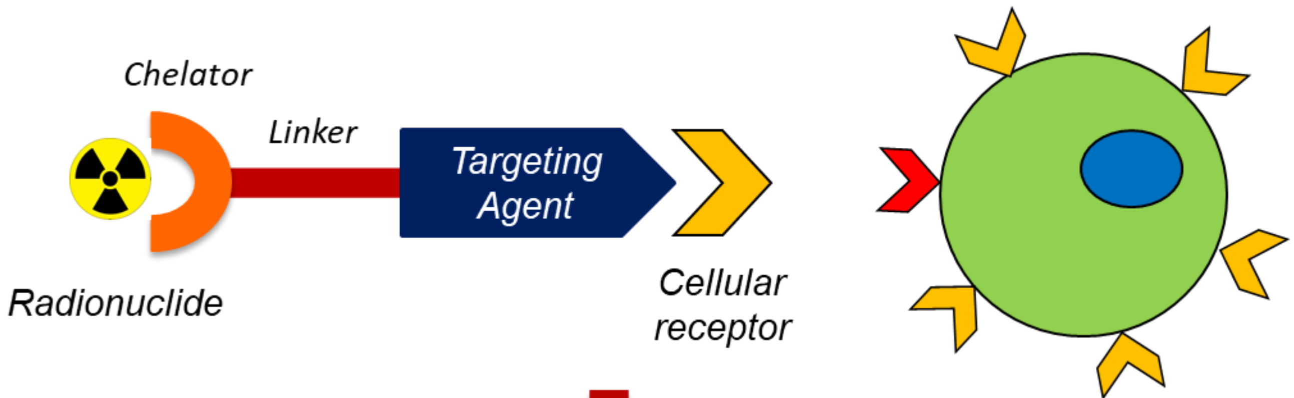
γ

SPES for medicine
Production of radionuclides for nuclear medicine

ISOLPHARM
SPES exotic beams for medicine

The main objective of the ISOLPHARM project is the production of carrier-free radionuclides for radiolabeling of bioactive molecules

Radiopharmaceuticals and Targeted Radionuclide Therapy



Depending on the production method:

Carrier-free radionuclides →

Carrier-added radionuclides →

Radioisotope production
The ISOLPHARM project at LNL

1 Cyclotrons	(3 Generators)	2 Nuclear reactors

Cyclotrons

- ✓ Radionuclides can be produced in big amounts
- ✓ High specific activity radionuclides can be produced in some cases if enriched targets are used, which are often very expensive
- ✗ A difficult and precise beam energy tuning is required in order to preserve radionuclide purity.

Nuclear reactors

- ✓ Radionuclides for therapy can be produced in big amounts
- ✓ Parent nuclides for generators can be produced
- ✗ Radionuclides produced by direct reactions are often carrier added

ISOLPHARM


Acknowledgement of receipt

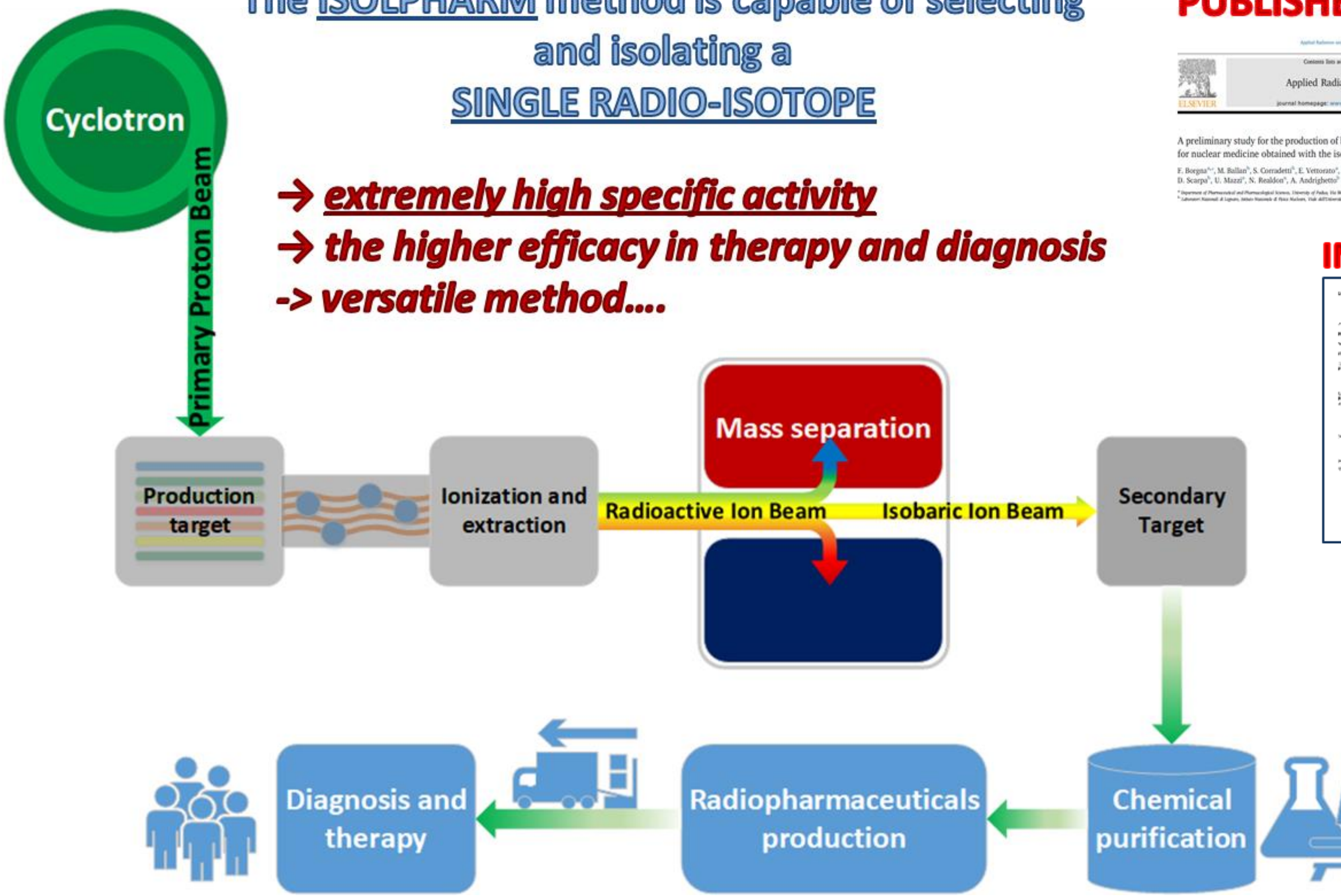
- ✓ Instrinsically carrier-free radionuclides can be produced
- ✓ With the same target numerous radionuclides can be produced only by changing the mass separator settings
- ✓ Designing specific targets a wide range of radionuclides can be prodcued, including radionuclides which can be hardly produced with the traditional techniques
- ✗ Production yields are lower than those of cyclotrons and nuclear reactors

The ISOLPHARM method is capable of selecting and isolating a SINGLE RADIO-ISOTOPE

→ ***extremely high specific activity***

→ ***the higher efficacy in therapy and diagnosis***

-> ***versatile method....***



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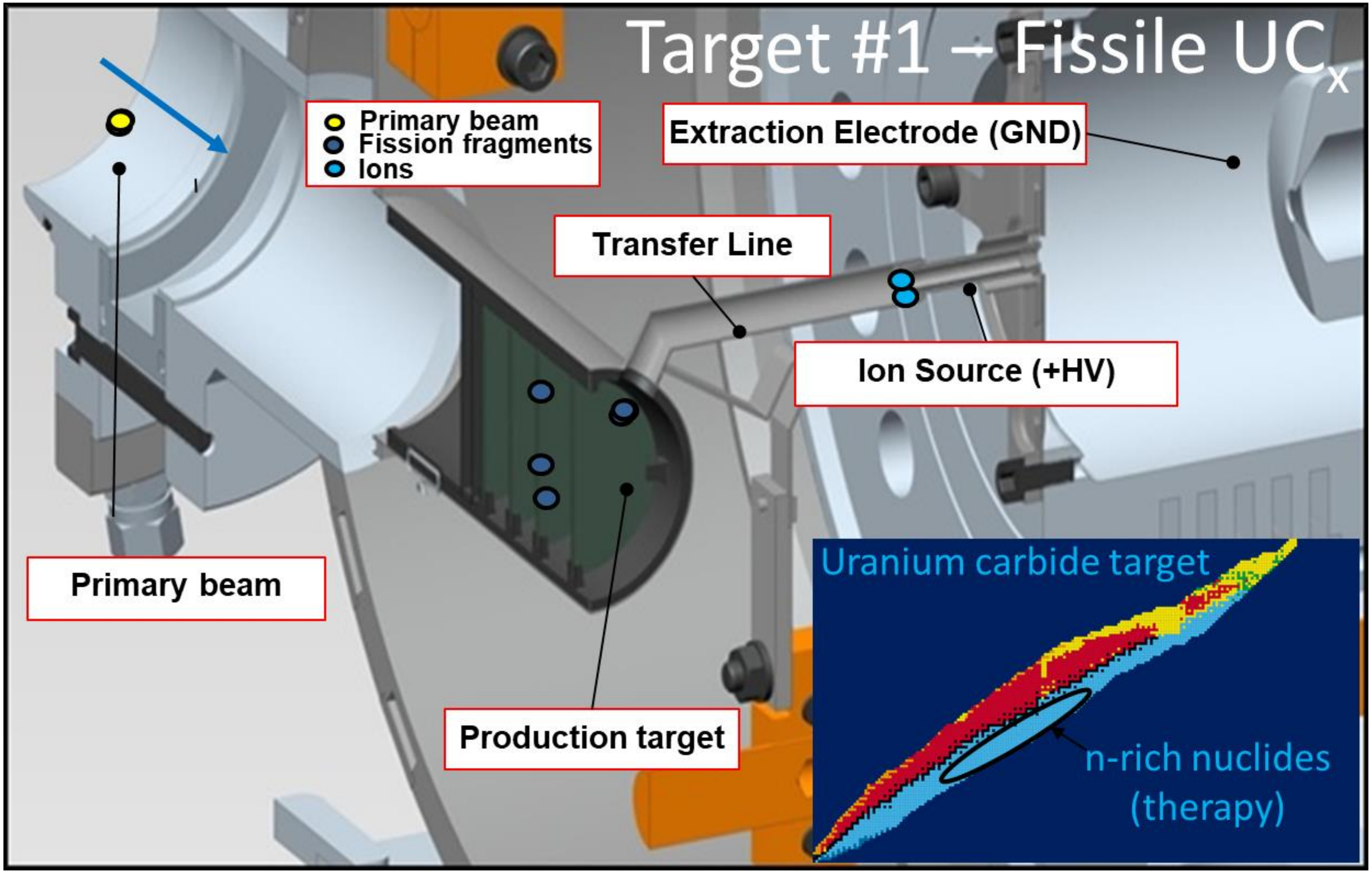
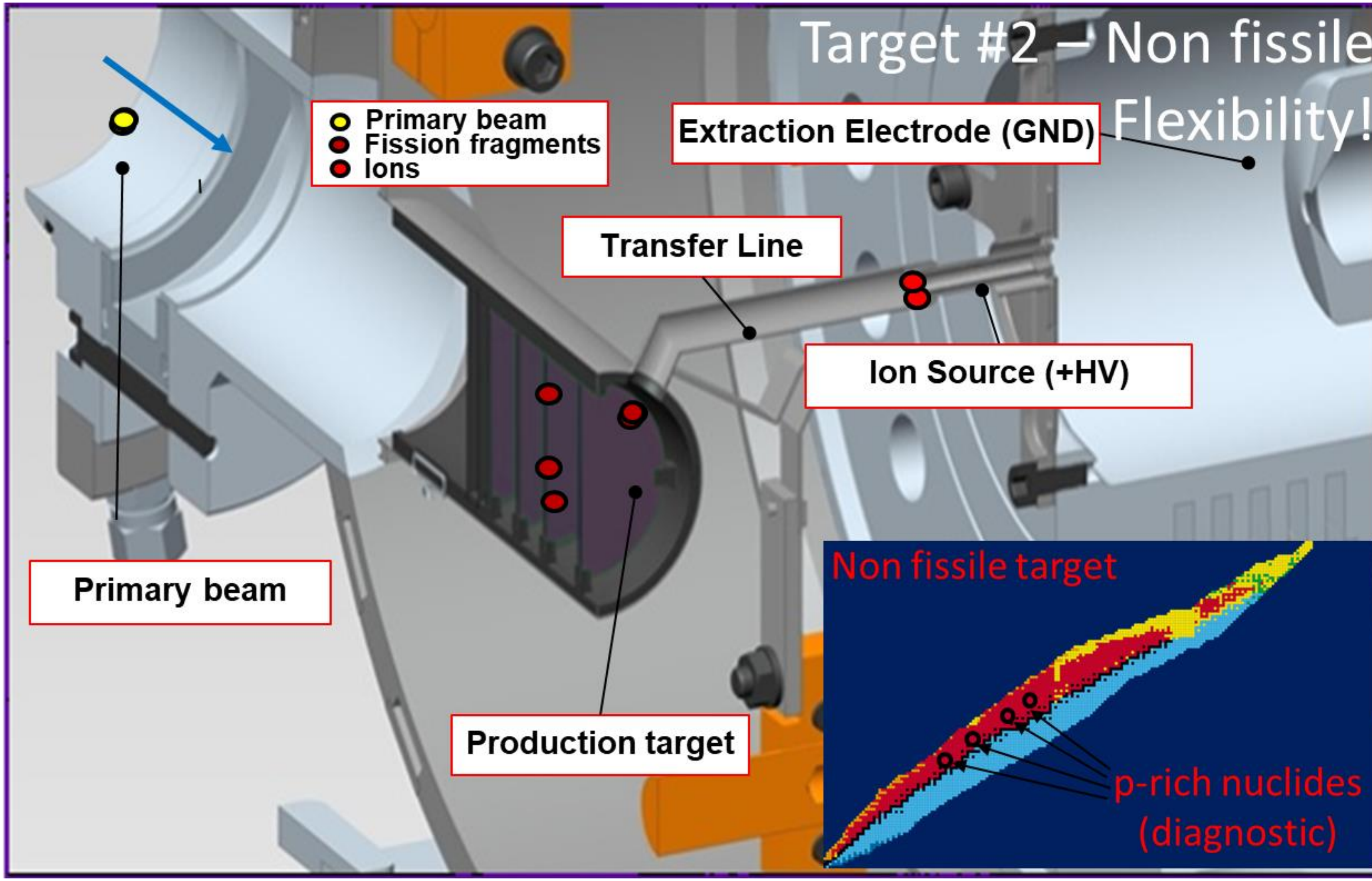
Radioisotope production
The ISOLPHARM project at LNL



Radioisotope production
The ISOLPHARM project at LNL

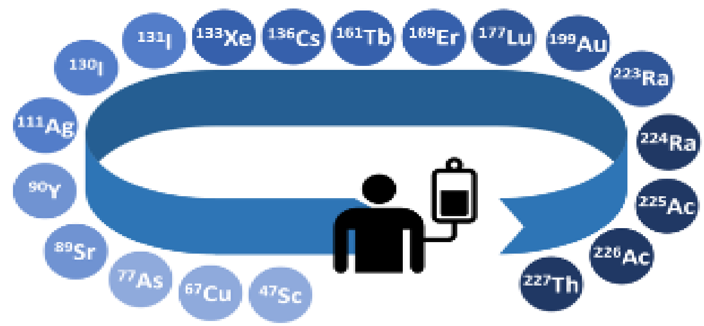


ISOLPHARM:

Radionuclides that can be produced at LNL

Diagnostic isotopes

Therapeutic isotopes



Theragnostic isotopes

See poster by M. Ballan

UC_x target

Production of ^{111}Ag

SPES UC_x isotope production (200 μA 40 MeV PPB, 5 irradiation days)												
Isotope	Half-life	Decay radiations								Produced activity		Notes
	$t_{1/2}$	β-		β+/ϵ		γ		Auger		[MBq]	[mCi]	
^{77}As	38,83 h	100%	0,683 MeV	/	/	1,59%	239 keV	0,06%	(9,67 keV)	2,21E+03	59,73	
^{86}Rb	18,642 d	99,99%	1,776 MeV	0,01%	ϵ	8,64%	1077 keV	0,01%	(10,8 keV)	6,06E+01	1,64	
^{89}Sr	50,53 d	100%	1,5 MeV	/	/	/	/	/	/	8,85E+03	239,15	
^{90}Sr	28,9 y	NR	NR	NR	NR	NR	NR	NR	NR	5,16E+01	1,39	^{90}Y generator
^{90}Y	64,053 h	100%	2,28 MeV	/	/	/	/	0,00%	(13,4 keV)	1,88E+02	5,08	
^{111}Ag	7,45 d	100%	1,036 MeV	/	/	6,70%	342 keV	0,04%	(19,3 keV)	8,29E+04	2241,85	
^{122}Sb	2,7238 d	97,59%	1,984 MeV	2,41%	β+	70,67%	564 keV	0,29%	(21 keV)	1,32E+03	35,80	
^{125}I	59,407 d	/	/	100%	ϵ	6,68%	35,49 keV	19,80%	22,7 keV	1,70E+00	0,05	
^{126}I	12,93 d	47,30%	1,258 MeV	52,70%	β+	32,90%	666,33 keV	5,53%	22,7 keV	3,65E+01	0,99	
^{130}I	12,36 h	100%	2,949 MeV	/	/	11,30%	1157 keV	0,19%	(24,6 keV)	2,82E+04	760,84	
^{131}I	8,0252 d	100%	0,970 MeV	/	/	81,50%	364 keV	0,68%	(24,6 keV)	6,57E+04	1774,77	
^{133}Xe	5,2475 d	100%	0,427 MeV	/	/	36,90%	80,99 keV	5,67%	25,5 keV	8,59E+04	2320,76	
^{129}Cs	32,06 h	/	/	100,00%	β+	30,60%	371,92 keV	13,10%	24,6 keV	4,62E+00	0,12	Many Auger e^- emissions
^{131}Cs	9,689 d	/	/	100,00%	ϵ	/	/	9,30%	24,6 keV	3,68E+01	0,99	Many Auger e^- emissions
^{132}Cs	6,480 d	2%	1,279 MeV	98,13%	β+	1,58%	464 keV	9,40%	24,6 keV	2,14E+02	5,79	Many Auger e^- emissions
^{136}Cs	13,04 d	100%	2,548 MeV	/	/	80,00%	1048 keV	1,24%	26,4 keV	1,16E+04	313,75	
^{161}Tb	6,89 d	100%	0,593 MeV	/	/	10,20%	75 keV	1,46%	37,2 keV	1,73E+02	4,67	
^{169}Er	9,392 d	100%	0,351 MeV	/	/	0,00%	109,77 keV	0,00%	(5,67 keV)	1,54E+00	0,04	

ZrGe target

Production of ^{64}Cu and ^{67}Cu

^{67}Cu production ($t_{1/2}$: 61,83 h)							
ZrGe target (100 µA, 40 MeV)				ZrGe target (100 µA, 70 MeV)			
Time	Activity		Nuclei	Time	Activity		Nuclei
[days]	[MBq]	[mCi]	[#]	[days]	[MBq]	[mCi]	[#]
0,5	2,01E+01	0,54	6,47E+12	0,5	2,37E+02	6,40	7,61E+13
1	3,77E+01	1,02	1,21E+13	1	4,44E+02	11,99	1,43E+14
1,5	5,31E+01	1,43	1,71E+13	1,5	6,24E+02	16,87	2,01E+14
2	6,65E+01	1,80	2,14E+13	2	7,82E+02	21,15	2,52E+14
3	8,85E+01	2,39	2,85E+13	3	1,04E+03	28,14	3,35E+14
4	1,05E+02	2,85	3,39E+13	4	1,24E+03	33,49	3,99E+14
5	1,18E+02	3,19	3,80E+13	5	1,39E+03	37,58	4,47E+14
6	1,28E+02	3,46	4,12E+13	6	1,51E+03	40,70	4,84E+14

^{64}Cu production ($t_{1/2}$: 12,7 h)							
ZrGe target (100 µA, 40 MeV)				ZrGe target (100 µA, 70 MeV)			
Time	Activity		Nuclei	Time	Activity		Nuclei
[days]	[MBq]	[Ci]	[#]	[days]	[MBq]	[Ci]	[#]
0,5	2,97E+03	80,22	1,96E+14	0,5	2,66E+04	717,62	1,75E+15
1	4,51E+03	121,90	2,97E+14	1	4,03E+04	1090,43	2,66E+15
1,5	5,31E+03	143,55	3,50E+14	1,5	4,75E+04	1284,08	3,13E+15
2	5,73E+03	154,79	3,78E+14	2	5,12E+04	1384,68	3,38E+15
3	6,06E+03	163,67	3,99E+14	3	5,42E+04	1464,08	3,57E+15
4	6,14E+03	166,06	4,05E+14	4	5,50E+04	1485,51	3,62E+15
5	6,17E+03	166,71	4,07E+14	5	5,52E+04	1491,30	3,64E+15
6	6,17E+03	166,88	4,07E+14	6	5,52E+04	1492,84	3,64E+15

^{67}Cu is hardly produced with traditional techniques, but has very good decay properties for therapy

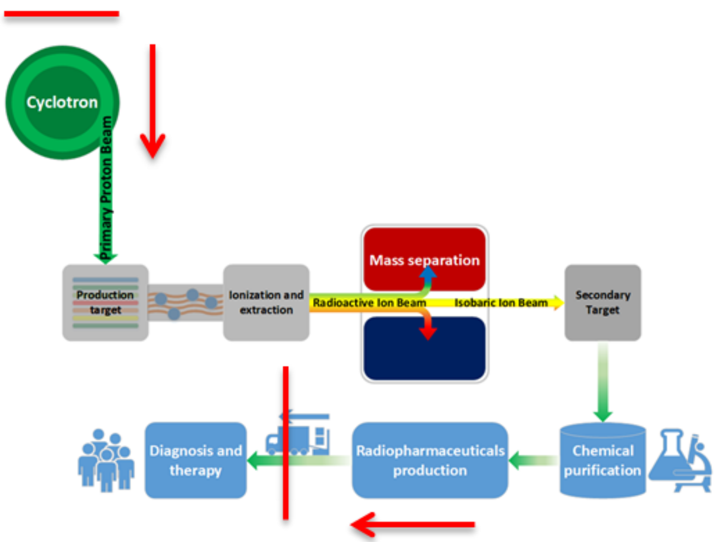
TiC target

Production of ^{43}Sc, ^{44}Sc and ^{47}Sc

TiC isotope production (100 µA 40 MeV PPB, 5 irradiation days)												
Isotope	Half-life	Decay radiations								Produced activity		Notes
	$t_{1/2}$	β-		β+/ϵ		γ		Auger		[MBq]	[mCi]	
^{47}Ca	4,563 d	NR	NR	NR	NR	NR	NR	NR	NR	6,67E+00	0,18	^{47}Sc generator
^{43}Sc	3,891 h	/	/	100%	β+	22,50%	373 keV	8,93%	3,3 keV	3,23E+04	873,14	
^{44}Sc	3,97 h	/	/	100%	β+	99,90%	1157 keV	4,14%	3,3 keV	2,39E+05	6445,95	
^{47}Sc	3,3492 d	100%	0,6 MeV	/	/	68,30%	159 keV	0,22%	(4 keV)	8,14E+04	2199,08	

➡ Very promising radionuclides, extremely challenging production!

Experimental activities: overview



Step 1
The cyclotron commisioning

Step 2
Production targets development

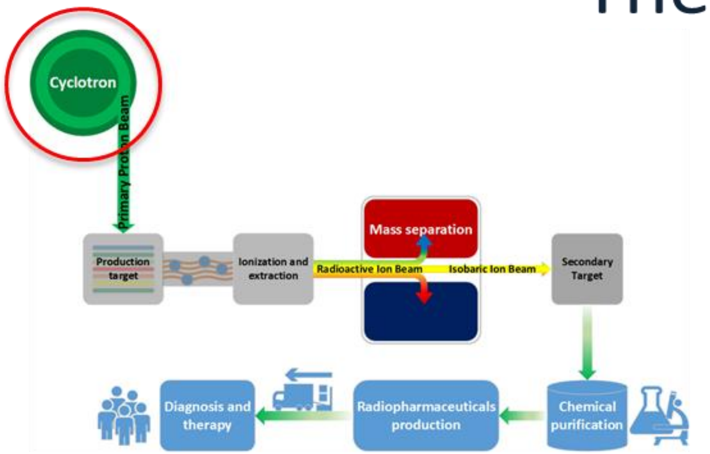
Step 3
Ion beams production

Step 4
Secondary targets development and ions recovery

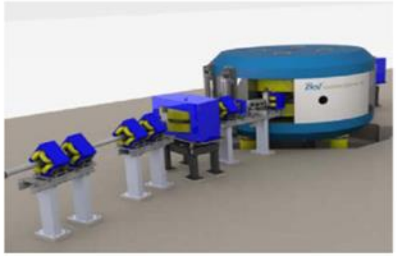
Step 5
Purification processes development

Step 6
Radiolabeling studies

The proton driver



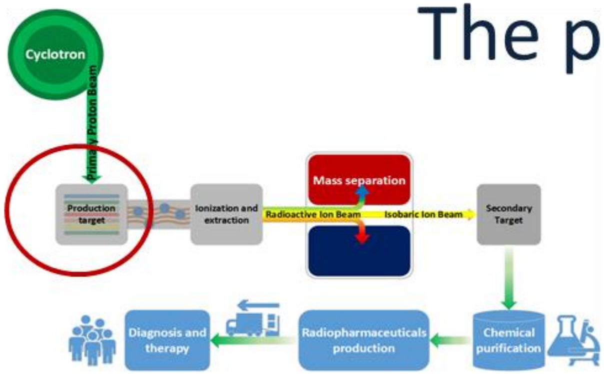
- 1 → reached 70 MeV few microA
- 2 → acceleration, extraction and delivery of beam in A6 with intermediate power (up to 15kW)
- 3 → High power (35 kW)
- 4 -> Endurance test (1 week continually) - > to be done



Main Dimensions
Diameter = 4.5 m
Height= 1.7 m
Weight = 210 tons

Accelerated Particle	H-
Extracted Particle	Protons
Energy	35-70 MeV (variable)
Current	> 700 uA (variable)
Extraction System	By stripping → simultaneous dual beam extraction
Injection System	Axial Injection → External Multicusp Ion Source 15-20mA DC
Main Magnet	Bmax = 1,6 T Coil current = 127 kAt Power supply = 30 kW 4 sectors, deep valley
RF System	2 resonators Frequency= 58 MHz Harmonic mode=4 Dissipated Power=15 kW per cavity DEE voltage=60-80 kV
Operational Vacuum	2 e -7 mbar

The production targets



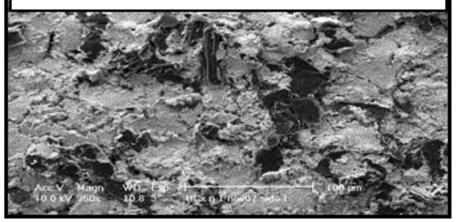
UC$_x$ target already developed and tested on-line!

Other targets under development for specific radionuclides production:

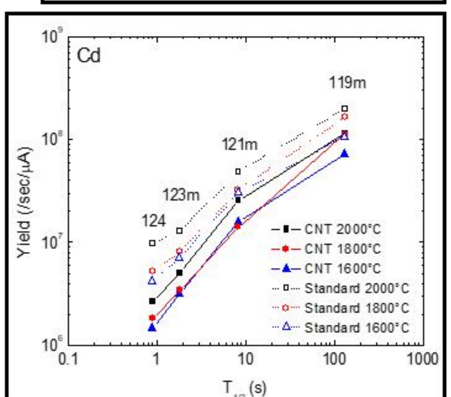
ZrGe: ^{64}Cu, ^{67}Cu

TiC: ^{43}Sc, ^{44}Sc, ^{47}Sc

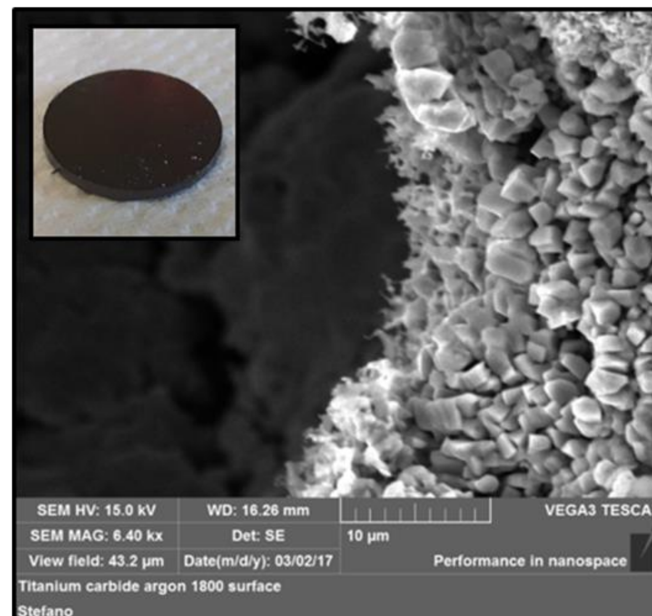
UC$_x$ target prototype



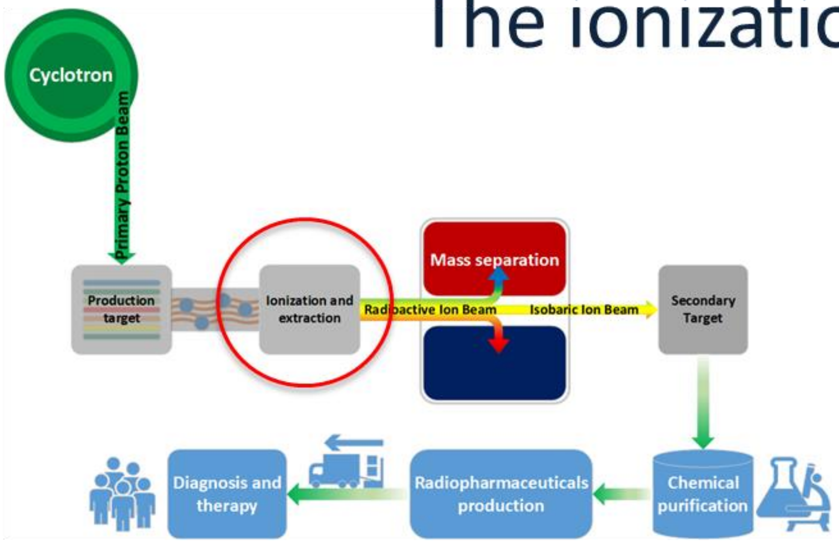
	Standard (graphite)	Low density (MWCNTs)
Density (g/cm³)	4.25	2.59
Diameter (mm)	12.50	13.07
Thickness (g/cm²)	0.41	0.41
Calculated porosity (%)	58	75



Porous titanium carbide (TiC)

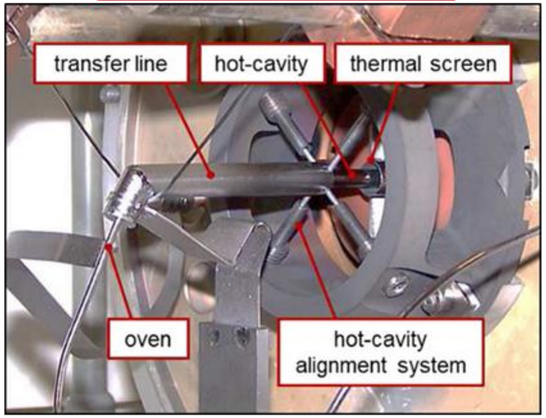


The ionization source

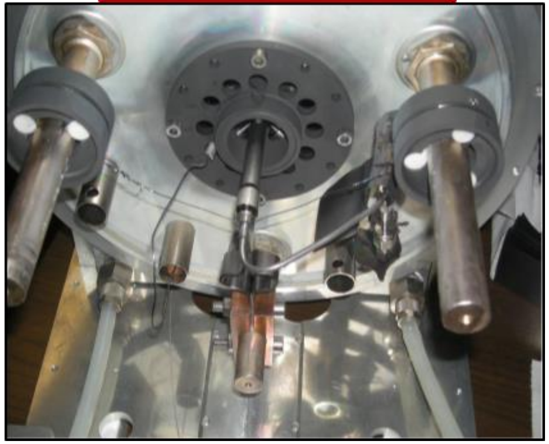


Ionized element	Desired radionuclide	Ionization source	Efficiency
Sr	^{89}Sr, ^{90}Sr/^{90}Y	SIS	~ 20 %
Y	^{90}Y	PIS	~ 1 %
I	^{125}I, ^{126}I and ^{131}I	PIS	~ 20 %
Cu	^{64}Cu, ^{67}Cu	PIS	~ 10 %
Ag	^{111}Ag	PIS	~ 10 %

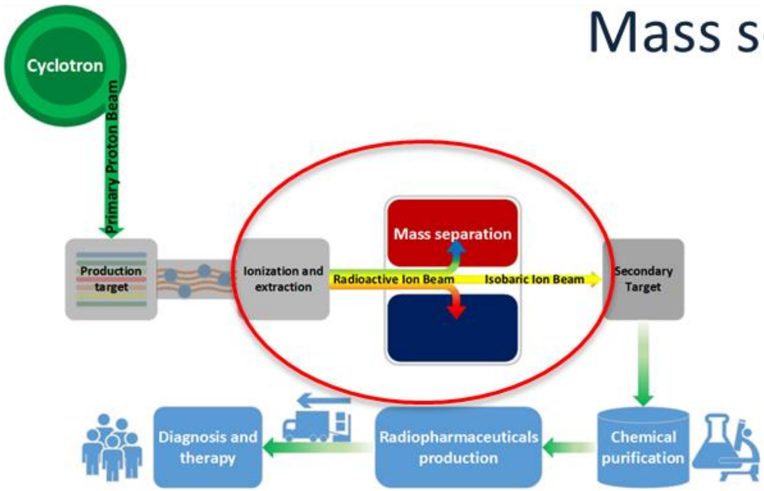
Surface Ion Source (SIS)



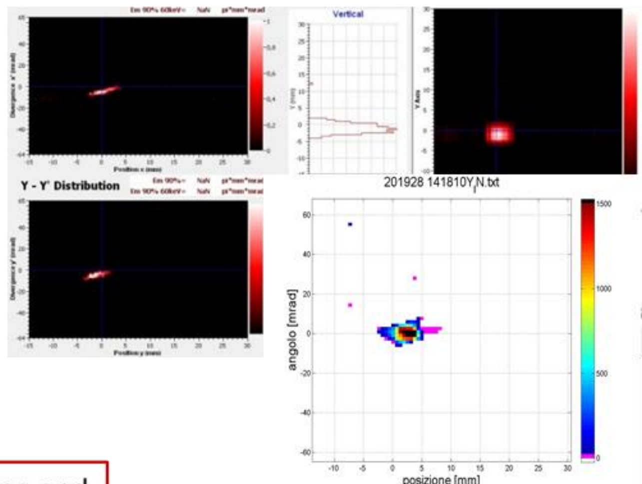
Plasma Ion Source (PIS)



Beam extraction and Mass separation



Strontium and yttrium beams focalization



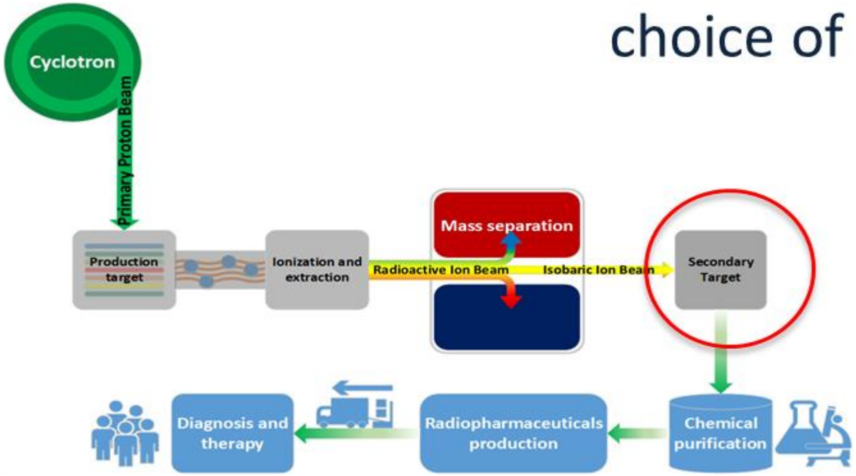
Beam Transmission ~ 100%

Electrostatic Triplets Quadrupoles and steereers system

Extraction -> 25 - 40 kV

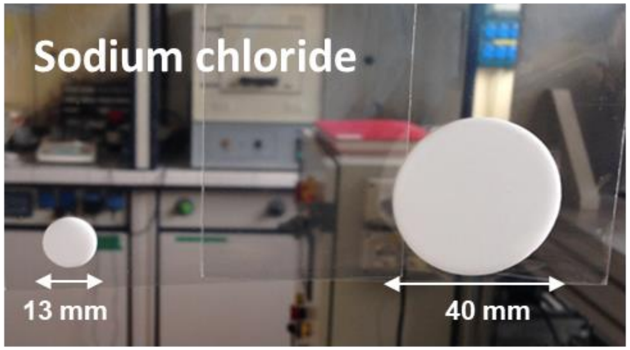
Diagnostic boxes 1 and 2
(2 Faraday Cups and 2 Beam profilers)

Secondary targets production: choice of the material



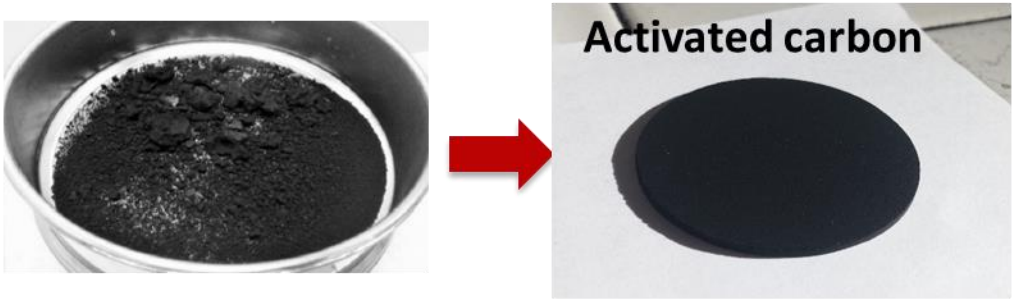
Secondary target requirements:

1. Chemical compatibility with the element
2. Absence of metal contaminants
3. No incompabilities with the production of a radiopharmaceutical for human administration
4. No interference with purification processes



→ Yttrium: ^{90}Y

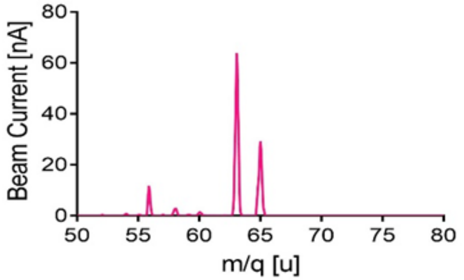
→ Copper: $^{64}Cu/^{67}Cu$



→ Iodine: ^{125}I, ^{131}I

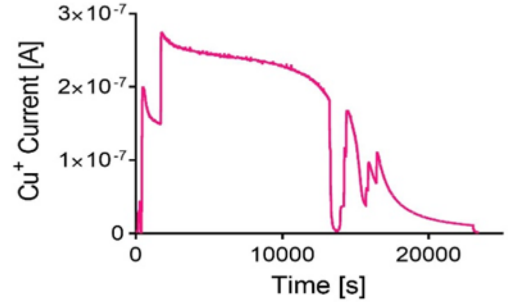
Copper beams

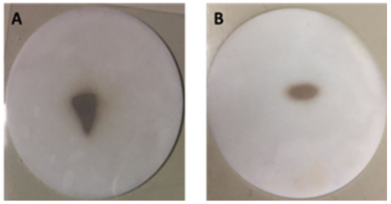
1) ^{63}Cu and ^{65}Cu identification (69.17% and 30.83%)



Ionization efficiency: 10%

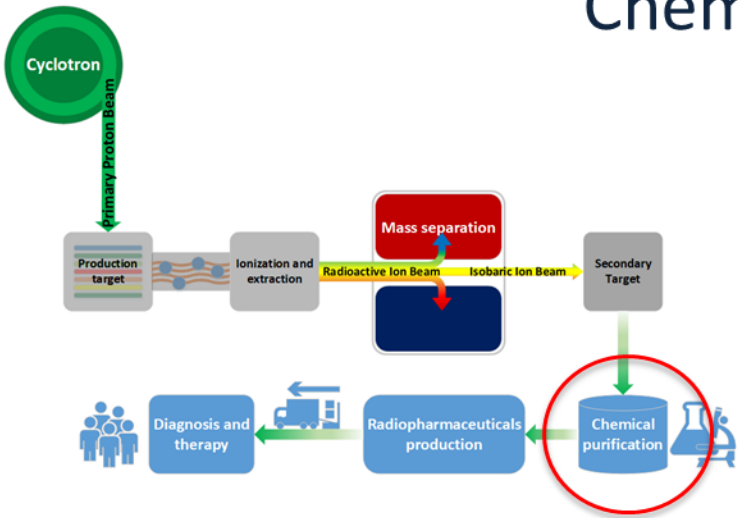
2) ^{63}Cu deposition

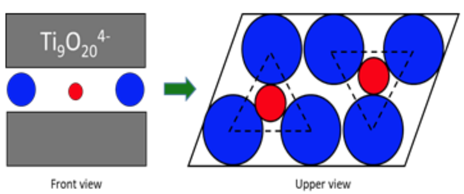




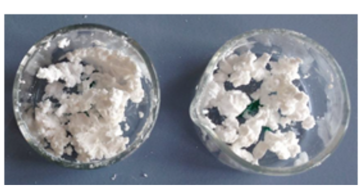
	Copper (current) measured in FC2 and integrated in time [µg]	Copper measured via GF-AAS [µg]	
1st deposition	9.94	1.46	Target dissolved in HNO_3 0.5 M, mild heating
2nd deposition	5.21	1.09	Target dissolved in HNO_3 0.5 M, mild heating
3rd deposition	1.12	0.54	Target dissolved in concentrated HNO_3, 180 °C for 20 min
4th deposition	0.94	0.50	Target dissolved in concentrated HNO_3, 180 °C for 20 min

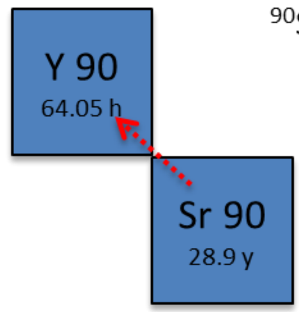
Chemical purification





$$9Ti(OC_3H_7)_4 + 4NaOH \longrightarrow Na_4Ti_9O_6 \cdot xH_2O$$



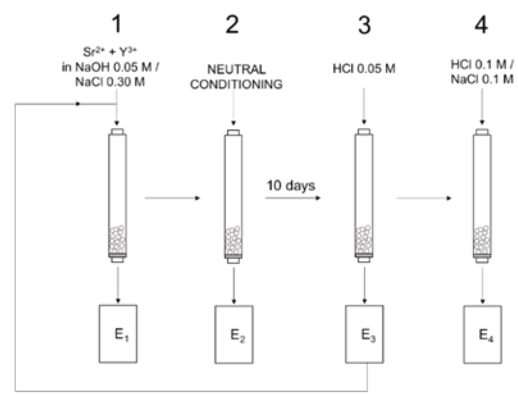


The case of ^{90}Y

↓

^{90}Sr main contaminant, but a source of ^{90}Y as well

^{90}Y directly produced +
the ^{90}Y from the decay of ^{90}Sr



The ISOLPHARM network and related projects

ISOLPHARM

SPES exotic beams for medicine

First new project derived from ISOLPHARM in collaboration with PSI

PAUL SCHERRER INSTITUT

PSI

ISOLPHARM_AG

Istituto Nazionale di Fisica Nucleare – Sezione di Padova

Istituto Nazionale di Fisica Nucleare – Laboratori Nazionali di Legnaro

Università degli Studi di Padova – dsf

Università degli Studi di Padova – DiSC

BIOtech – Università degli Studi di Trento

TIFPA – Trento Institute for Fundamental Physics and Applications

ISOLPHARM_Ag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Chromatographic separation of the theranostic radionuclide ^{111}Ag from a proton irradiated thorium matrix

Tara Mastren [a], Valery Radchenko [a,1], Jonathan W. Engle [a,2], John W. Weidner [a], Allison Owens [b], Lance E. Wyant [b], Roy Copping [b], Mark Brugh [a], F. Meiring Nortier [a], Eva R. Birnbaum [a], Kevin D. John [a], Michael E. Fassbender [a,*]

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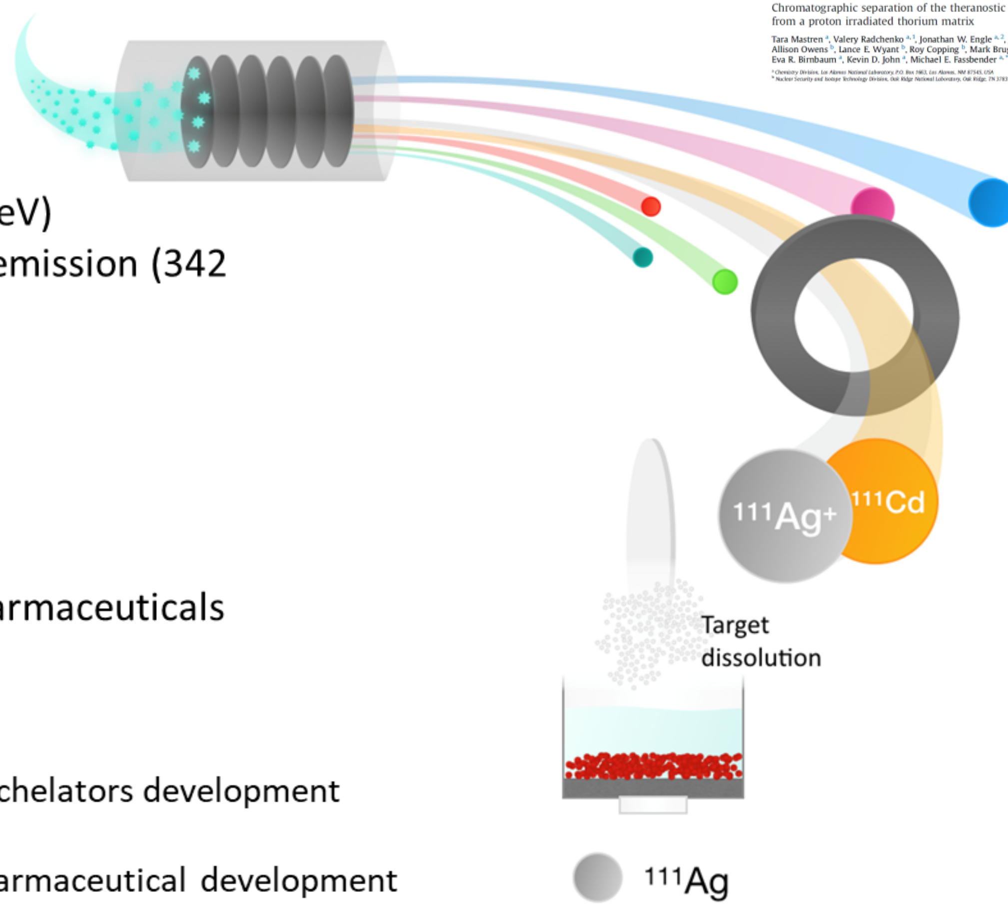
^{111}Ag

Promising radionuclide for therapy:

- β^- emitter (average energy 360 keV)
- Low percentage of associated γ-emission (342 keV, 6.7%)
- $t_{1/2}$: 7.45 days



Development of Ag-based radiopharmaceuticals

Task 1: physics and computing

Task 2: production of Ag^+, purification and chelators development

Task 3: cellular targets studies and radiopharmaceutical development

Task 1: activities at LNL and UNIPD

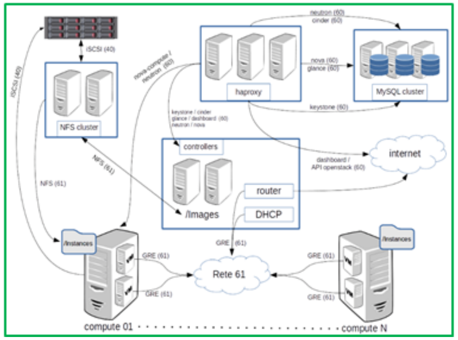
	Year 1				Year 2			
	M3	M6	M9	M12	M15	M18	M21	M24
Task 1 - Computing			MS1	MS2				MS3-4
Setup and maintenance of cloud	■	■	■	■	■	■	■	■
Creation of dedicated workflows	■	■	■	■				
Development of a web-based user portal					■	■	■	■
MC code development and running case study 1	■	■	■	■				
MC code development and running case study 2					■	■	■	■

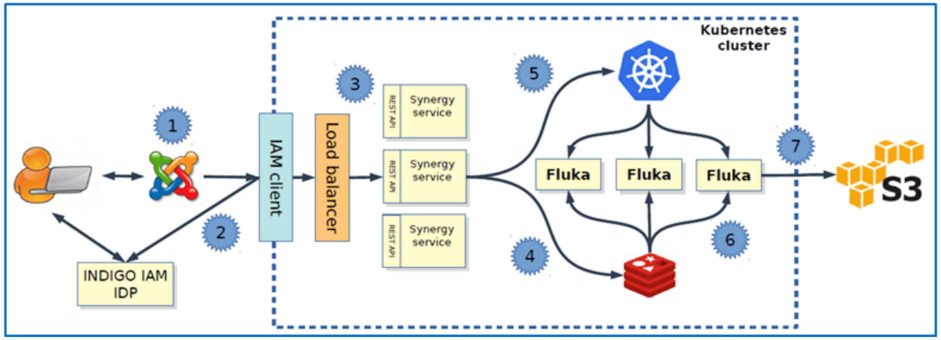
30-09-2018 MS1: Porting and operation of MC framework in cloud environment

1. Setup of the ISOLPHARM_Ag project in Cloudveneto infrastrucuture
2. Docker containers for Fluka and G4 created and used for real simulation on the cloud infrastructure (see next slide)
3. Common uniform description of input parameters for Fluka and G4

30-09-2018 MS2: First results of Ag production with different codes

1. First production Fluka/G4 run starting in September on the cloud framework delivered in MS1





Task 2: activities at LNL and UNIPD

	Year 1				Year 2			
	M3	M6	M9	M12	M15	M18	M21	M24
WP2 - Cold chemistry			MS5	MS6				MS7-8
Ionization and acceleration of Ag	■	■	■					
Development of purification methods for Ag					■	■	■	■
Synthesis of first Ag-based complexes	■	■	■	■				
Characterization of Ag-based complexes					■	■	■	■
Complete chelators for Ag library and selection of the most stable ones					■	■	■	■
Toxicity studies					■	■	■	■

Completed activity @ LNL

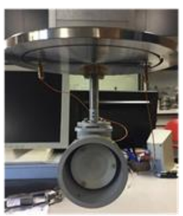
Preliminar screening activity completed @ UNIPD, complete synthesis and preliminar characterization by the end of 2018

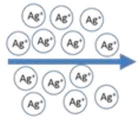
30-09-2018

MS5: Ionizzazione e deposito di Ag stabile presso FE SPES

Deposito Ag^{+} su target da 40 mm di $NaNO_3$

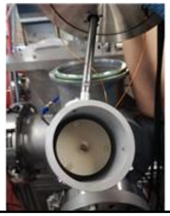
Target secondari (40 mm)

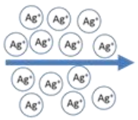


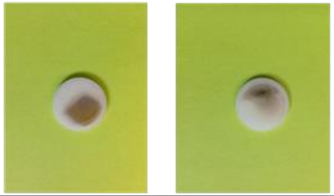


Deposito su target da 13 mm

Target secondari (13 mm)



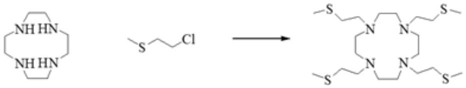




31-12-2018

MS6: Sintesi di una gamma di complessi a base Ag

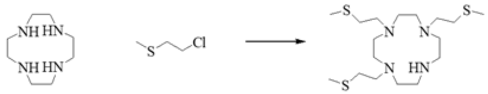
Condizioni di reazione:
- solvente: ACN
- Base: K_2CO_3
- Rapporto cyclen: 2 – cloroetilmetilsolfuro 1:8
- Termostata a 40 °C per 6 giorni



DOTETE 1

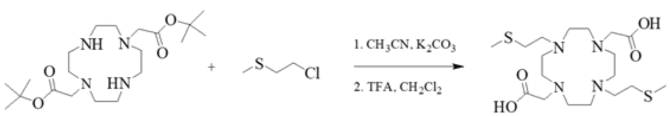
Purificazione mediante colonna cromatografica (eluente $CHCl_3$/MeOH 9/1)

Condizioni di reazione:
- solvente: ACN
- Base: K_2CO_3
- Rapporto cyclen: 2 – cloroetilmetilsolfuro 1:3
- Termostata a 40 °C per 5 giorni



DOT3 2

Purificazione mediante colonna cromatografica (eluente $CHCl_3$/MeOH 9/1)



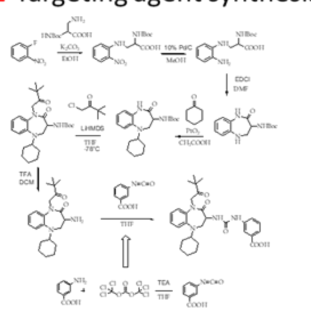
DOT2-$(CH_2COOH)_2$ 3

Task 3: activities at LNL, UNIPD and TIFPA

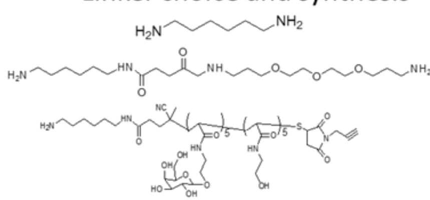
	Year 1				Year 2			
	M3	M6	M9	M12	M15	M18	M21	M24
WP3 - Molecular biology				MS9				MS10-11
Synthesis of CRT-CCK2R targeted molecules								
Radiolabeling of CRT-CCK2R targeted molecules								
Design of suitable 3D scaffold for in vitro tissue mimicking								
Setup of the dynamic cell culture conditions and exposure to ionizing radiation								
Targeting studies in dynamic conditions								

31-12-2018 MS9: First CRT-CCK2R targeted molecules synthesized

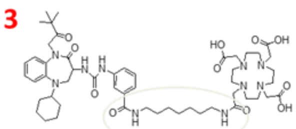
1 Targeting agent synthesis



2 Linker choice and synthesis



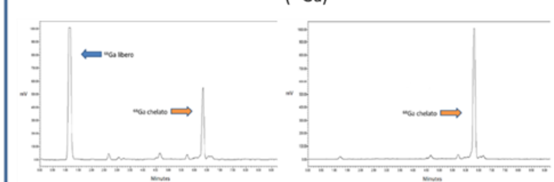
3



IP1 and IP2 synthesis accomplished

IP3 ongoing

4 IP1 radiolabeling – very preliminary (^{68}Ga)



Preliminar screening activity completed @ UNIPD, complete synthesis and preliminar characterization by the end of 2018

Providing to cells a suitable artificial microenvironment capable of mimicking a living tissue is important to obtain reliable results with in vitro experiments.
This can be obtained using degradable hydrogels leaded with cells (B16).
Materials chosen: chemically modified Gelatin and Silk Fibroin
Methacrilation procedure for Gelatin is **achieved**.
Methacrilation procedure for silk Fiborin is **in progress.** *

Master thesis from September

Radioisotope production
The ISOLPHARM project at LNL

The Italian Network

Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali di Legnaro

Istituto Nazionale di Fisica Nucleare
Sezione di Padova

Trento Institute for Fundamental Physics and Applications

Università degli Studi di Padova

- Pharmaceutical and Pharmacological Sciences
- Chemical sciences
- Industrial engineering
- Management and engineering
- Information engineering
- Physics and astronomy

BIOtech Biomedical Technologies at University of Trento - Italy

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

Ospedale Sacro Cuore Don Calabria
Presidio ospedaliero accreditato - Regione Veneto

Regione del Veneto
ULSS2 Marca Trevigiana

I.O.V. Istituto Oncologico Veneto I.R.C.C.S

The International Network

POLATOM

Paul Scherrer Institut PSI

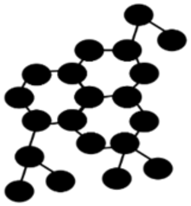
DEMOKRITOS
National Center for Scientific Research

Medicis Promed

6 invited talks at Italian and international conferences

Conclusions

At SPES it will be possible to **produce radionuclides for medical purposes** using the ISOL technique.



The ISOLPHARM method (patent deposited) is focused on the production of radiopharmaceutical precursors with **high specific activity** using a proton beam at intermediate energies.

The ISOLPHARM collaboration started 4 years ago. An increasing **experimental activity** is under development. **2 PhD thesis, 10 master thesis**

Some radionuclides (as ^{111}Ag , ^{43}Sc, etc) are extremely interesting and could be used as precursors for **new radiopharmaceuticals.**

First step: to produce **first radionuclides of medical interest** for research (small quantities) when the first SPES RIB will be delivered.

Thank you for your attention

The SPES/ISOLPHARM group