Novel methods for the production of radionuclides of medical interest with accelerators

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On behalf of the SPES target, ISOLPHARM and ISOLPHARM_Ag groups

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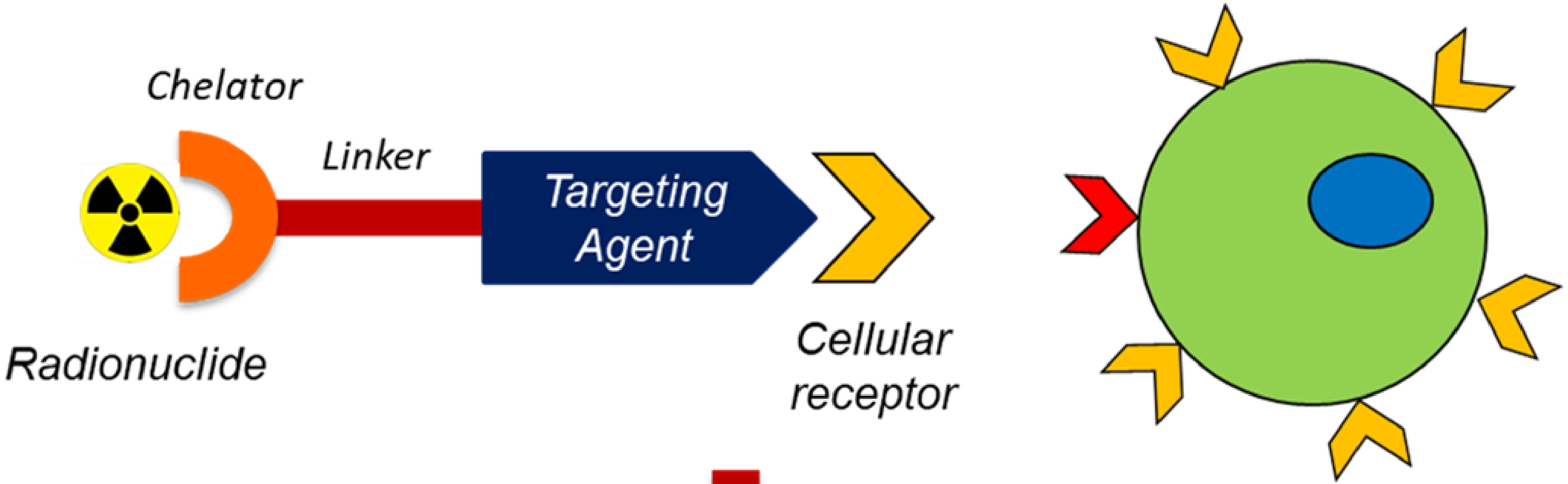
Lanzhou, 22nd-26th October 2018

Outline

- Radionuclides production: traditional methods
- ISOL technique for radionuclides production: the ISOLPHARM project
- ISOLPHARM_Ag: a case study
- Other ISOL-based radionuclide production facilities

Radiopharmaceuticals and targeted radionuclide therapy



Depending on the production method:

Carrier-free radionuclides

Carrier-added radionuclides

Radionuclides production method

Table 1 Common types of radionuclide sources

	Nuclear Reactors	Generators	Cyclotrons
Principle of production	Target material inserted in the neutron flux field undergoes fission or neutron activation transmuting into radionuclide of interest	Long-lived parent radionuclide decays to short-lived daughter nuclide of interest. Daughter nuclide elution follows in pre-determined cycles	Target material irradiation by charged particle beams. Inducing nuclear reactions that transmute the material into radionuclide of interest
Transmutation base	Neutrons	Decay	p, d, t, ^{3}He, α or heavy ion beams
Advantages	- Production of neutron rich radionuclides, mostly for therapeutic use - High production efficiency - Centralized production: one research reactor able to supply to large regions or in some cases globally	- Available on site, no need for logistics - Mostly long shelf life - Easy to use - Limited radioactive waste: returned to manufacturer after use	- Production of proton rich elements used as β^{+} emitters for PET scans - Decentralized production allows for back-up chains - High uptime - High specific activity in most cases - Small investment in comparison to nuclear reactor - Little long-lived radioactive waste
Disadvantages	- Extremely high investment cost - High operational costs - Considerable amounts of long-lived radioactive waste - Long out-of-service periods - Trouble to back-up in case of unforeseen downtime - Demanding logistics, often involving air transport - Public safety concerns - Non-proliferation treaty concerns	- Supplies in cycles according to possible elution frequency; in-house use must be timed accordingly - Trace contaminants of long-lived parent nuclide in eluted product	- Regional network of cyclotrons and complex logistics needed for short-lived produced radionuclides - Radionuclide production limited depending on installed beam energy

Courtesy of M.A. Synowiecki

M.A. Synowiecki, L.R. Perk, J.F.W. Nijsen, EJNMMI Radiopharmacy and Chemistry (2018) 3:3

Accelerators for medical radionuclide production

Cyclotrons

- Most used accelerators
- Compact designs
- Long commercial experience
- Natural limitation in beam current
- (Usually) low energy proton beams are ok

Linacs

- Ion linacs
- More competitive for α and heavier projectiles, and high currents
- Electron linacs (photoneutron-photoproton reactions)
- (Sc isotopes from titanium based targets)

Others

- Tandem
- Laser (laser-plasma) acceleration
- Neutron sources driven by accelerators

U. Koster, M.C. Cantone, *Radioisotope Production* in F. Azaiez, A. Bracco, J. Dobeš, A. Jokinen, G.E. Körner, A. Maj, A. Murphy, P. Van Duppen (eds.), Nuclear Physics for Medicine, NUPECC 2014
V. Starovoitova et al., Applied Radiation and Isotopes 85 (2014) 39–44
Y. Nagai, Physics Procedia 66 (2015) 370 – 375
M. Mamtimin et al., Applied Radiation and Isotopes 102 (2015) 1-4
K. Minegishi et al., Applied Radiation and Isotopes 116 (2016) 8-12

Radionuclides production: cyclotrons

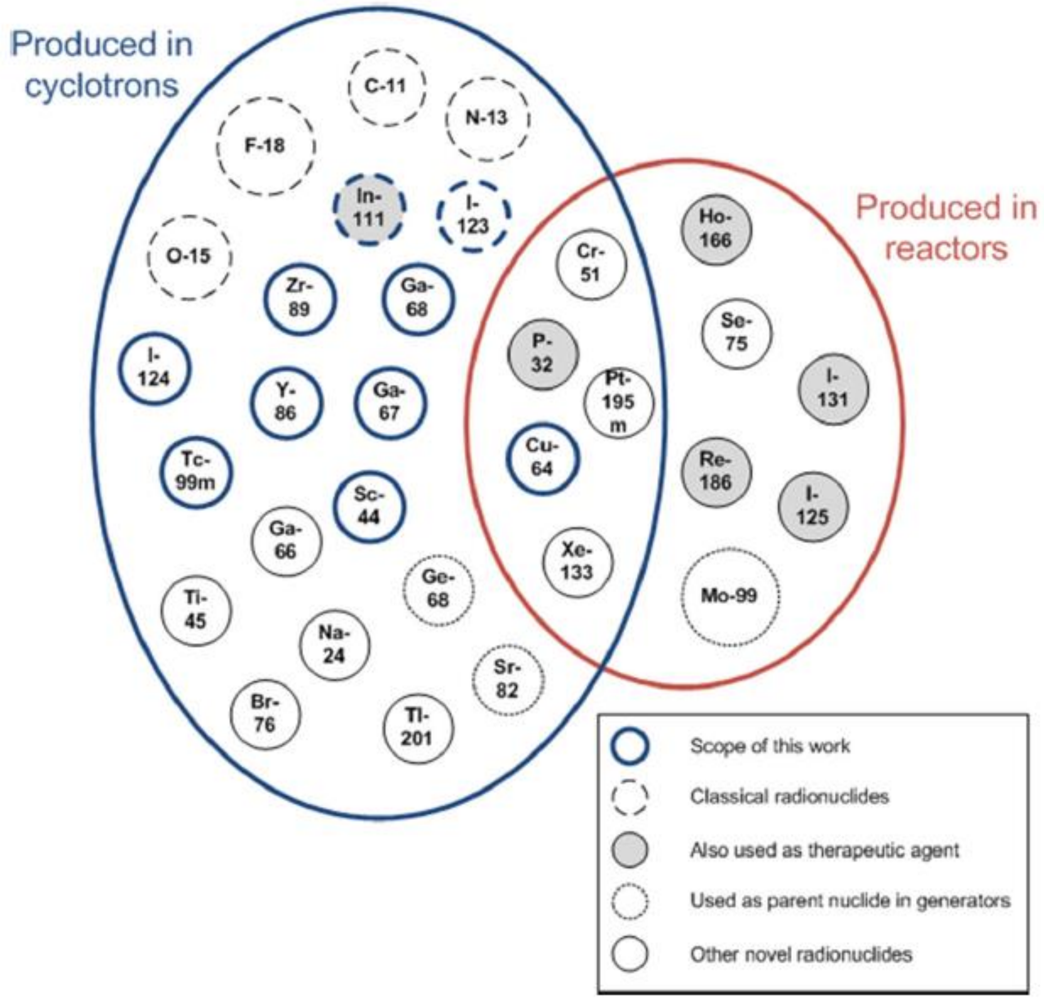


Fig. 1 *Radionuclides used in nuclear medicine diagnostics*

over the last two decades and the number is still increasing. In 2008, almost 700 cyclotrons were installed worldwide (IAEA, Cyclotron Produced Radionuclides: Principles and Practice, 2008). Only seven years later, according to *Goethals* et al. (Goethals and Zimmermann, 2015), that number has increased to 1218 cyclotrons whereof approximately 1000 are SMCs (Table 2). Most of the SMCs are located in the developed countries, although

Table 2 Distinction of cyclotron types (Goethals and Zimmermann, 2015)

Cyclotron type	Energy Range (MeV)	Approximate number	Typical location
Small medical cyclotron (SMC)	< 20 MeV	1050	- hospitals - universities - local commercial plants
Intermediate energy cyclotron	20–35 MeV	100	- regional commercial plants - research institutes
High energy cyclotron	> 35 MeV	50[a]	- research institutes - cancer proton therapy centers

[a]Excluding proton therapy cyclotrons

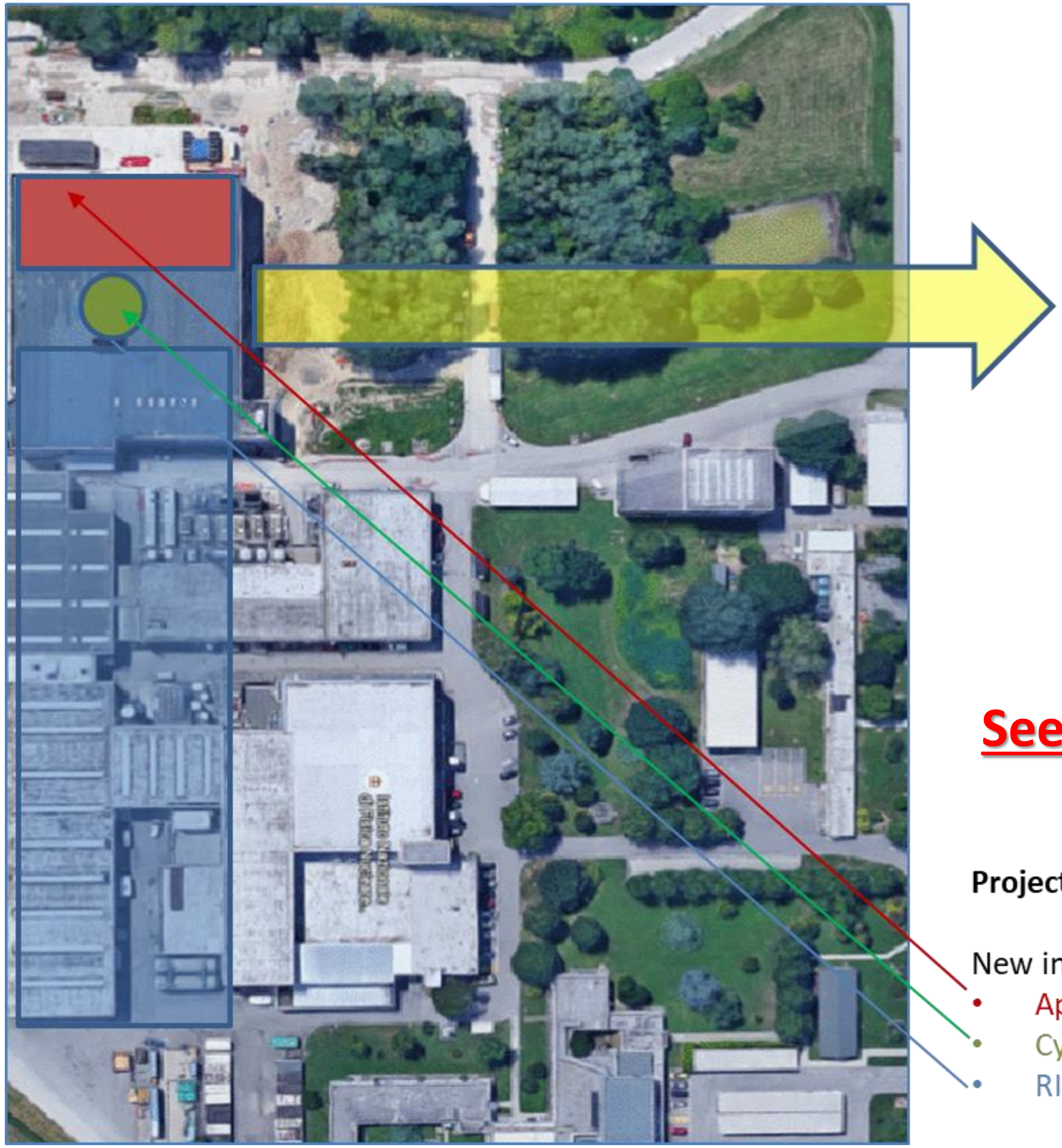
Courtesy of M.A. Synowiecki

M.A. Synowiecki, L.R. Perk, J.F.W. Nijsen, EJNMMI Radiopharmacy and Chemistry (2018) 3:3

Data taken from:

- Goethals PE, Zimmermann RG. Cyclotrons used in Nuclear Medicine World Market Report & Directory. 2015th ed; 2015.
- IAEA, Cyclotron Produced Radionuclides: Principles and Practice. Technical report series no.465. Vienna: International Atomic Energy Agency; 2008.

The SPES project at LNL



See presentations by M. Comunian and C. Baltador

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

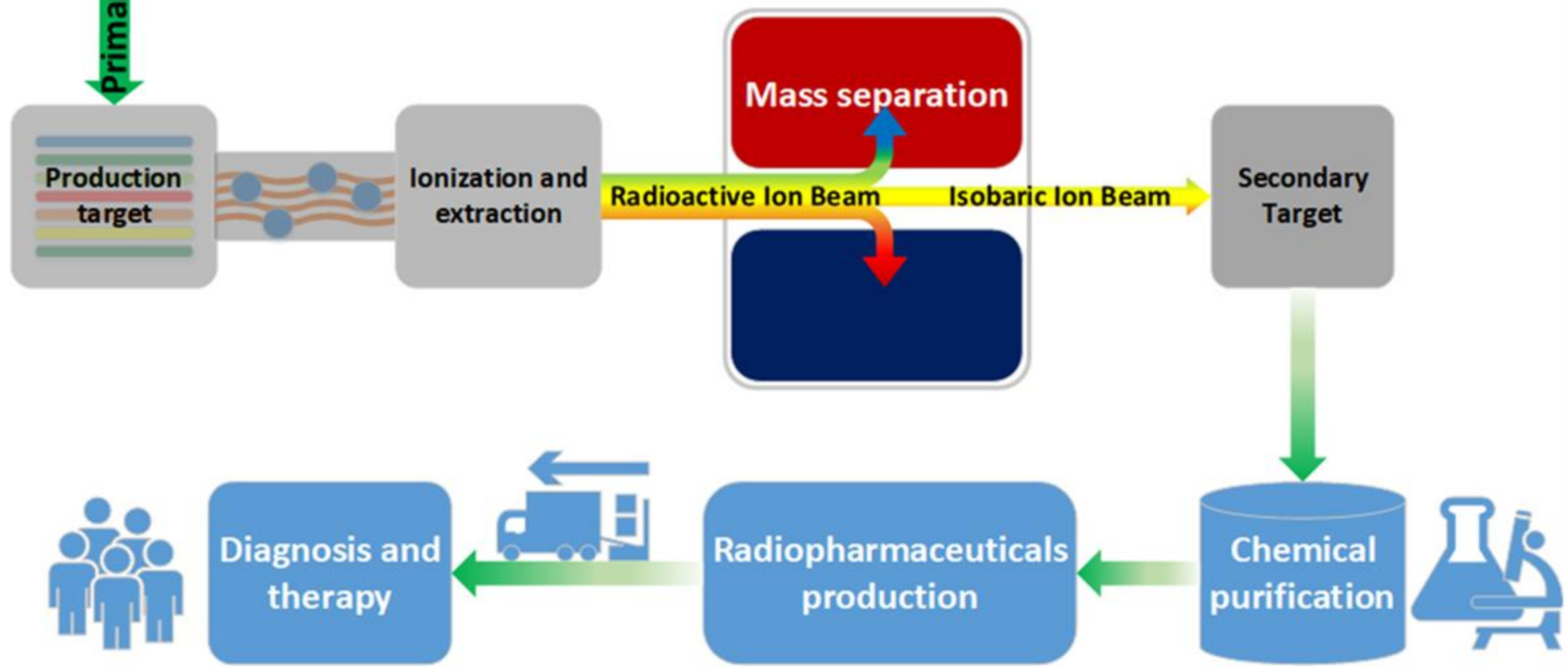
ISOLPHARM
SPES exotic beams for medicine

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

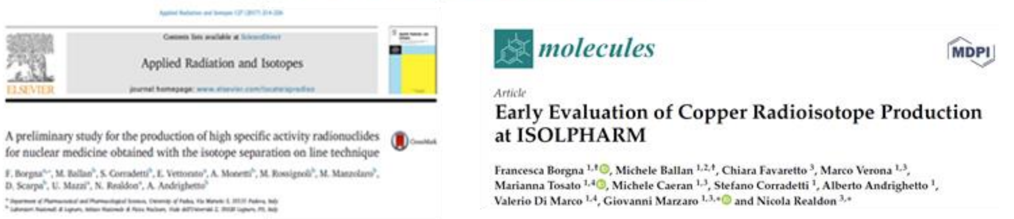
The ISOLPHARM project at LNL

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….***



PUBLISHED PAPERS


Applied Radiation and Isotopes

A preliminary study for the production of high specific activity radionuclides for nuclear medicine obtained with the isotope separation on line technique

molecules

Article

Early Evaluation of Copper Radioisotope Production at ISOLPHARM

Francesca Borgna, Michele Ballan, Chiara Favaretto, Marco Verona, Marianna Tosato, Michele Caeran, Stefano Corradetti, Alberto Andrighetto, Valerio Di Marco, Giovanni Marzaro and Nicola Realdon

INFN PATENT

The ISOLPHARM project at LNL

1 Cyclotrons

(3 Generators)

2 Nuclear reactors

1 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.

2 Nuclear reactors

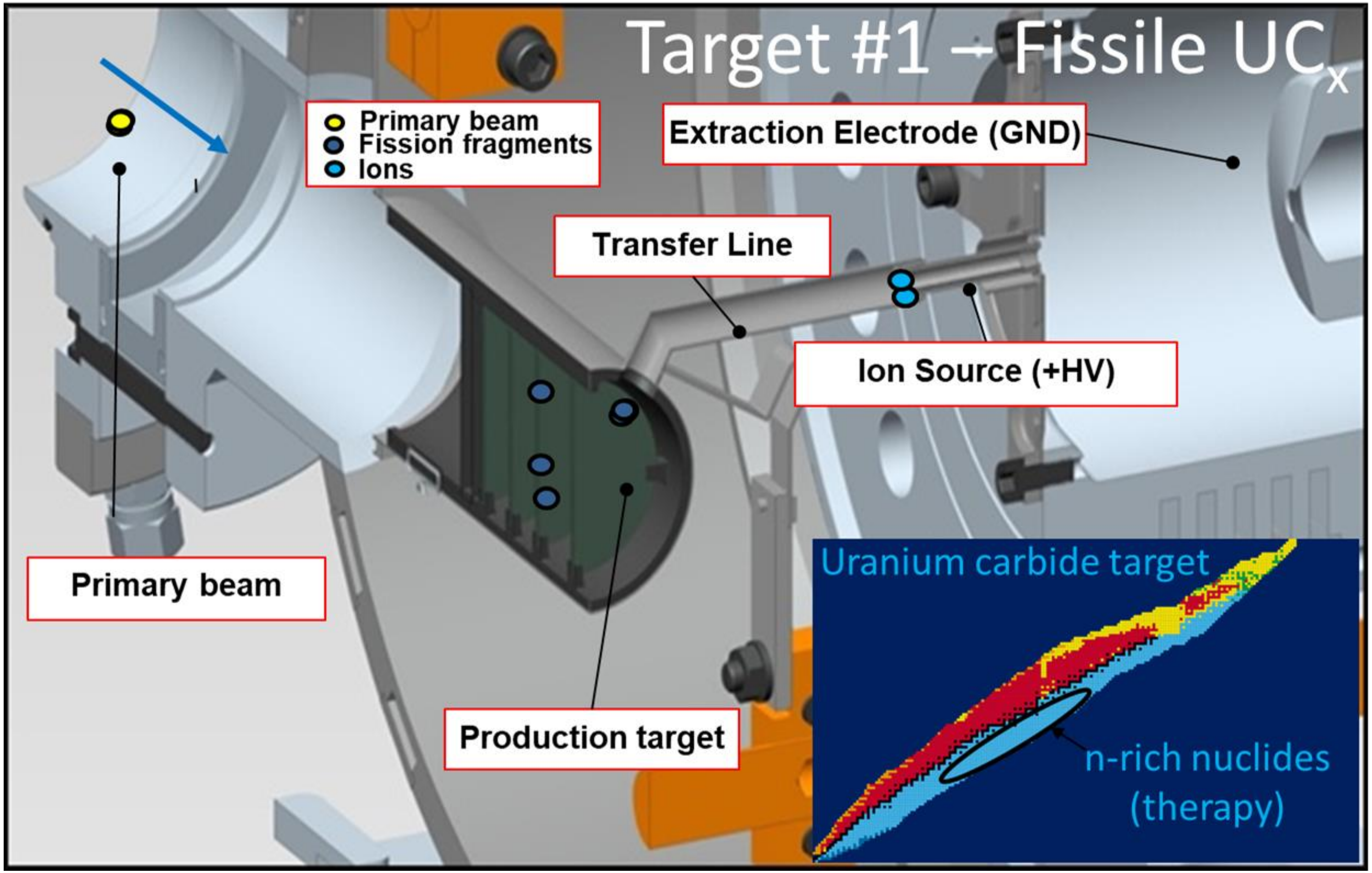
- ✓ Radionuclides for therapy can be produced in big amounts
- ✓ Parent nuclides for generators can be produced
- ✗ Radionuclides produced by direct reactions are often carrier added

ISOLPHARM

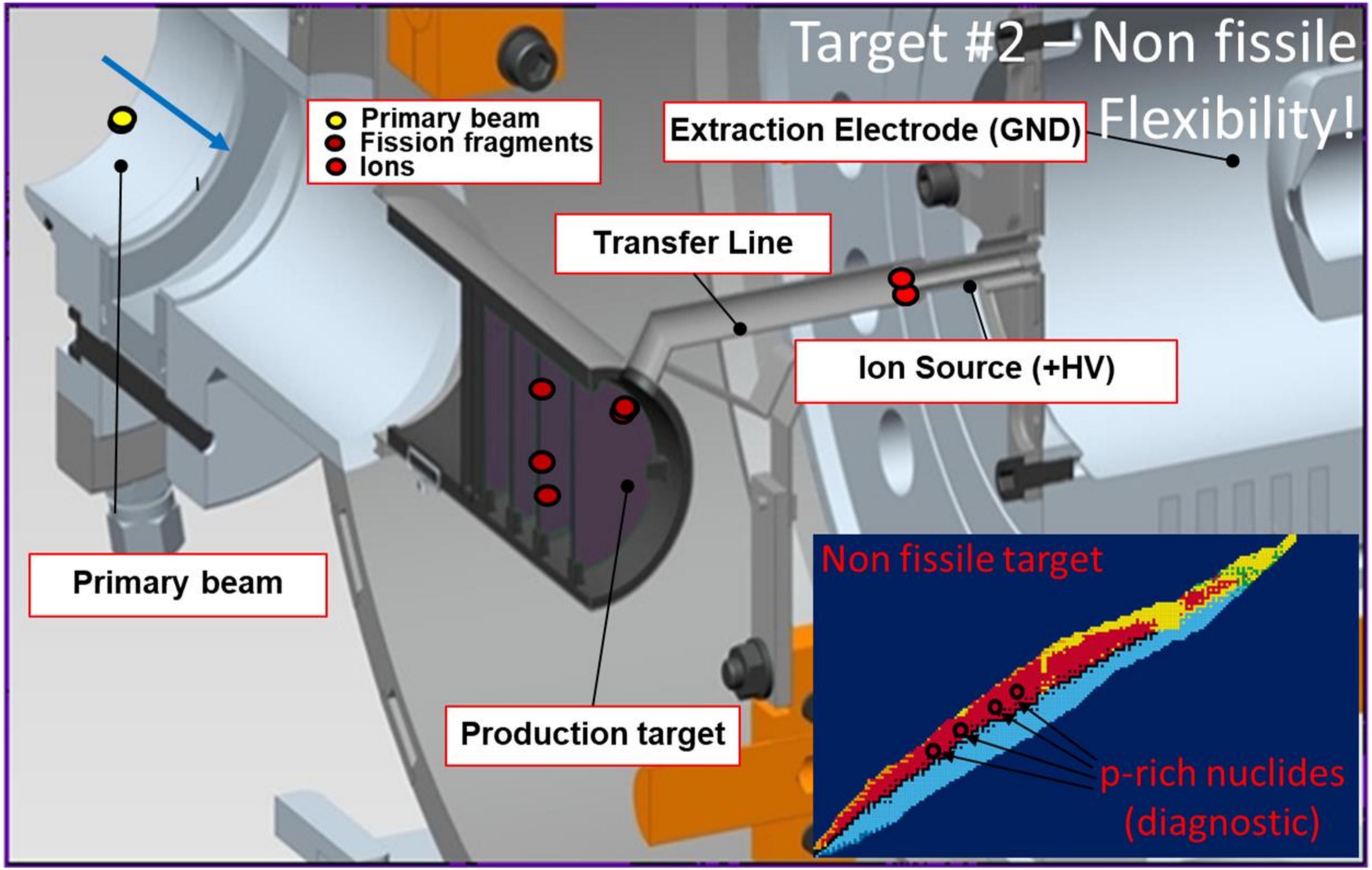
Acknowledgement of receipt

- ✓ 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 project at LNL

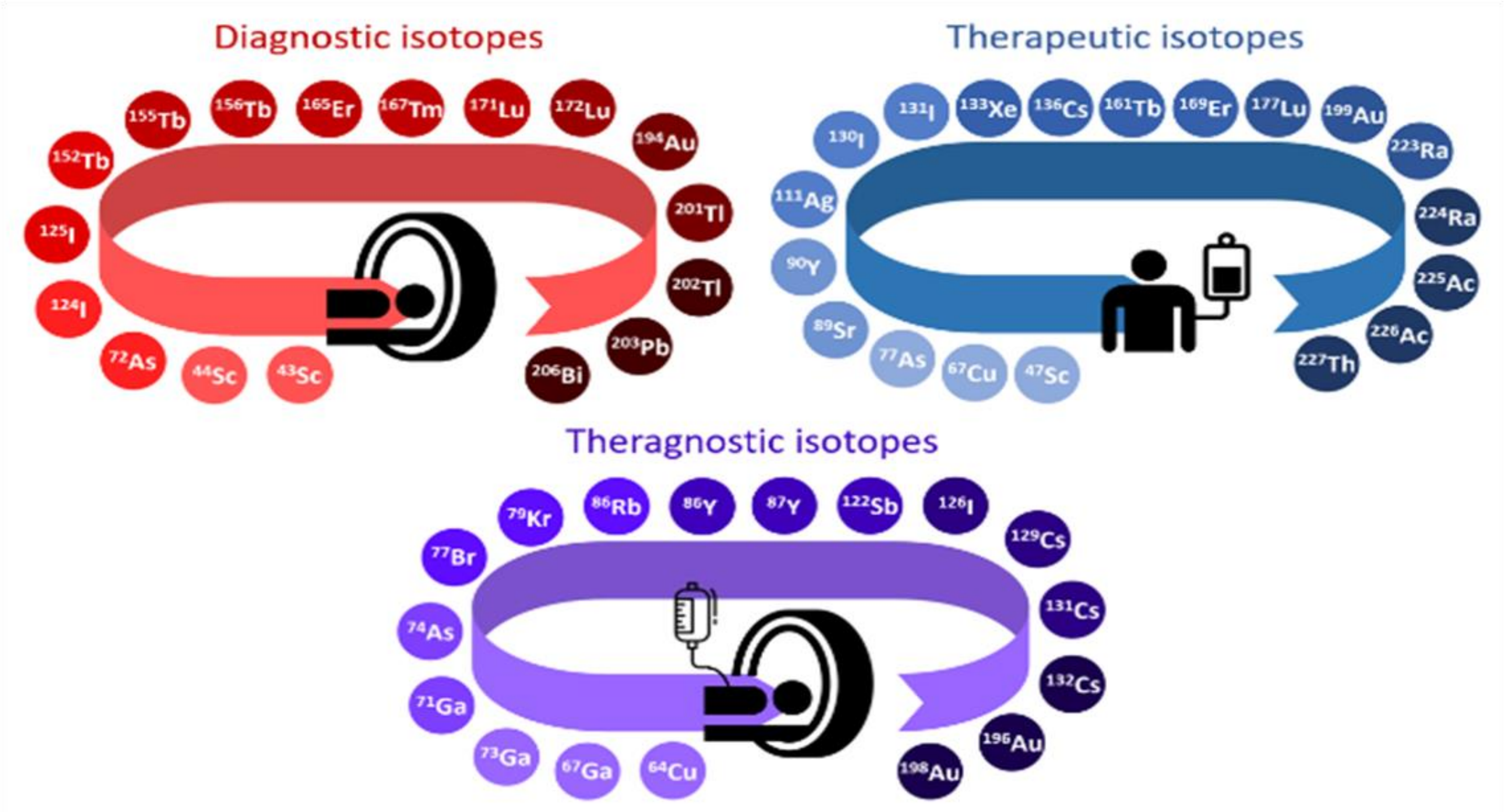


The ISOLPHARM project at LNL



ISOLPHARM:

Radionuclides that could be produced at LNL

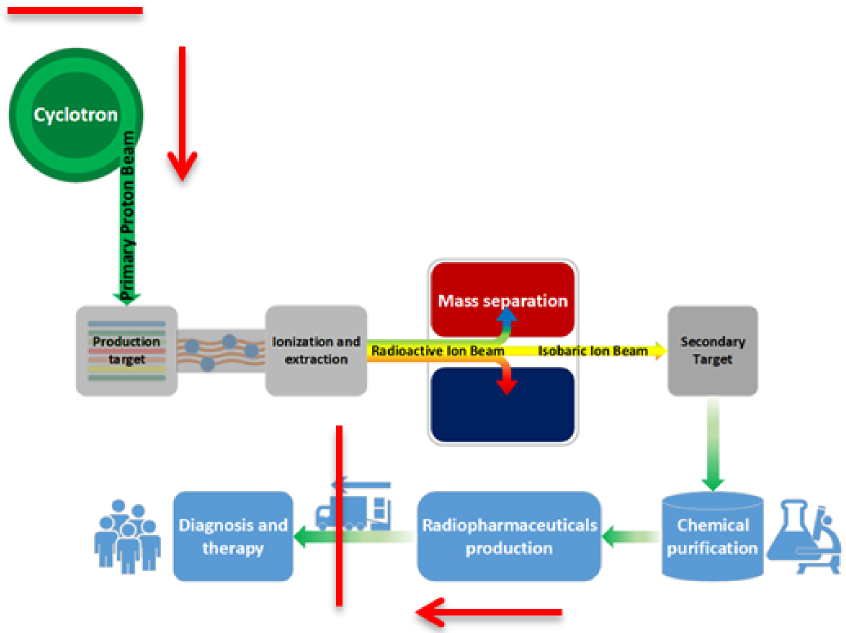


UC_x target

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	

Experimental activities: overview



Step 1
The cyclotron commisioning

Commissioning completed by the LNL cyclotron group

Step 2
Production targets development

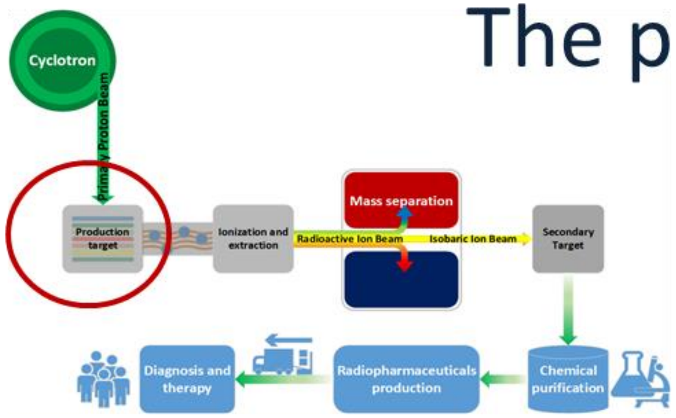
Step 3
Ion beams production

Step 4
Secondary targets development and ions recovery

Step 5
Purification processes development

Step 6
Radiolabeling studies

The production targets



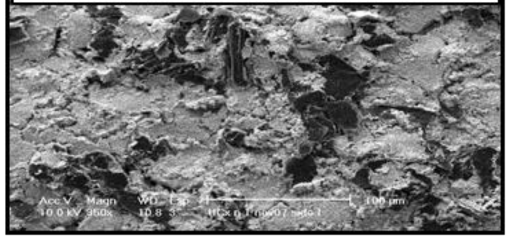
<u>UC_x target already developed and tested on-line!</u>

Other targets under development for specific radionuclides production:

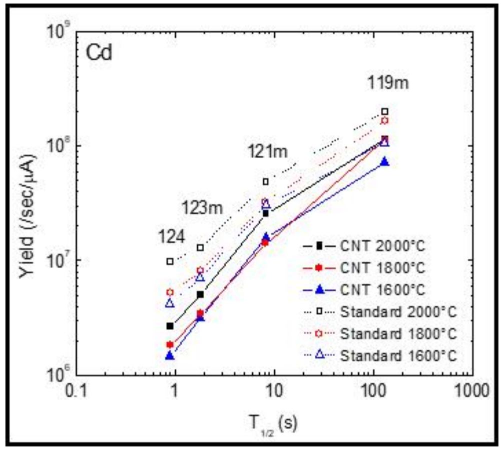
ZrGe: ^{64}Cu, ^{67}Cu

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

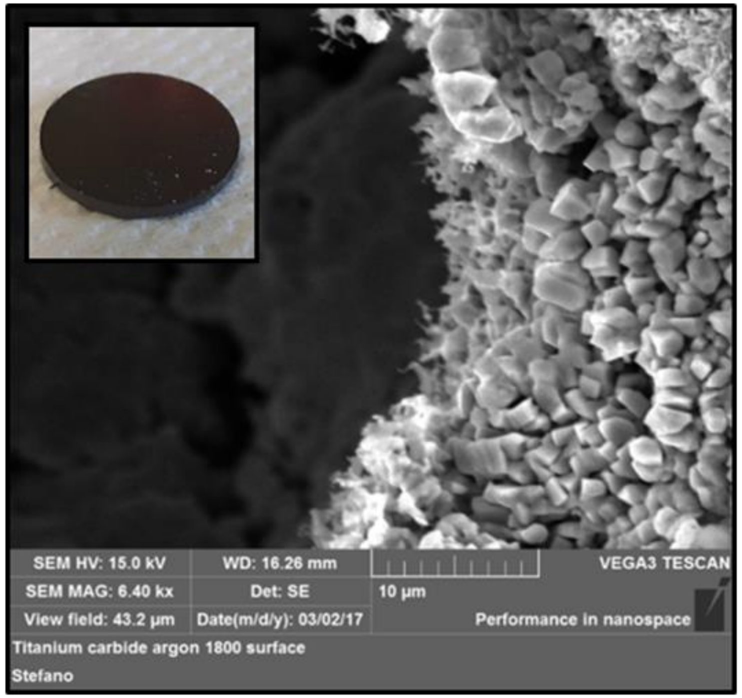
UC_x target prototype



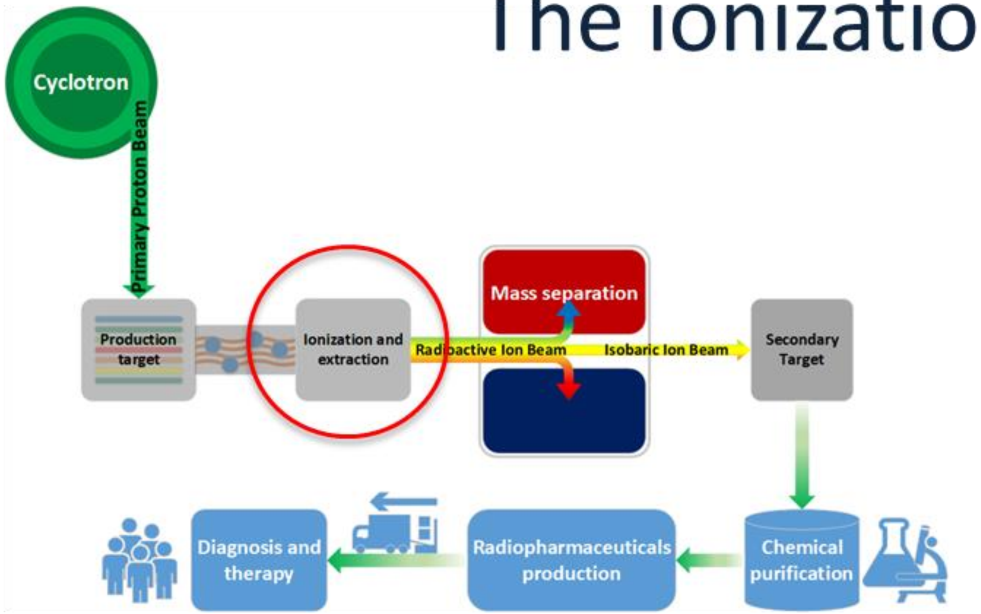
	Standard (graphite)	Low density (MWCNTs)
Density (g/cm³)	4.25	2.59
Diameter (mm)	12.50	13.07
Thickness (g/cm²)	0.41	0.41
Calculated porosity (%)	58	75



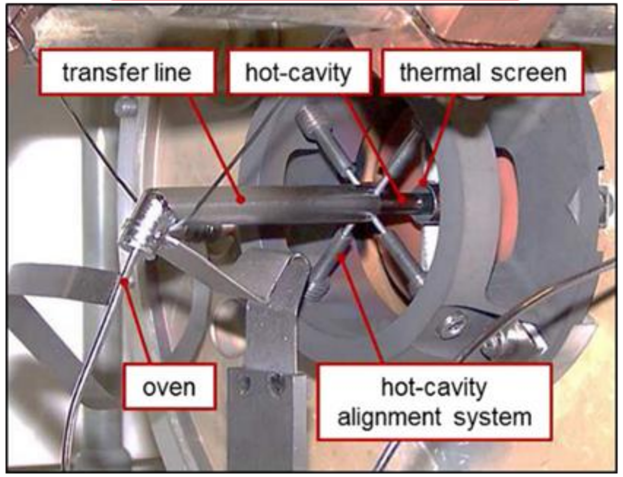
Porous titanium carbide (TiC)



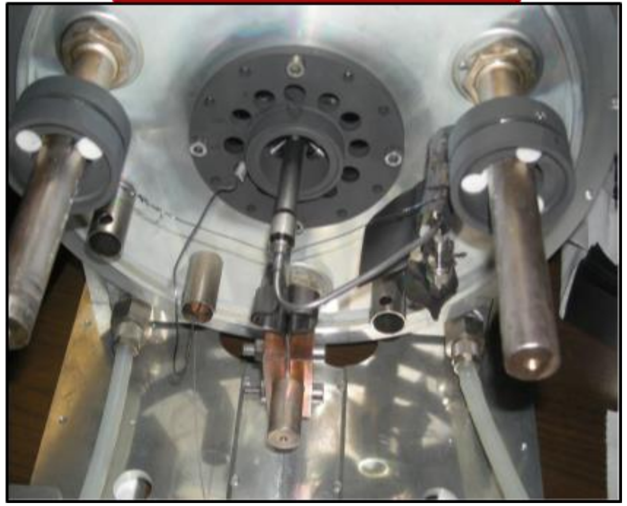
The ionization source



Surface Ion Source (SIS)

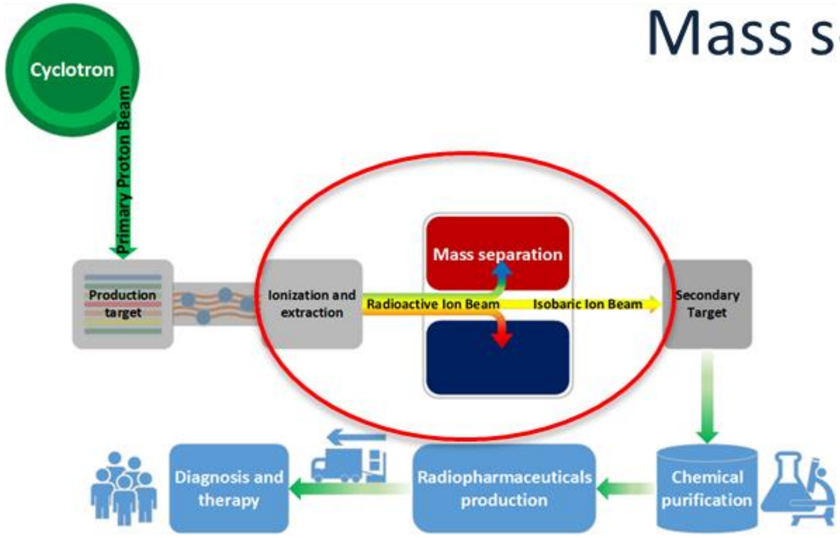


Plasma Ion Source (PIS)

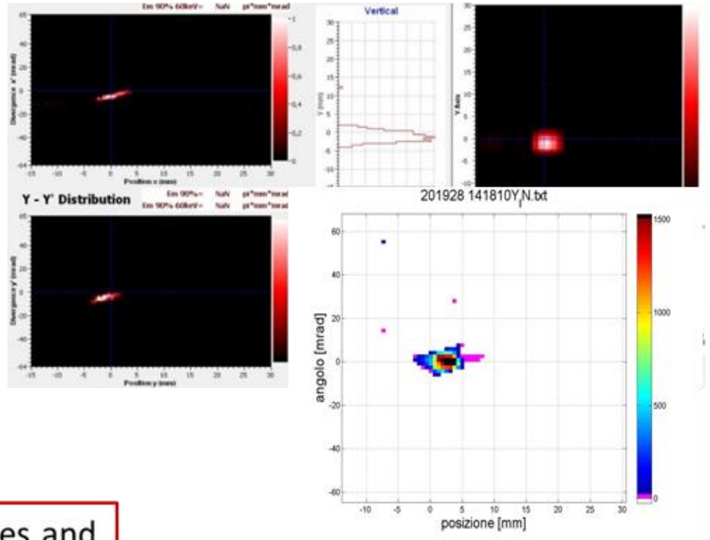


Ionized element	Desired radionuclide	Ionization source	Efficiency
Sr	^{89}Sr, ^{90}Sr/^{90}Y	SIS	~ 20 %
Y	^{90}Y	PIS	~ 1 %
I	^{125}I, ^{126}I and ^{131}I	PIS	~ 20 %
Cu	^{64}Cu, ^{67}Cu	PIS	~ 10 %
Ag	^{111}Ag	PIS	~ 10 %

Beam extraction and Mass separation



Strontium and yttrium beams focalization



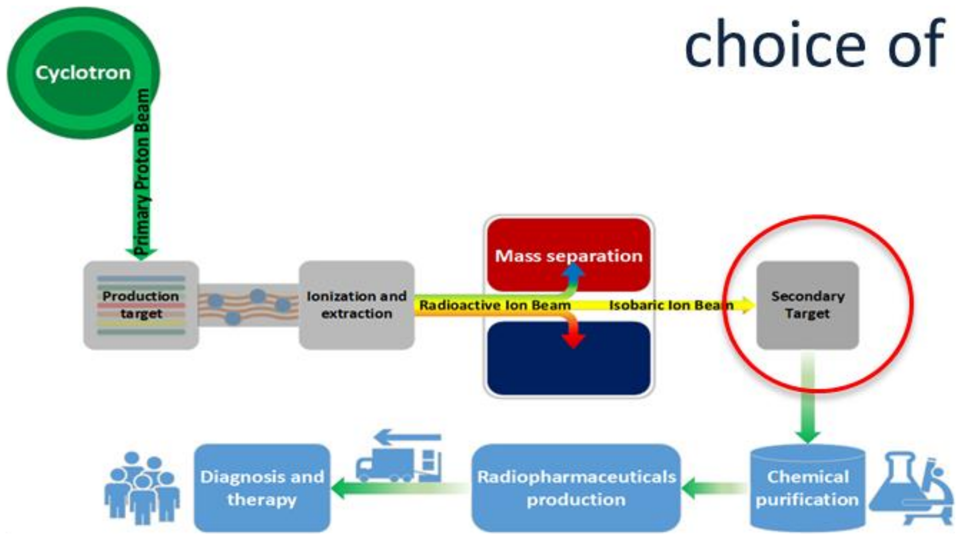
Beam Transmission ~ 100%

Electrostatic Triplets Quadrupoles and steereers system

Extraction -> 25 - 40 kV

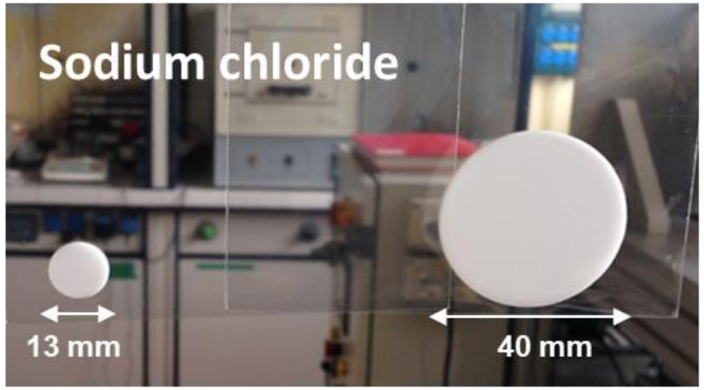
Diagnostic boxes 1 and 2
(2 Faraday Cups and 2 Beam profilers)

Secondary targets production: choice of the material



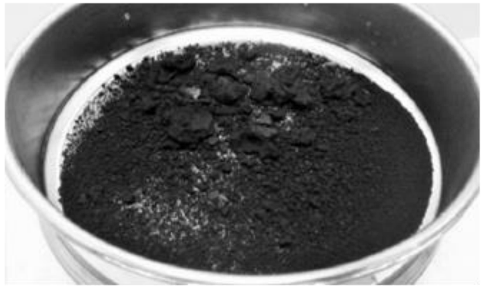
Secondary target requirements:

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

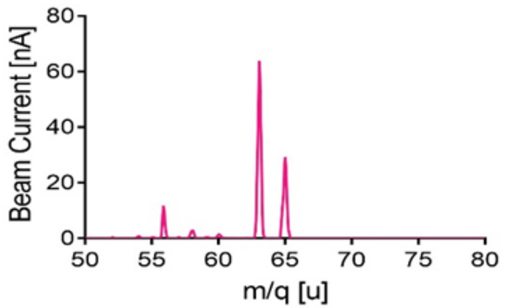
→ Copper: $^{64}Cu/^{67}Cu$



→ Iodine: ^{125}I, ^{131}I

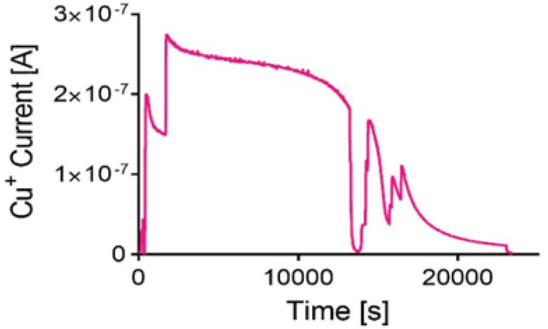
Copper beams

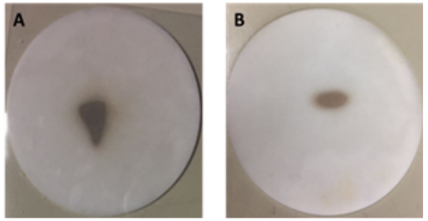
1) ^{63}Cu and ^{65}Cu identification (69.17% and 30.83%)



Ionization efficiency: 10%

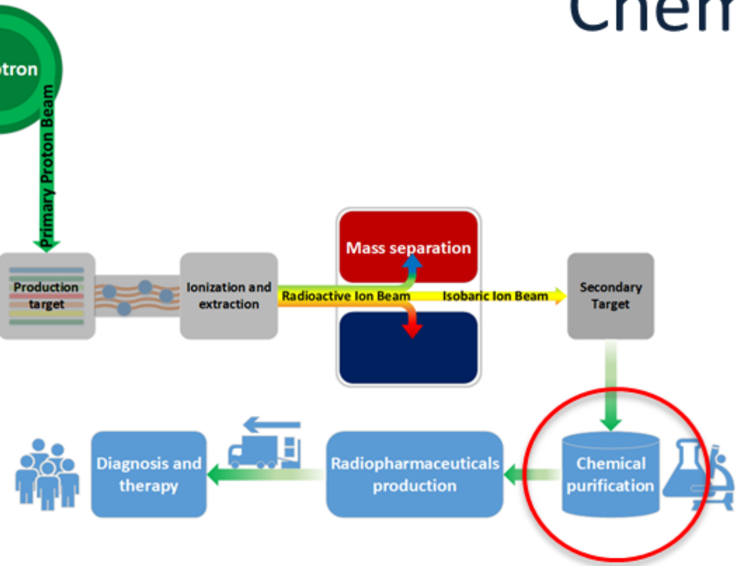
2) ^{63}Cu deposition

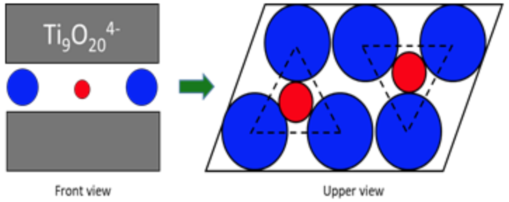




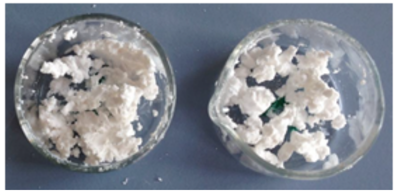
	Copper (current) measured in FC2 and integrated in time [μg]	Copper measured via GF-AAS [μg]	
1st deposition	9.94	1.46	Target dissolved in HNO_3 0.5 M, mild heating
2nd deposition	5.21	1.09	Target dissolved in HNO_3 0.5 M, mild heating
3rd deposition	1.12	0.54	Target dissolved in concentrated HNO_3,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

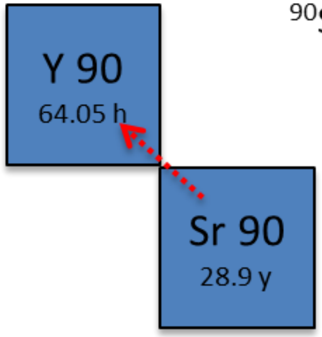
Chemical purification





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



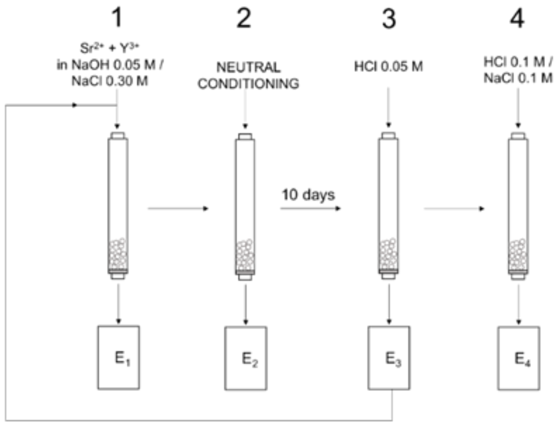


The case of ^{90}Y

↓

^{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



ISOLPHARM_Ag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journal homepage: www.elsevier.com/locate/aca

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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[b] Nuclear Security and Isotope Technology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831, USA

^{111}Ag

Promising radionuclide for therapy:

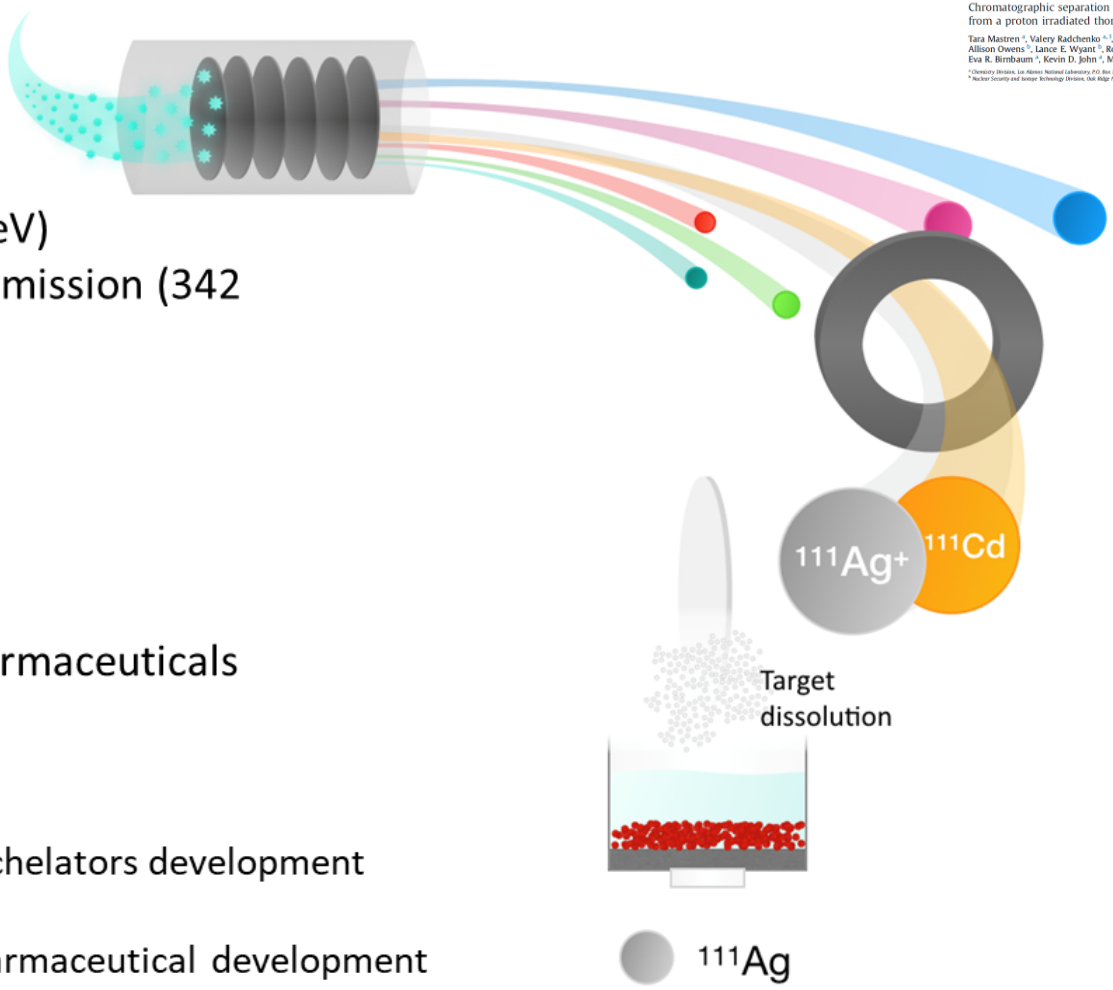
- β^- emitter (average energy 360 keV)
- Low percentage of associated γ-emission (342 keV, 6.7%)
- $t_{1/2}$: 7.45 days

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

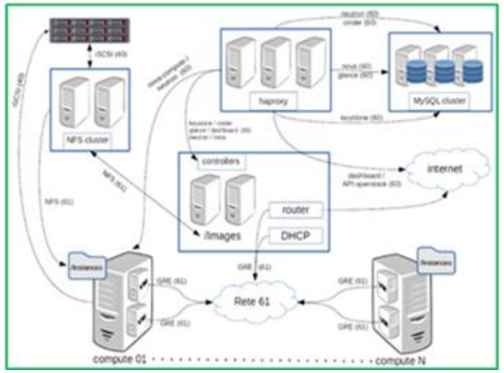
	Year 1				Year 2			
	M3	M6	M9	M12	M15	M18	M21	M24
Task 1 - Computing			MS1	MS2				MS3-4
Setup and maintenance of cloud	■	■	■	■	■	■	■	■
Creation of dedicated workflows	■	■	■	■				
Development of a web-based user portal					■	■	■	■
MC code development and running case study 1	■	■	■	■				
MC code development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

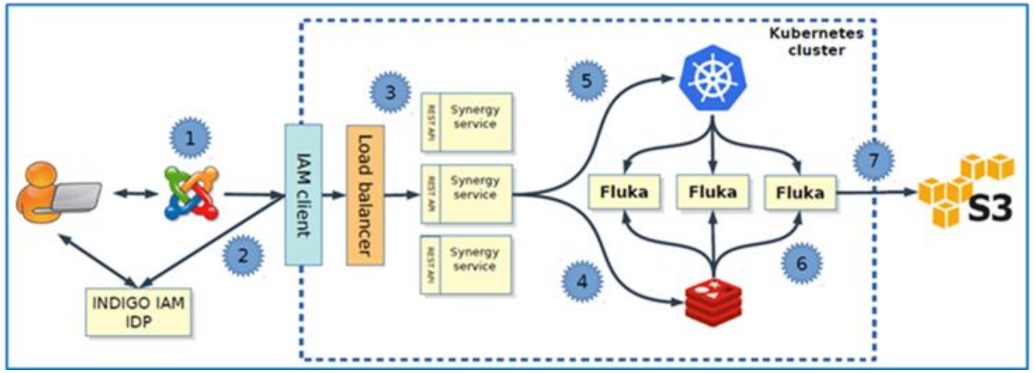
30-09-2018 MS1: Porting and operation of MC framework in cloud environment

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





The ISOLPHARM_Ag project

Task 2: activities at LNL and UNIPD

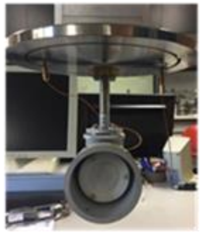
	Year 1				Year 2			
	M3	M6	M9	M12	M15	M18	M21	M24
WP2 - Cold chemistry			MS5	MS6				MS7-8
Ionization and acceleration of Ag								
Development of purification methods for Ag								
Synthesis of first Ag-based complexes								
Characterization of Ag-based complexes								
Complete chelators for Ag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

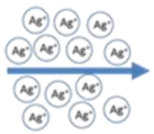
Completed activity @ LNL

30-09-2018

MS5: Ionizzazione e deposito di Ag stabile presso FE SPES

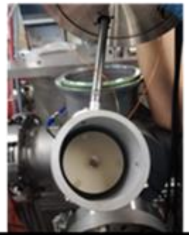
Deposito Ag^{+} su target da 40 mm di $NaNO_3$

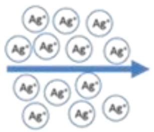




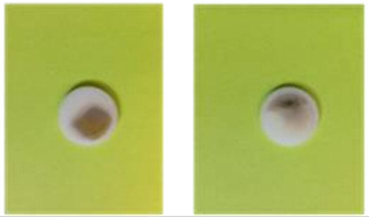
Target secondari (40 mm)

Deposito su target da 13 mm





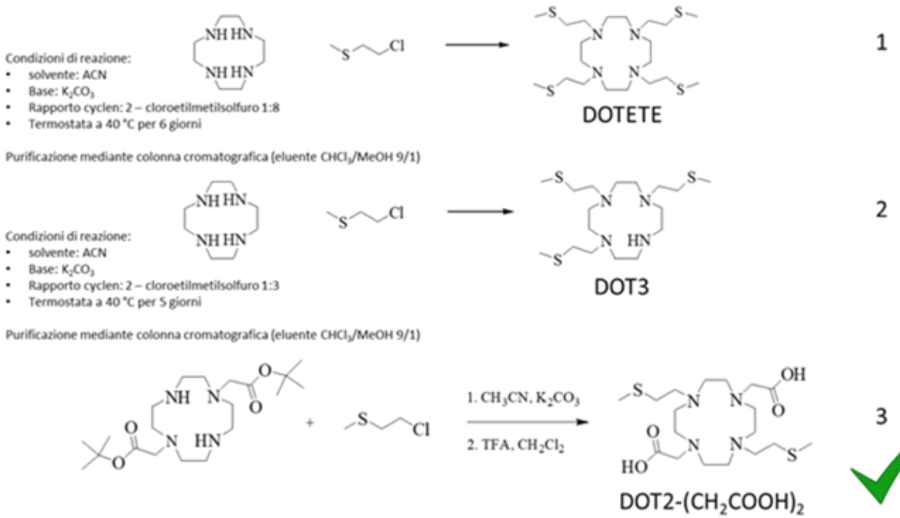
Target secondari (13 mm)



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

31-12-2018

MS6: Sintesi di una gamma di complessi a base Ag



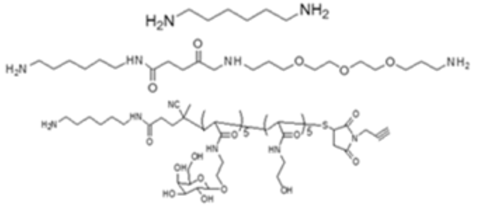
Task 3: activities at LNL, UNIPD and TIFPA

	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



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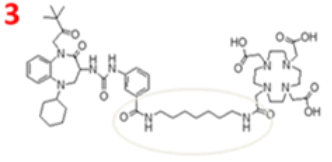
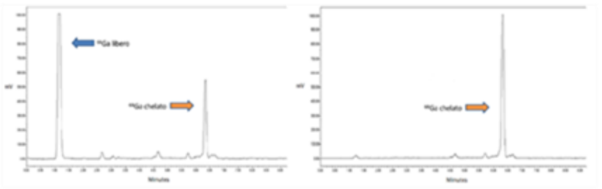


IP1 and IP2 synthesis accomplished

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

The ISOLPHARM network

The Italian Network

INFN Istituto Nazionale di Fisica Nucleare Laboratori Nazionali di Legnaro

INFN Istituto Nazionale di Fisica Nucleare Sezione di Padova

TIFPA 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
Negrar - Verona

Regione del Veneto ULSS2 Marca Trevigiana

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

The International Network

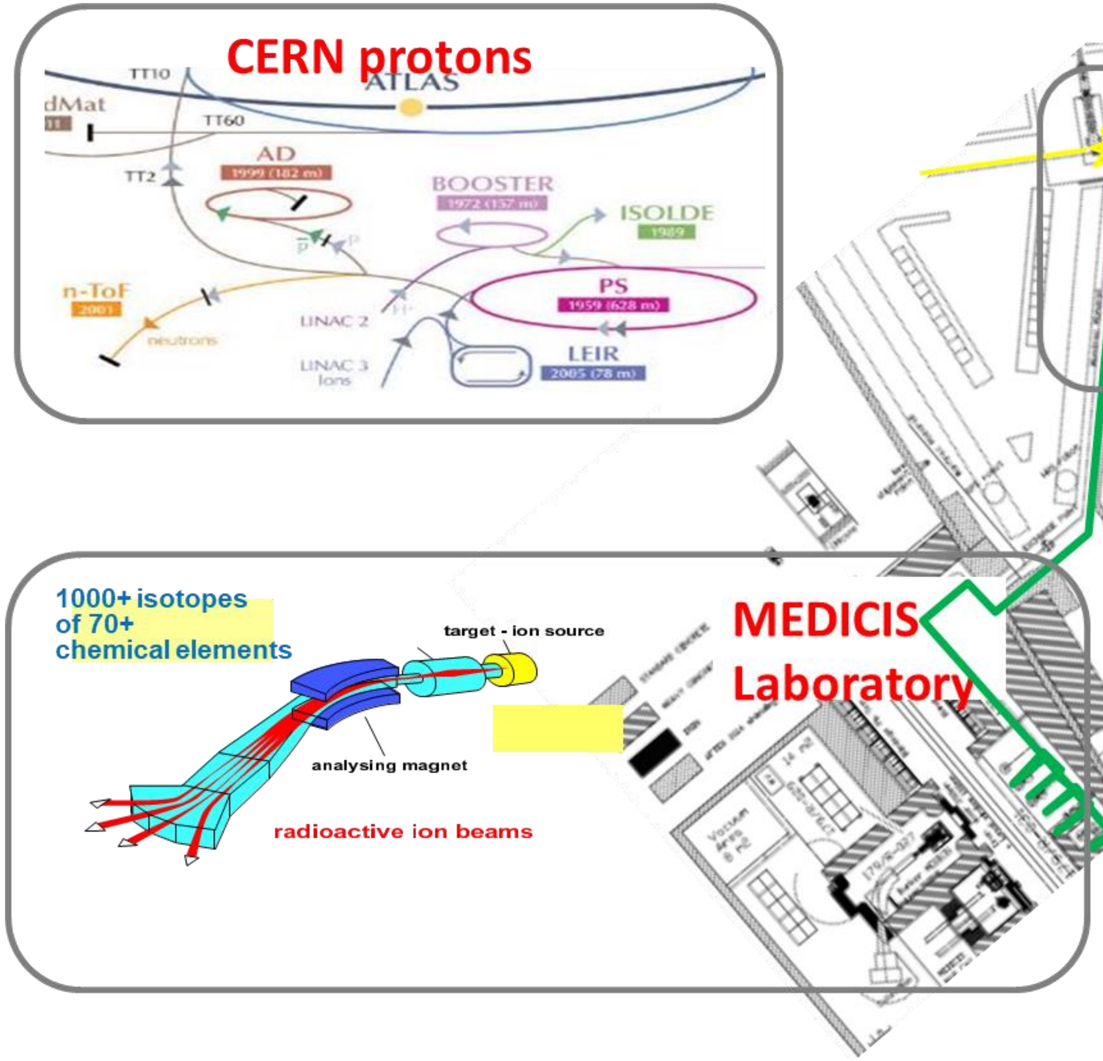
POLATOM

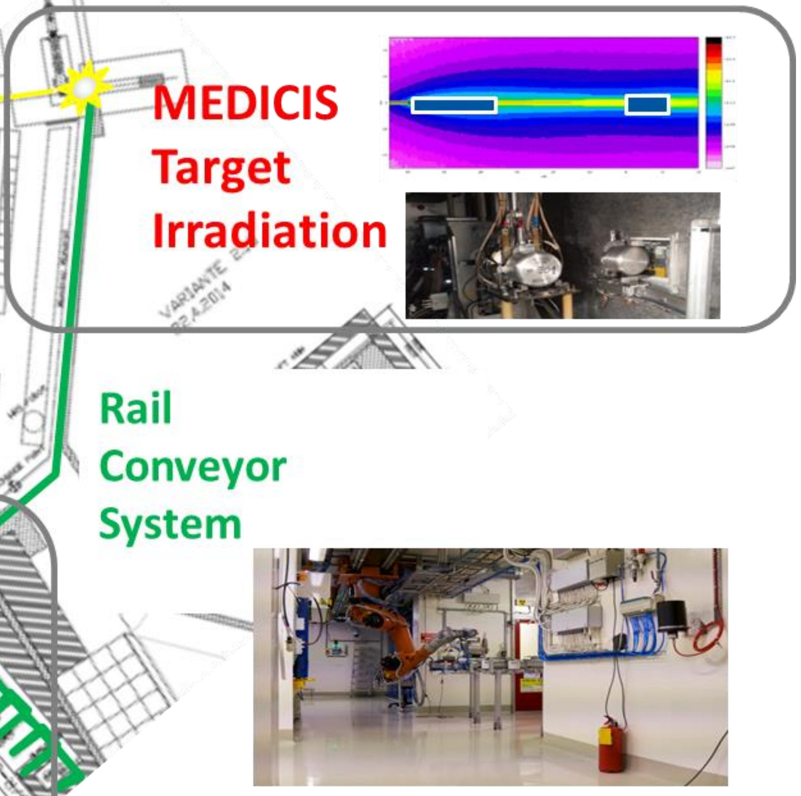
Paul Scherrer Institut PSI

Demokritos National Center for Scientific Research

Medicis Promed

CERN-MEDICIS



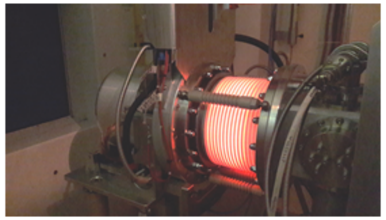


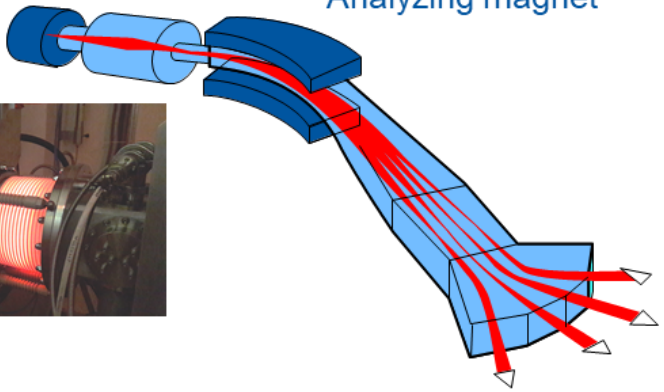
Courtesy of T. Stora,
MEDICIS Project Coordinator

CERN-MEDICIS

Recent update

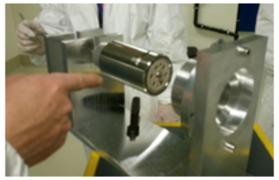
1st isotopes produced in ISOLDE HRS beam dump and separated in the lab during commissioning Dec 2017



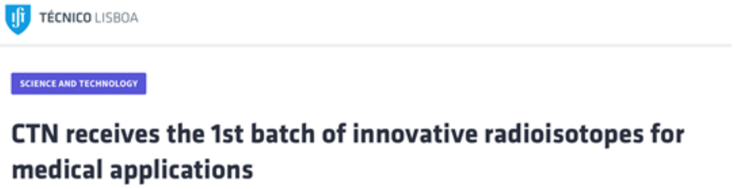


149/152/155/161Terbium ions collected in metal foils


le dauphiné libéré
BELLEGARDE & PAYS DE GEX
GENEVOIS LE SAVOIR DES PHYSICIENS AU SERVICE DE LA MÉDECINE DE DEMAIN
La lutte anti-cancer se prépare au Cern



Large Collaboration with regional and European Institutes


TÉCNICO LISBOA
SCIENCE AND TECHNOLOGY
CTN receives the 1st batch of innovative radioisotopes for medical applications

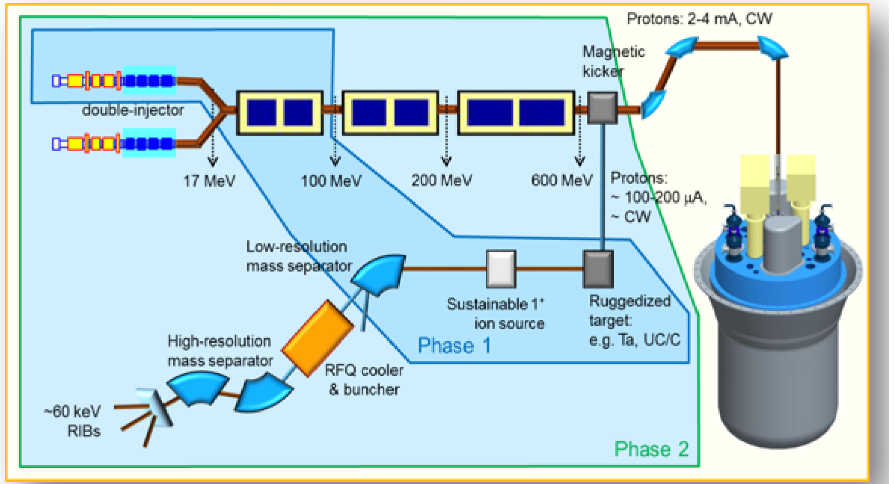
Courtesy of T. Stora,
MEDICIS Project Coordinator

10

ISOL@MYRRHA: an ISOL facility for physics research and applications

- MYRRHA - an Accelerator Driven System comprising the operation of a target facility (ISOL@MYRRHA) next to a sub-critical reactor system

	Energy	*Current*
ISOL@MYRRHA in phase 1	100 MeV	500 μA
ISOL@MYRRHA in phase 2	600 MeV	200 μA



Courtesy of L. Popescu, ISOL@MYRRHA

- Dedicated ISOL targets
  - Compact targets for the production of exotic/short-lived isotopes (physics)
  - Large high-power targets for the production of longer lived isotopes (applications)
    - Opportunity for extensive R&D programmes on innovative medical isotopes
    - Link to SCK•CEN's R&D programmes for radiopharmaceuticals development and pre-clinical research
    - Link to European initiatives (e.g. MEDICIS)
    - Large-scale production opportunities for alpha-emiters especially in phase 2 of the project, at 600-MeV proton beams.

SCK•CEN/30279060

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Thank you for your attention

The SPES/ISOLPHARM group