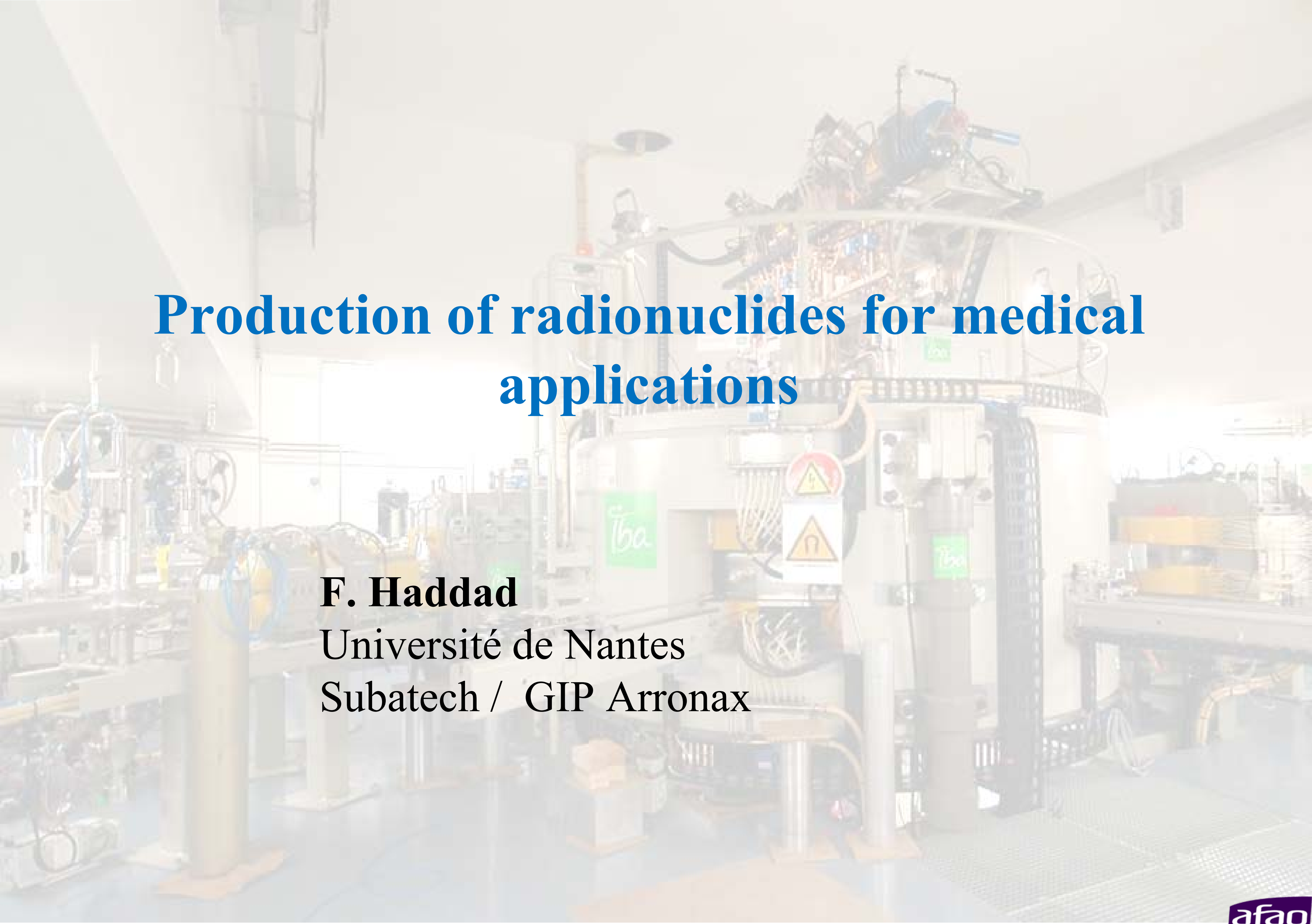


Production of radionuclides for medical applications

F. Haddad
Université de Nantes
Subatech / GIP Arronax

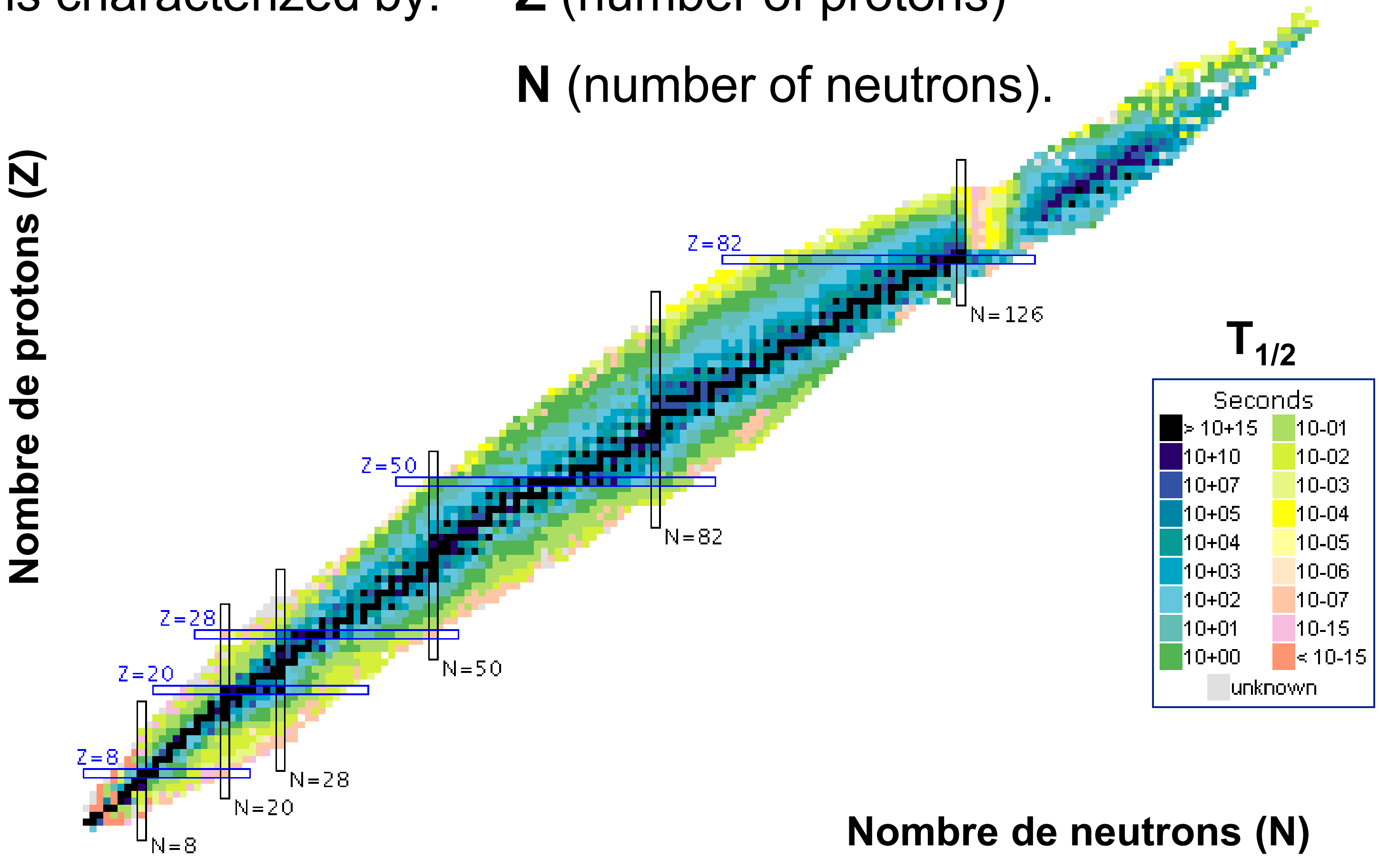
ARRONAX

afaq
ISO 9001
Qualité
AFNOR CERTIFICATION

Let's start with some nuclear physics

A nucleus is characterized by: **Z** (number of protons)

N (number of neutrons).

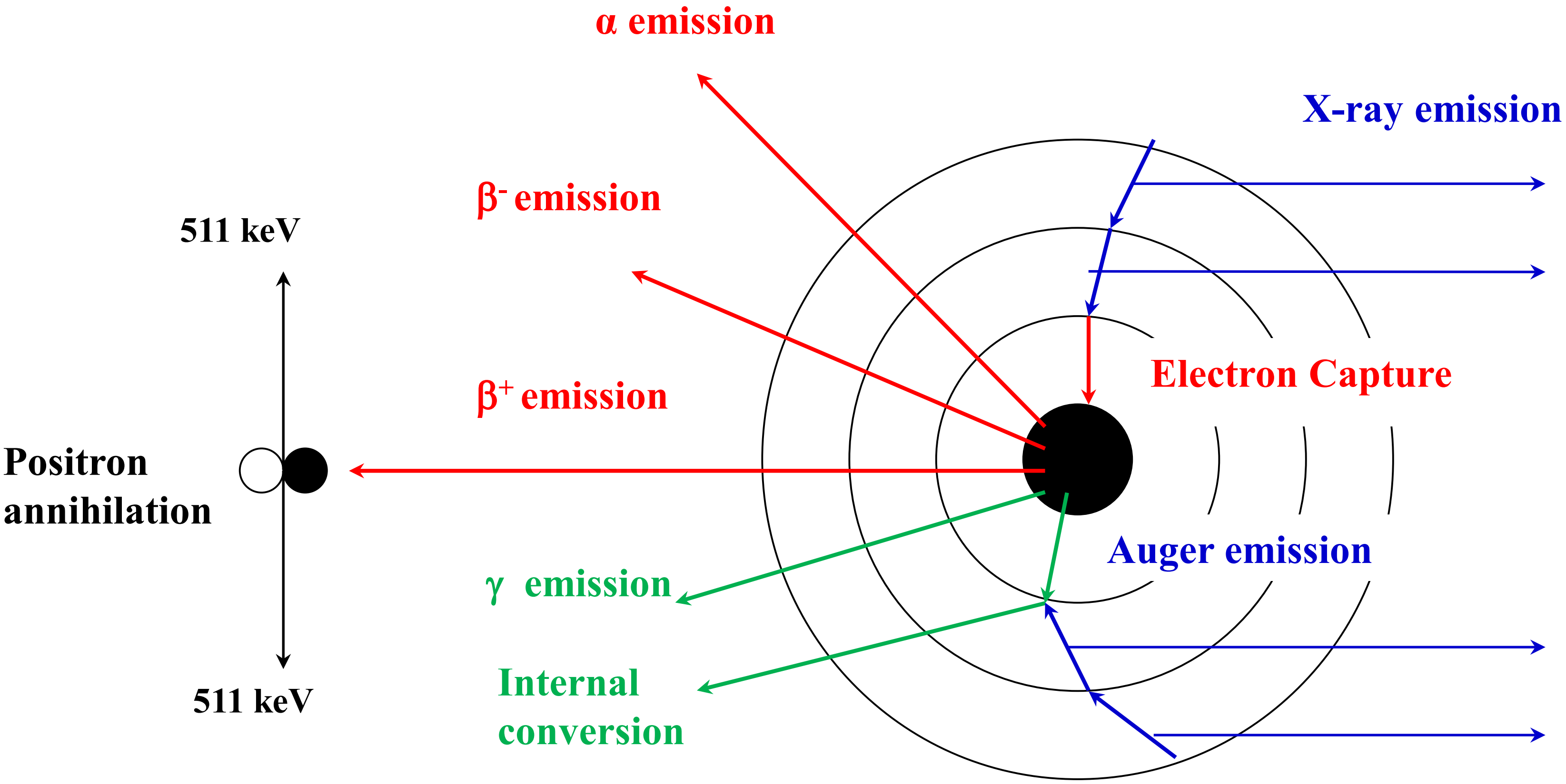


Two nuclei having the same **Z** but a different **A=N+Z** are **isotopes**

They have the same chemical properties

http://www.nndc.bnl.gov/nudat2/

Available radiation from radioactive decay



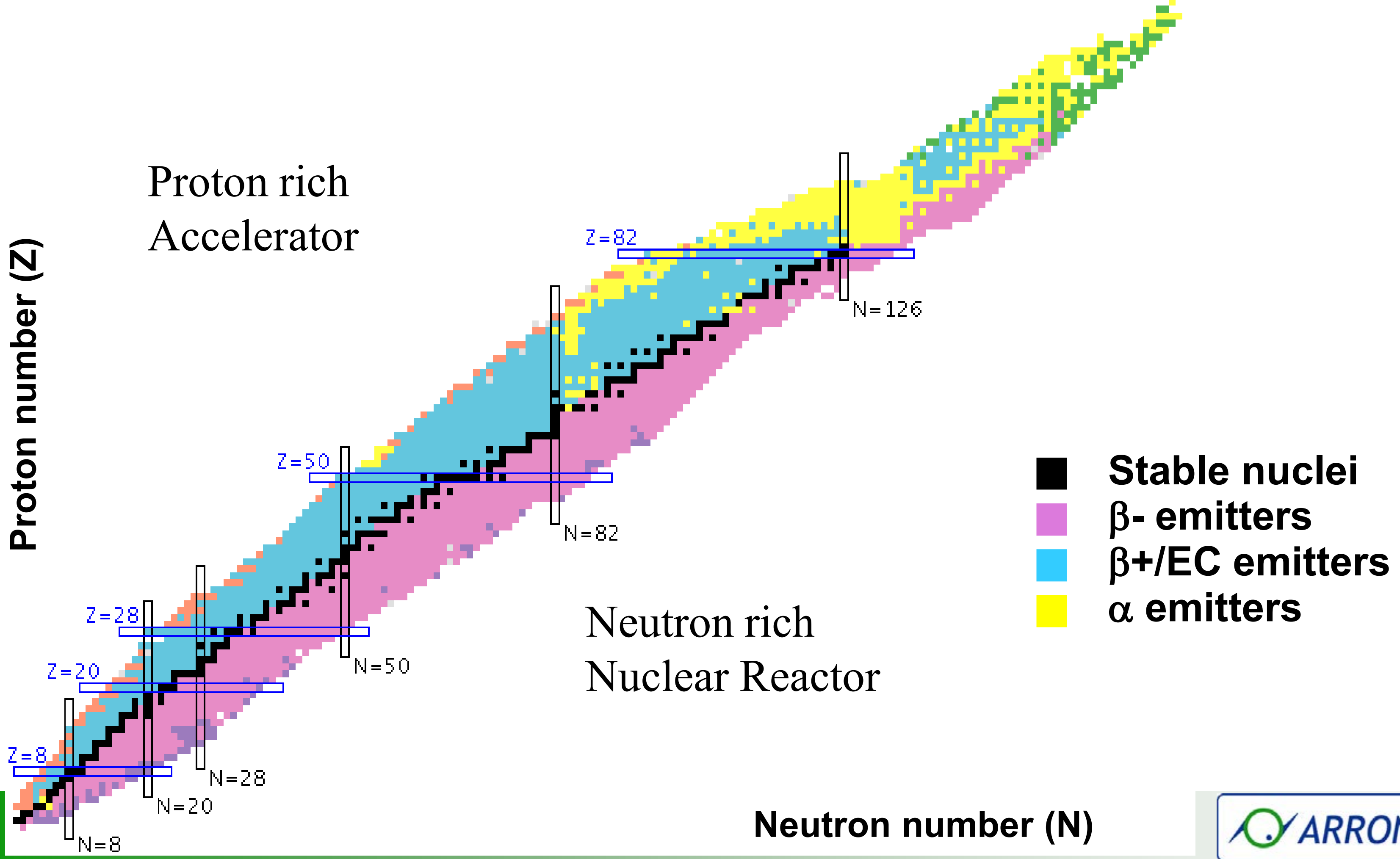
After a radioactive decay, a nucleus is often in an excited state.

The electron cloud of the atom is often disrupted

Chart of nuclides

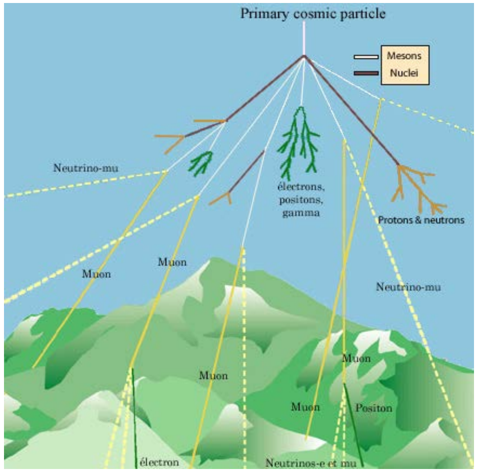
Nuclear medicine uses the interaction properties of these radiation with matter.

- *Highly penetrating* radiation are used **for imaging and diagnosis** (X, γ , β+)
- *Low penetrating* radiation are used for **therapy (α, β-,e-Auger)**



How can we get radionuclides for medical applications?

Some are available in our environment



- Some radioisotopes are created by interaction of cosmic rays with the atmosphere (^{14}C, ^{3}H, ^{7}Be, ^{39}Ar,…).

  → **None are useful for medical applications**

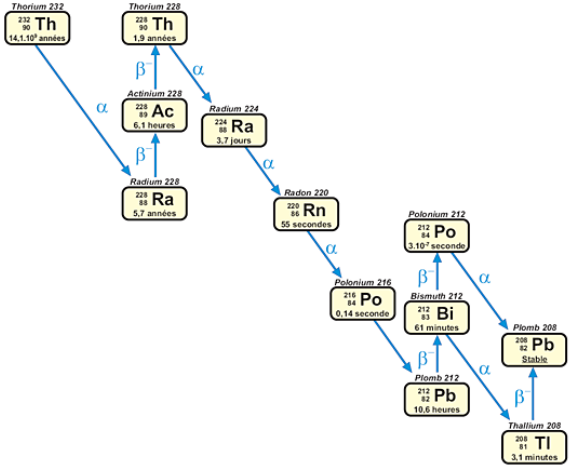
- Radionuclides from decay chain of long lived radioisotopes

  → **Few are used for medical applications**

Xofigo®
Dicloruro de Radio223
INYECCIÓN

^{223}Ra: Belongs to the ^{235}U decay chain.
Xofigo ($RaCl_2$) used for bone metastases treatment.

^{212}Pb/^{212}Bi: Belongs to the ^{232}Th decay chain
Clinical trial underway in breast cancer.



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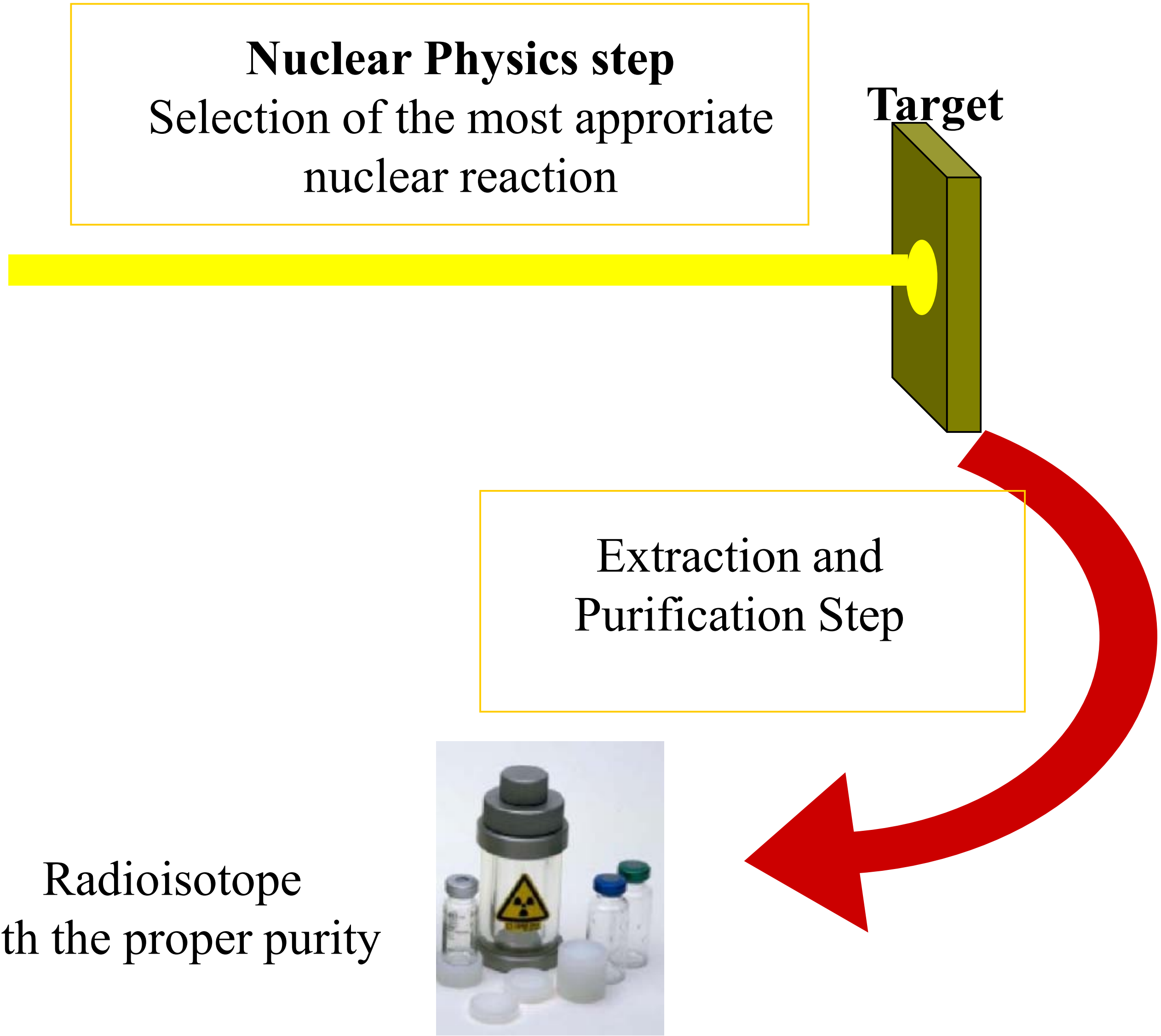
Most of the radionuclides are artificially created



Nuclear Physics step
Selection of the most approriate nuclear reaction

Target

projectile

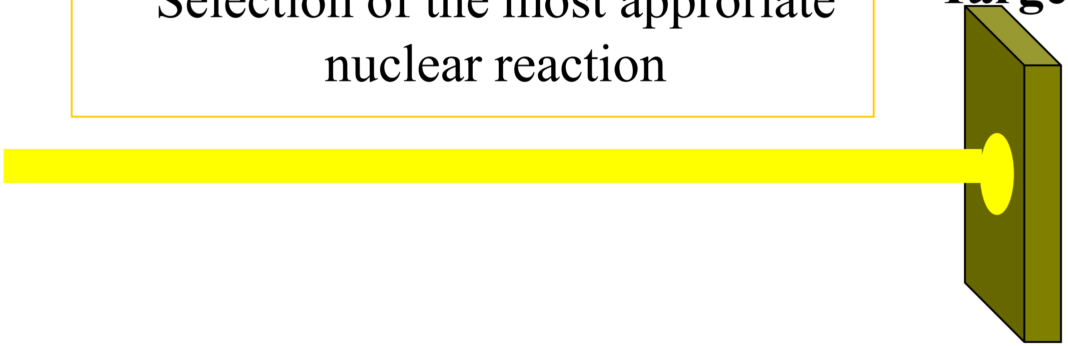
Extraction and Purification Step

Radioisotope
with the proper purity

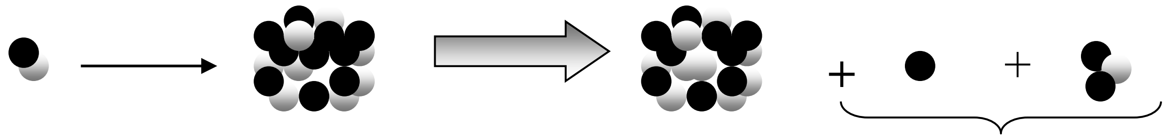
Most of the radionuclides are artificially created

Nuclear Physics step

Selection of the most approriate nuclear reaction



Artificially Induced Radioactivity



projectile **Target** **residue** **reaction products**

Charge and mass conservation are mandatory

Many different nuclear reactions can be used:

$$p + {}^{18}\mathrm{O} \rightarrow {}^{18}\mathrm{F} + n$$

$$\alpha + {}^{209}\mathrm{Bi} \rightarrow {}^{211}\mathrm{At} + 2\,n$$

$$n + {}^{176}\mathrm{Yb} \rightarrow {}^{177}\mathrm{Yb} + \gamma$$

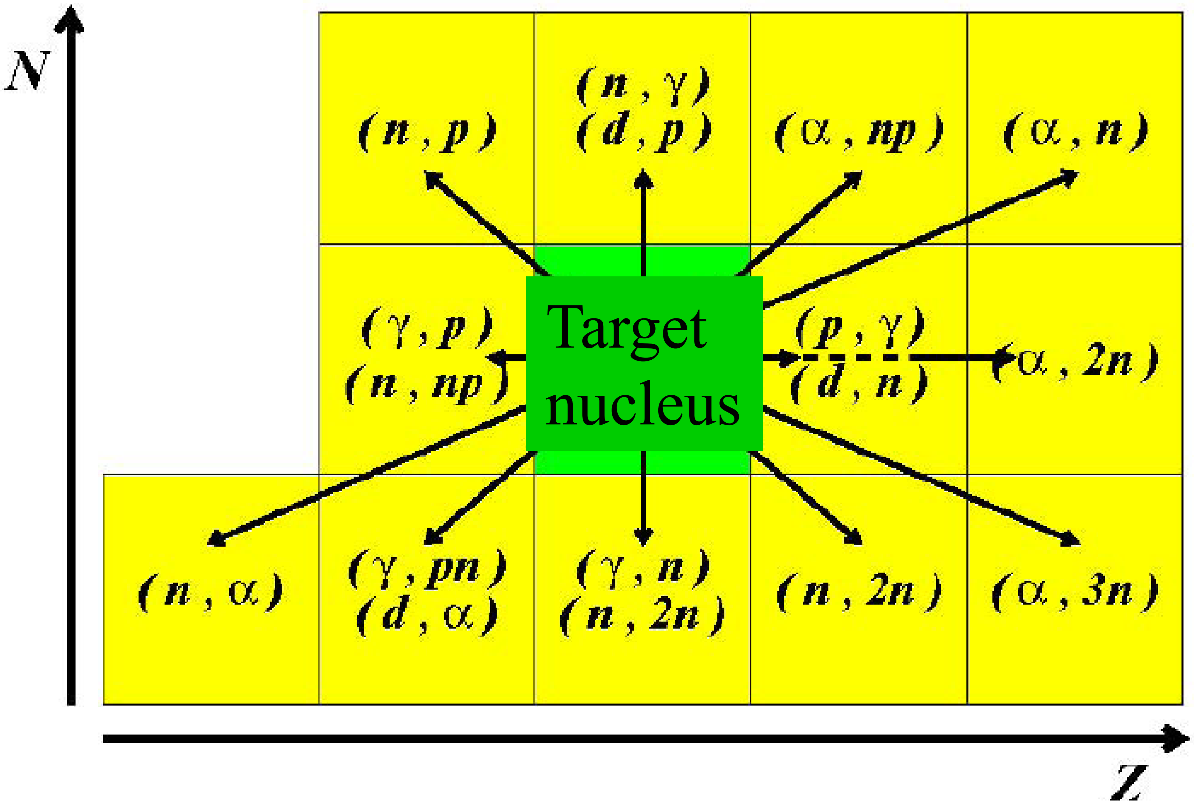
$$\gamma + {}^{68}\mathrm{Zn} \rightarrow {}^{67}\mathrm{Cu} + p$$

$$n + {}^{235}\mathrm{U} \rightarrow \text{fission}$$

As well as energy conservation

→ A **threshold projectile kinetic energy** exist in many cases

Nuclear reaction



Better if we start from stable material as target material

Production yield: use of thick target

Irradiation conditions

Reaction
Cross section

Produced Activity:

$$Act = \Phi \,.\, \chi \,.\, \frac{Na.\,\rho}{A} \,.\, \left(1 - \exp(-\lambda.t_{irr})\right) \,.\, \int_{E_{fin.}}^{E_{in.}} \frac{\sigma(E)}{\frac{dE}{dx}} \,.\, dE$$

Target characteristics

including enrichment

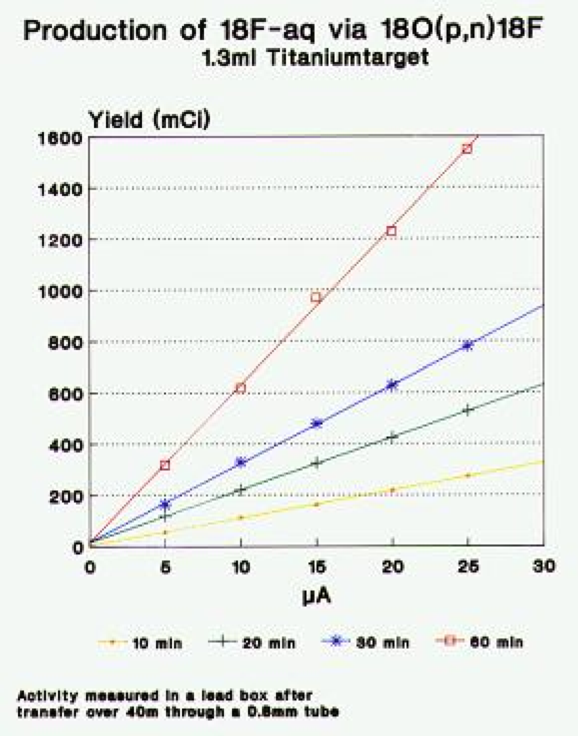
Radioactive decay

Decrease of the
projectile energy as it
penetrates into the
target material

- ➢ Energy is released in the target
- ➢ Heating of the target

How to increase the production yield?

- ✓Increase the irradiation time
- ✓Increase projectile number



How to increase the production yield?

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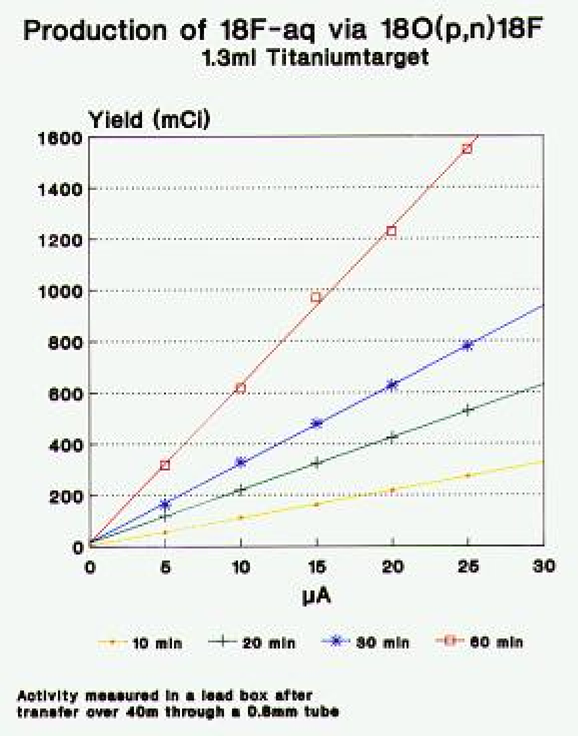
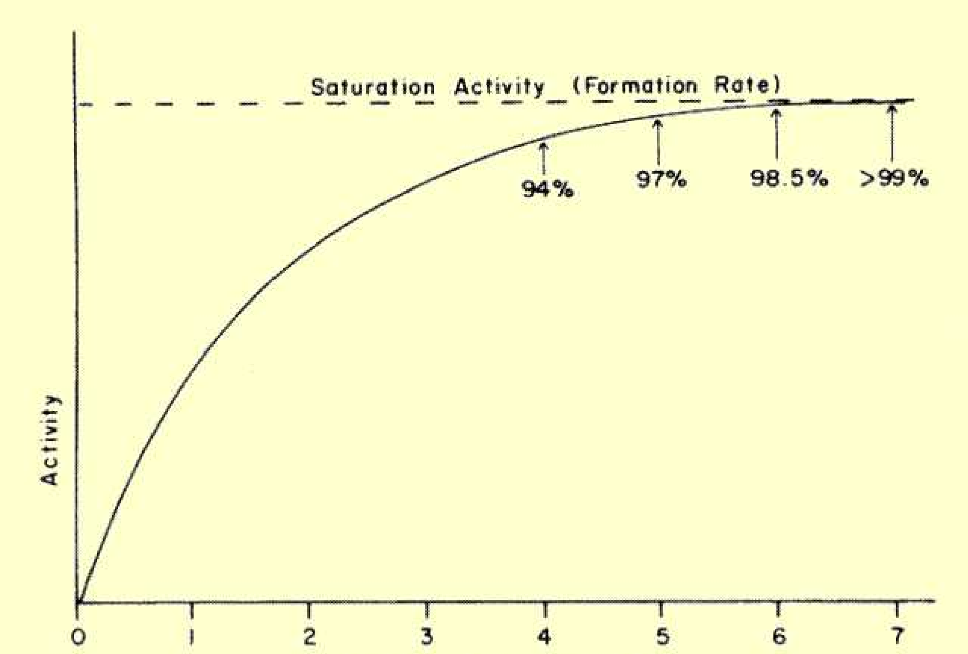
✓Increase projectile number



Production of 18F-aq via 18O(p,n)18F
1.3ml Titaniumtarget

Activity measured in a lead box after transfer over 40m through a 0.8mm tube



Elapsed time ($T_{1/2}$)

Limitations:

- Irradiation time < $T_{1/2}$
- Integrity of the target due to heating

How to increase the production yield?

✓Increase the irradiation time

✓Increase projectile number

✓Increase target quantity:

  - ➢ Target thickness
  - ➢ Use of enriched material

How to increase the production yield?

- ✓Increase the irradiation time

- ✓Increase projectile number

- ✓Increase target quantity:
  - ➢ Target thickness
  - ➢ Use of enriched material

Limitations:

- ➢ Integrity of the target due to heating
- ➢ Price of the target ^{64}Ni is 30$/mg
  Gold is 36.58€/g
- ➢ Target preparation:

Target preparation

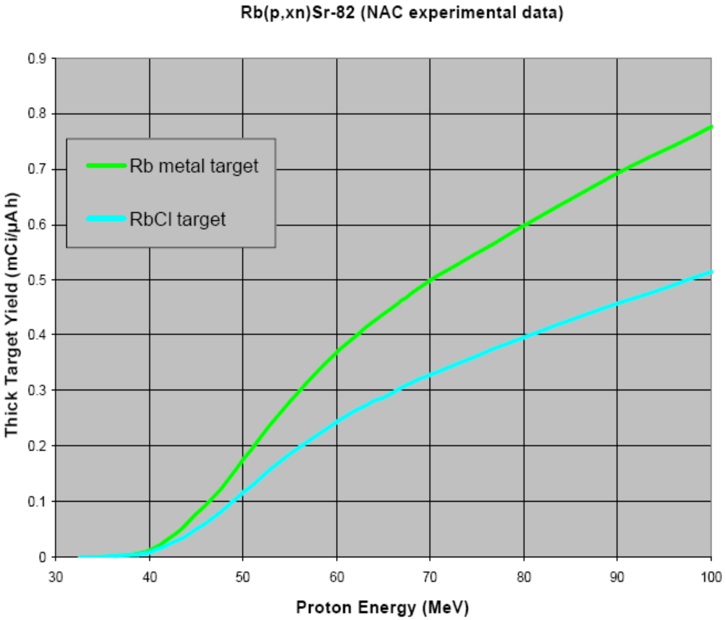
Selection of the target material chemical form:

p+Rb → ^{82}Sr + xn

2 possibilities: RbCl or Rb metal

Rb metal:

- Better yield
- Better thermal conductivity
  - → Higher beam current on target
- Far more reactive than RbCl



Target preparation

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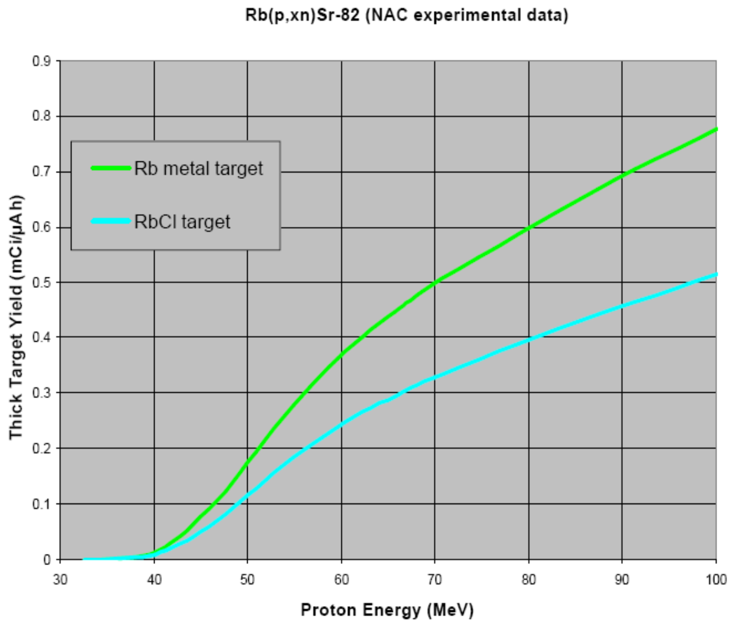
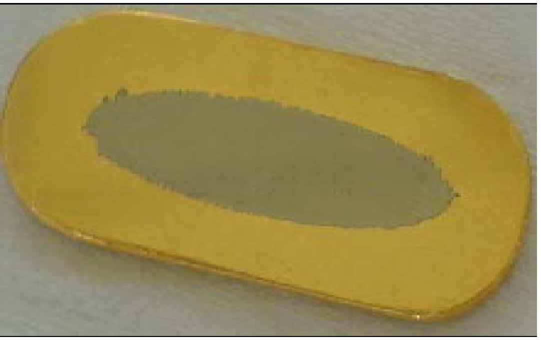
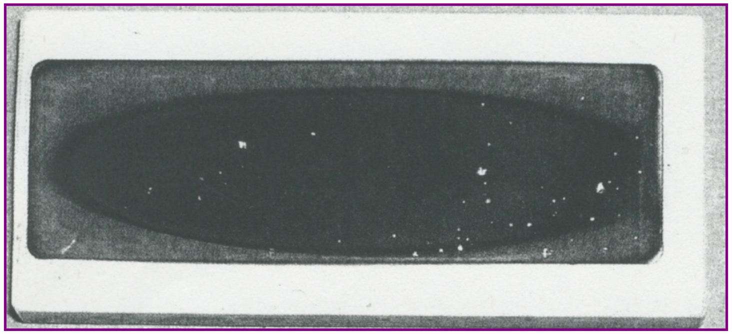


How to produce the target: Solid Targets



Electroplating
Ni onto Au



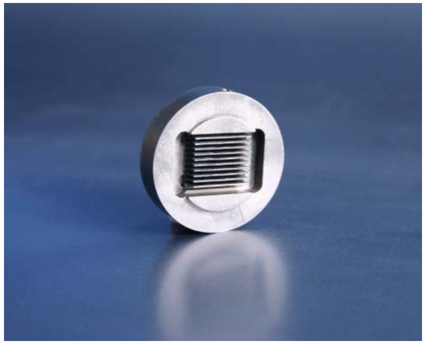
Deposition under vacuum
Bi onto Al

Pelletizing
CaCo3

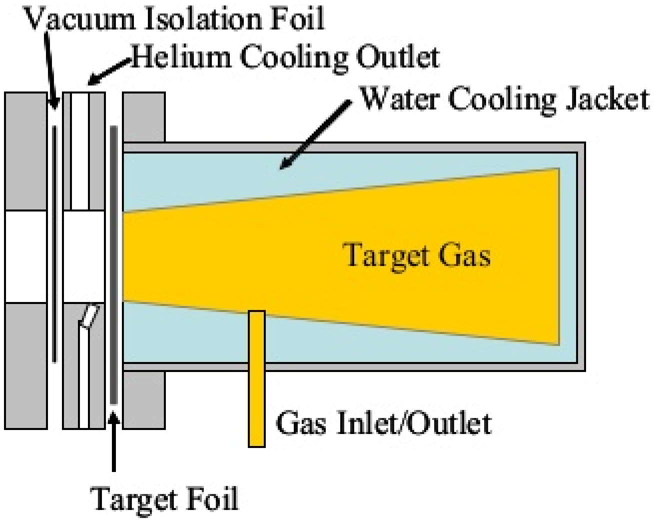
Target preparation

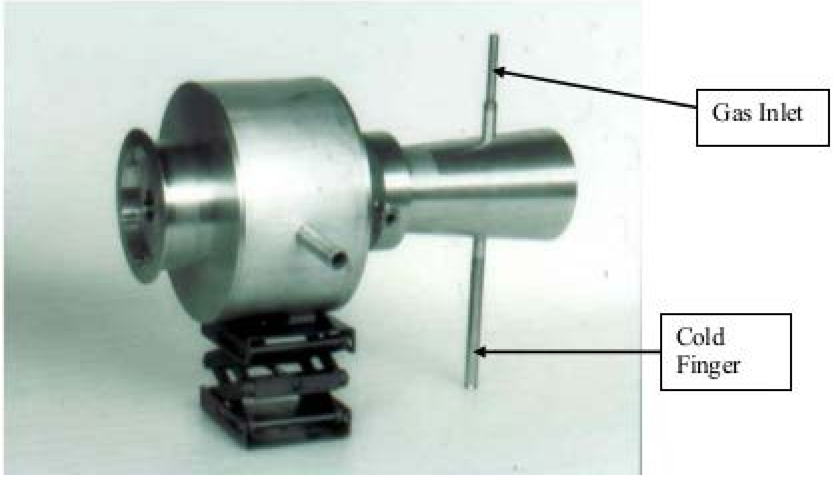
How to produce the target: Liquid and gas targets

H_2O for ^{18}F



^{124}Xe for ^{123}I





How to increase the production yield?

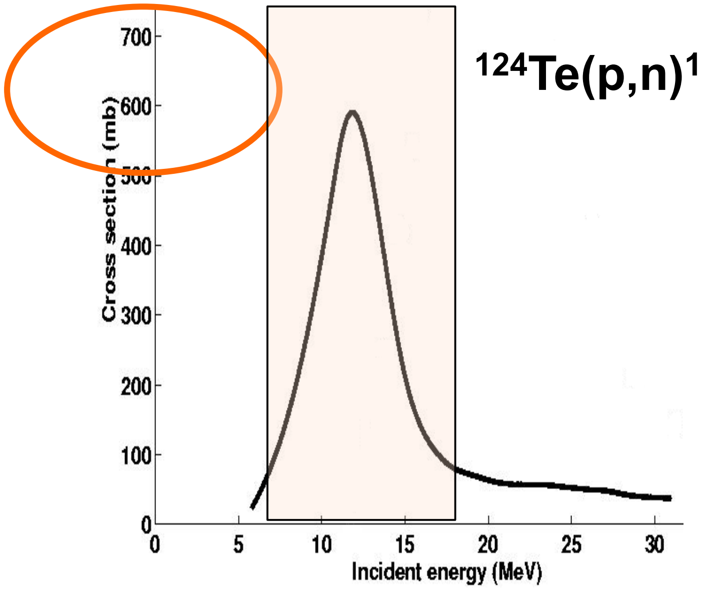
✓Increase the irradiation time

✓Increase projectile number

✓Increase target quantity

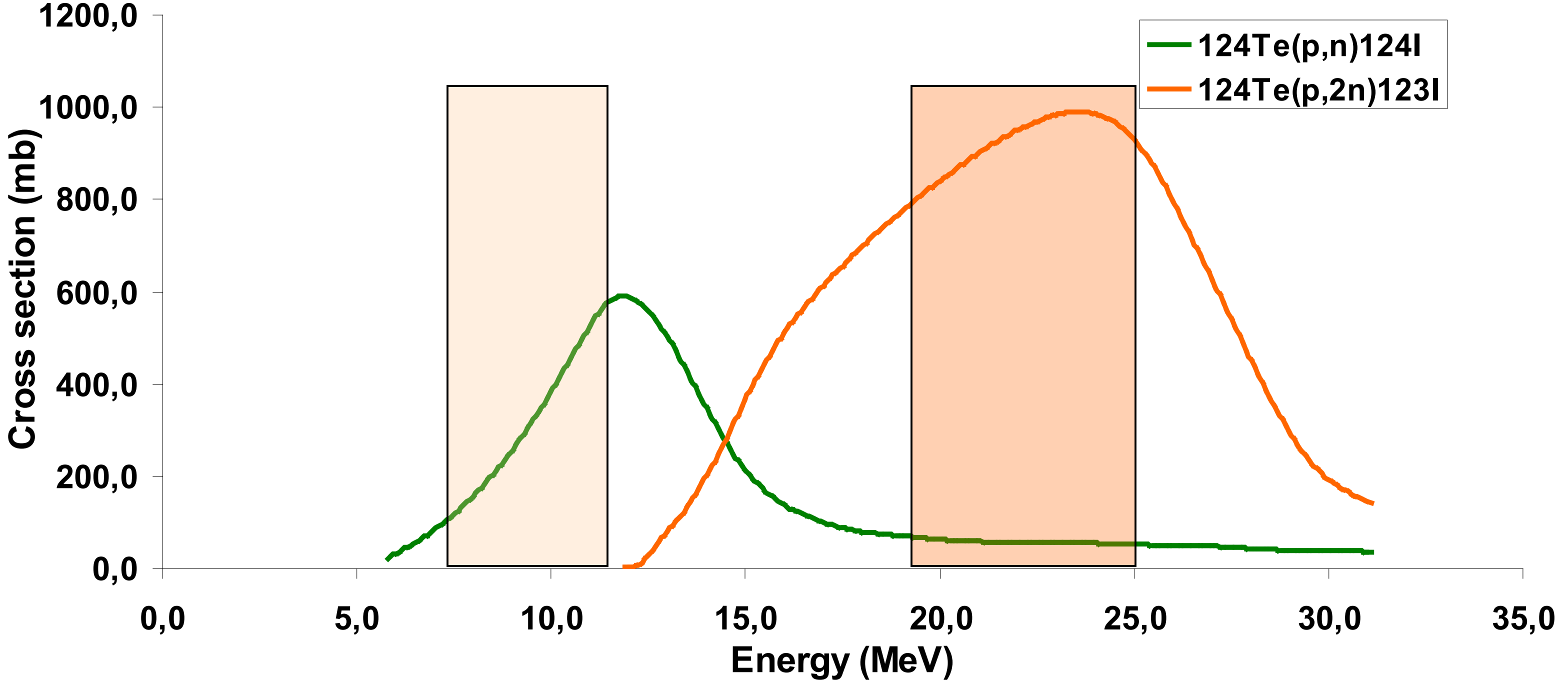
✓Use of enriched material

✓ Carefully select the nuclear reaction and the projectile energy.



^{124}Te(p,n)^{124}I

Carrefully select the nuclear reaction and the projectile energy.



By a smart choice of the incident energy and target thickness, one can:

- Maximizes the production yield
- Minimizes the production of contaminants.

Comparing production route for ^{124}I

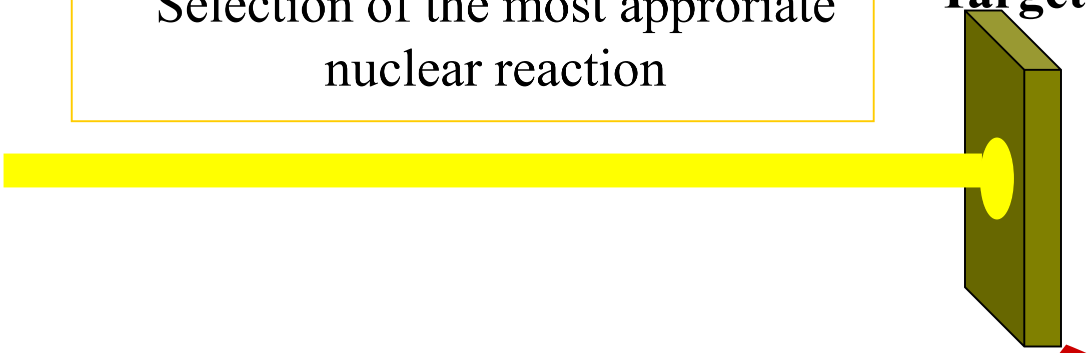
(calculated values – *Qaim et al - Julich*)

Nuclear reaction	Energy range [MeV]	Thick target yield of ^{124}I [MBq/µA·h]	Impurity [%]		
			^{123}I	^{125}I	^{126}I
^{124}Te(**p**,n)	12 → 8	16	1.0	< 0.1	-
^{124}Te(**d**,2n)	14 → 10	17.5	-	1.7	-
^{125}Te(**p**,2n)	21 → 15	81	7.4	0.9	-
^{126}Te(**p**,3n)	38 → 28	222	149	1.	1.
^{nat}Sb(α,xn)	22 → 13	1.02	890	13	16
^{nat}Sb(^{3}**He**,xn)	35 → 13	0.95	3877	0.6	0.6

- ^{124}Te(p,n)^{124}I – purest ^{124}I
- ^{126}Te(p,3n)^{124}I – greatest production quantity

Most of the radionuclides are artificially created

Nuclear Physics step
Selection of the most approriate
nuclear reaction



projectile

Target

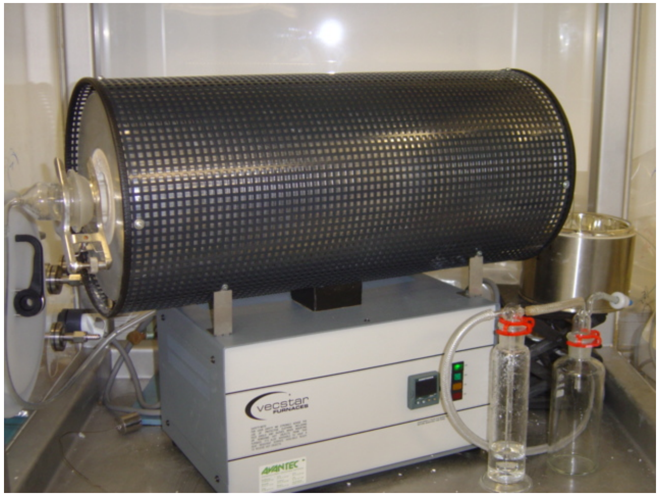
Extraction and
Purification step

Radionuclide
with the proper purity

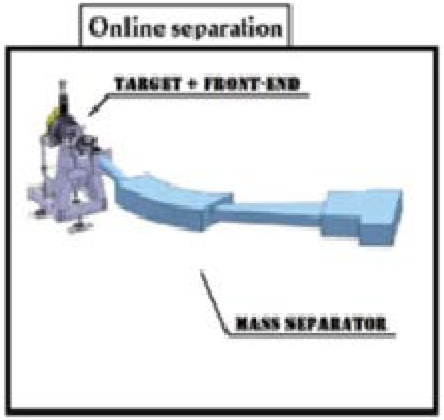
Extraction and Purification step

Wet chemistry
(chromatography using resin, liquid liquid separation, …)

Dry chemistry

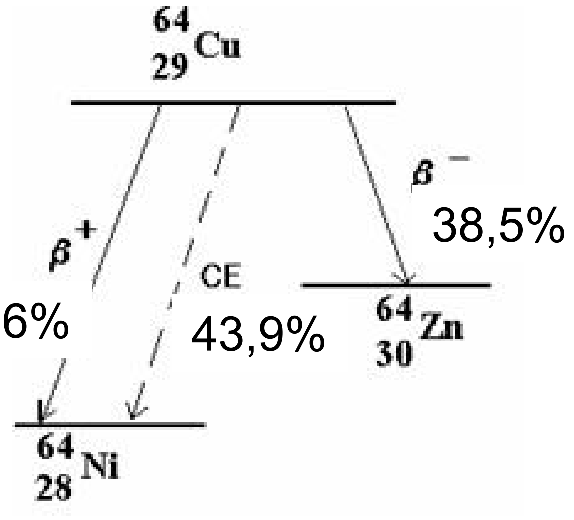


Mass separation:



^{64}Cu– PET imaging

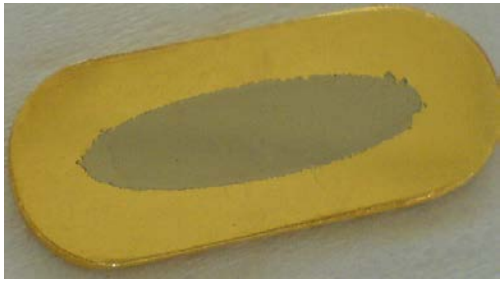
$T_{1/2} = 12,7$ h



Production: $^{64}Ni + p \longrightarrow {}^{64}Cu + n$

Proton energy range 12-10 MeV

Enriched Ni-64 target obtained through electroplating on a gold support



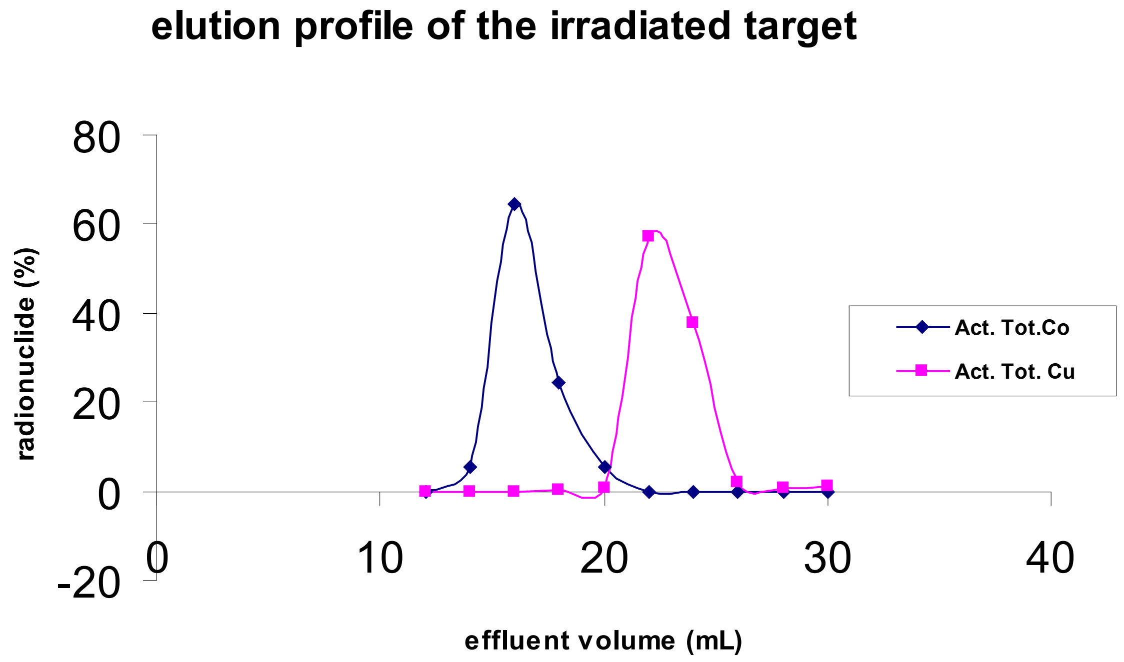
e = 20 µm
S =1.3 cm^2

Extraction and Purification step

Main impurties:

- **^{61} Co** produced via the (p,α) but also traces of other cobalt isotopes (^{55}Co, ^{56}Co, ^{57}Co).
- Recovery of expensive **^{64}Ni** needed

Extraction separation: dissolution in HNO_3 then use of AG1x8 resin.

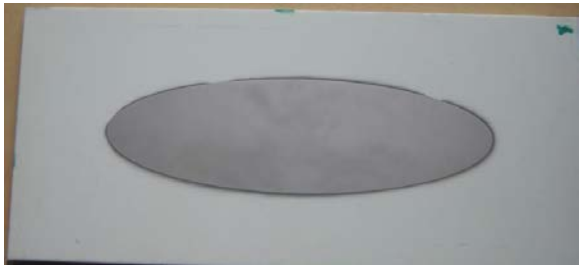


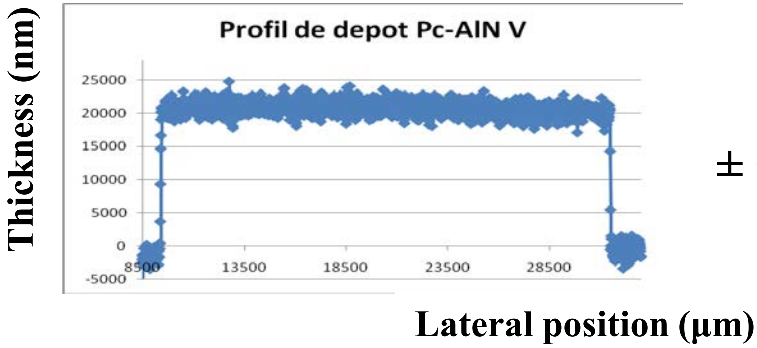
elution profile of the irradiated target

an example of dry chemistry: ^{211}At

Nuclear reaction: $^{209}Bi + \alpha \rightarrow {}^{211}At + 2n$

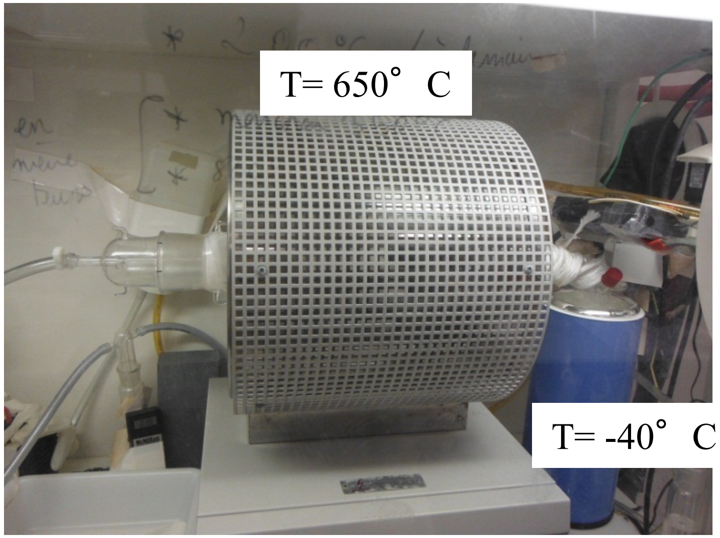
Bismuth target on its AlN backing





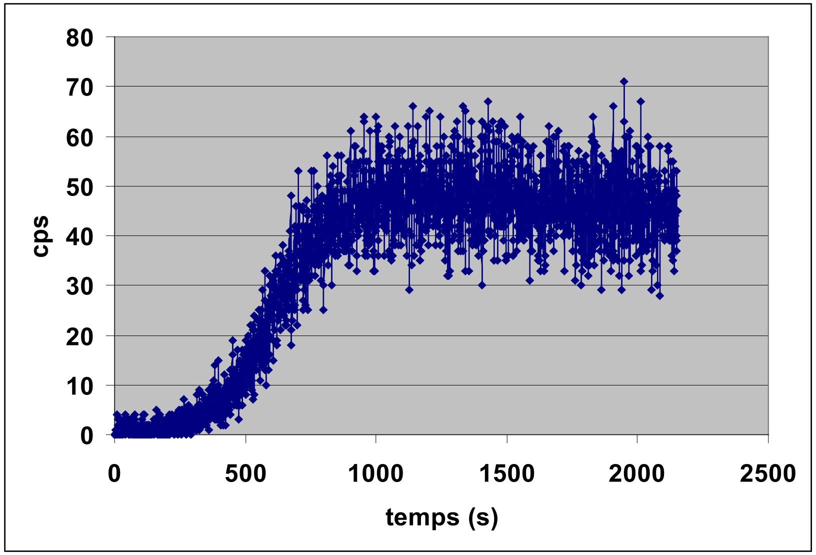
± 5 %

Dry extraction device



T= 650° C

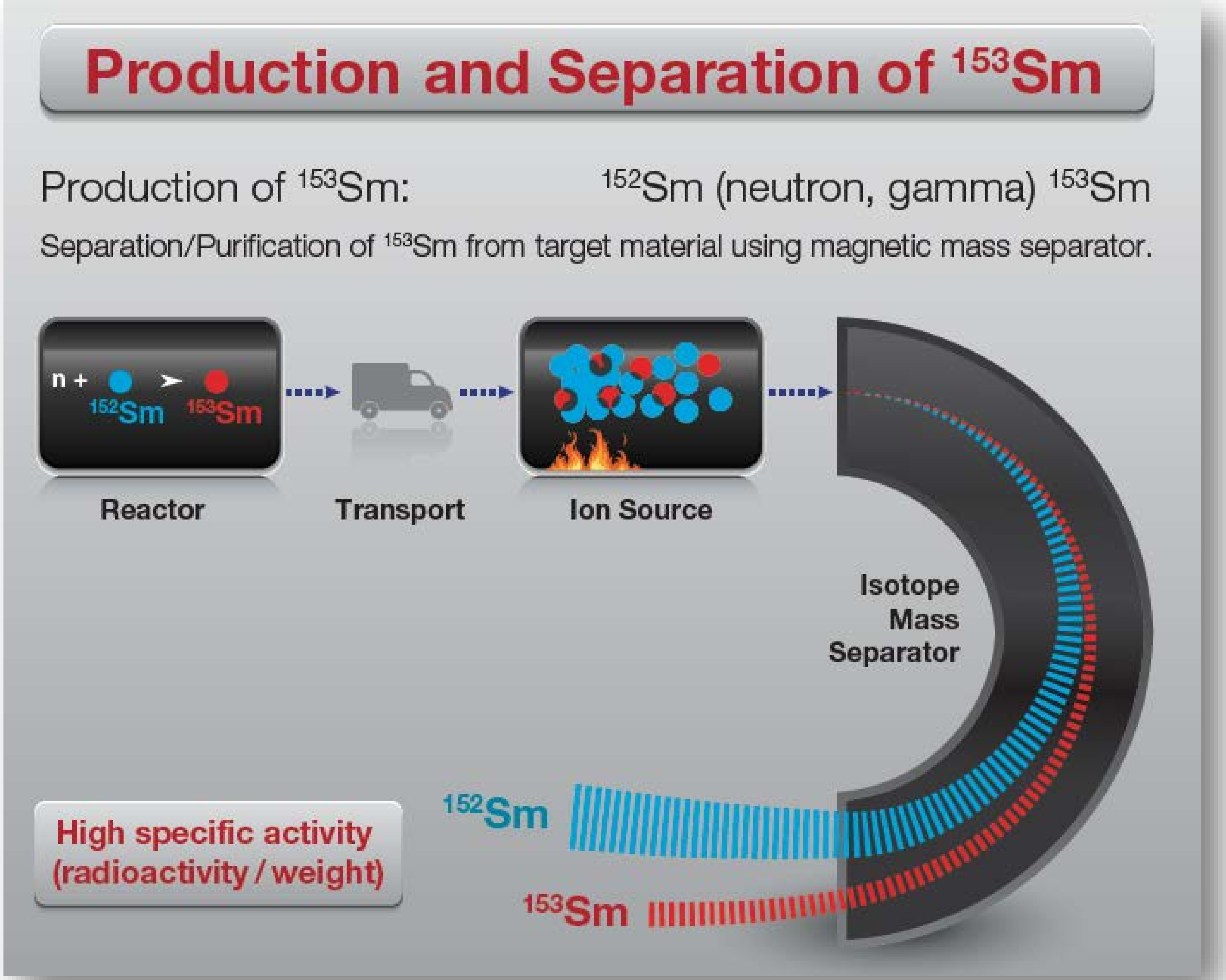
T= -40° C



Astatine starts to get out after few minutes and the total processing time is around 2h

Extraction yield > 80 %

High purity radioisotopes - Mass separation



Production and Separation of ^{153}Sm

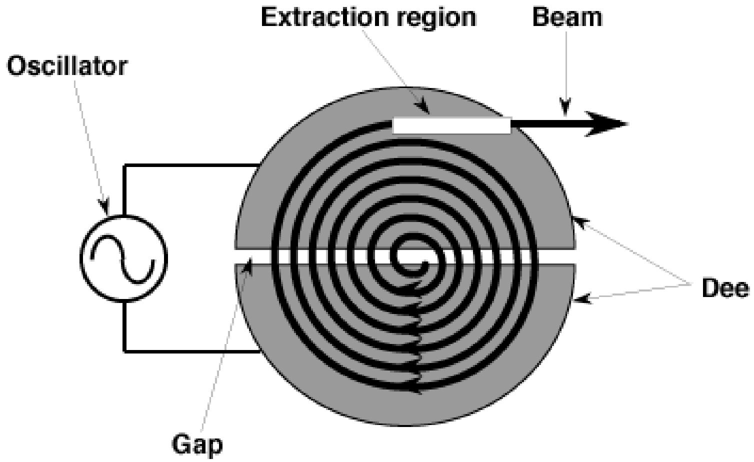
Production of ^{153}Sm: ^{152}Sm (neutron, gamma) ^{153}Sm

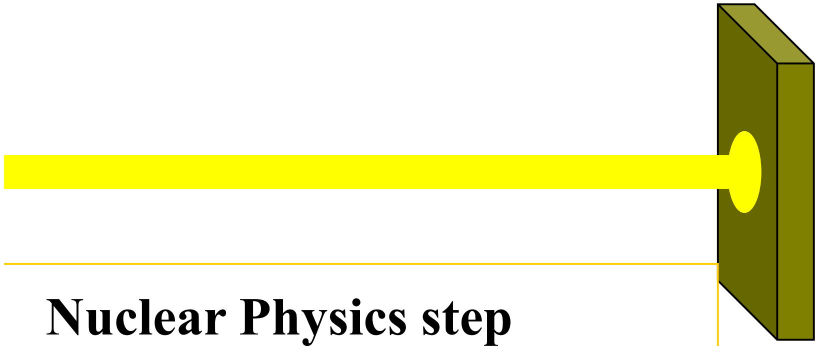
Separation/Purification of ^{153}Sm from target material using magnetic mass separator.

High specific activity (radioactivity / weight)

Dr. John D’Auria IsoTherapeutics Group LLC and Simon Fraser University

Development of a radiopharmaceutical



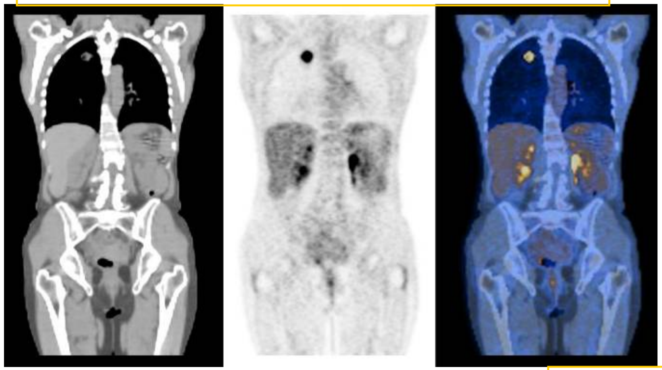


Nuclear Physics step
ection of the most approriate nuclear reaction

Radiochemistry Step
Extraction and Purification

Radiopharmacy Step
Radiolabeling

Medical validation

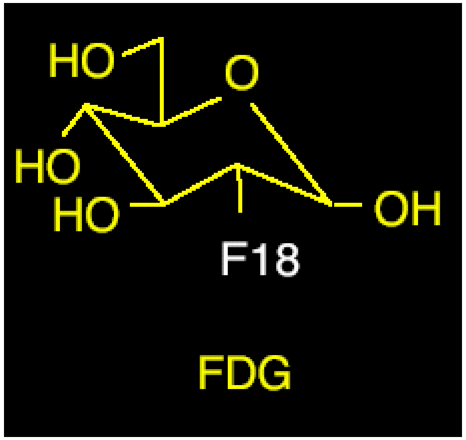


Radiopharmaceutical

Radionuclide of interest for PET

Main positron emitters

Oxygen-15	2mn
Nitrogen-13	10 mn
Carbon-11	20mn
Fluorine-18	110mn



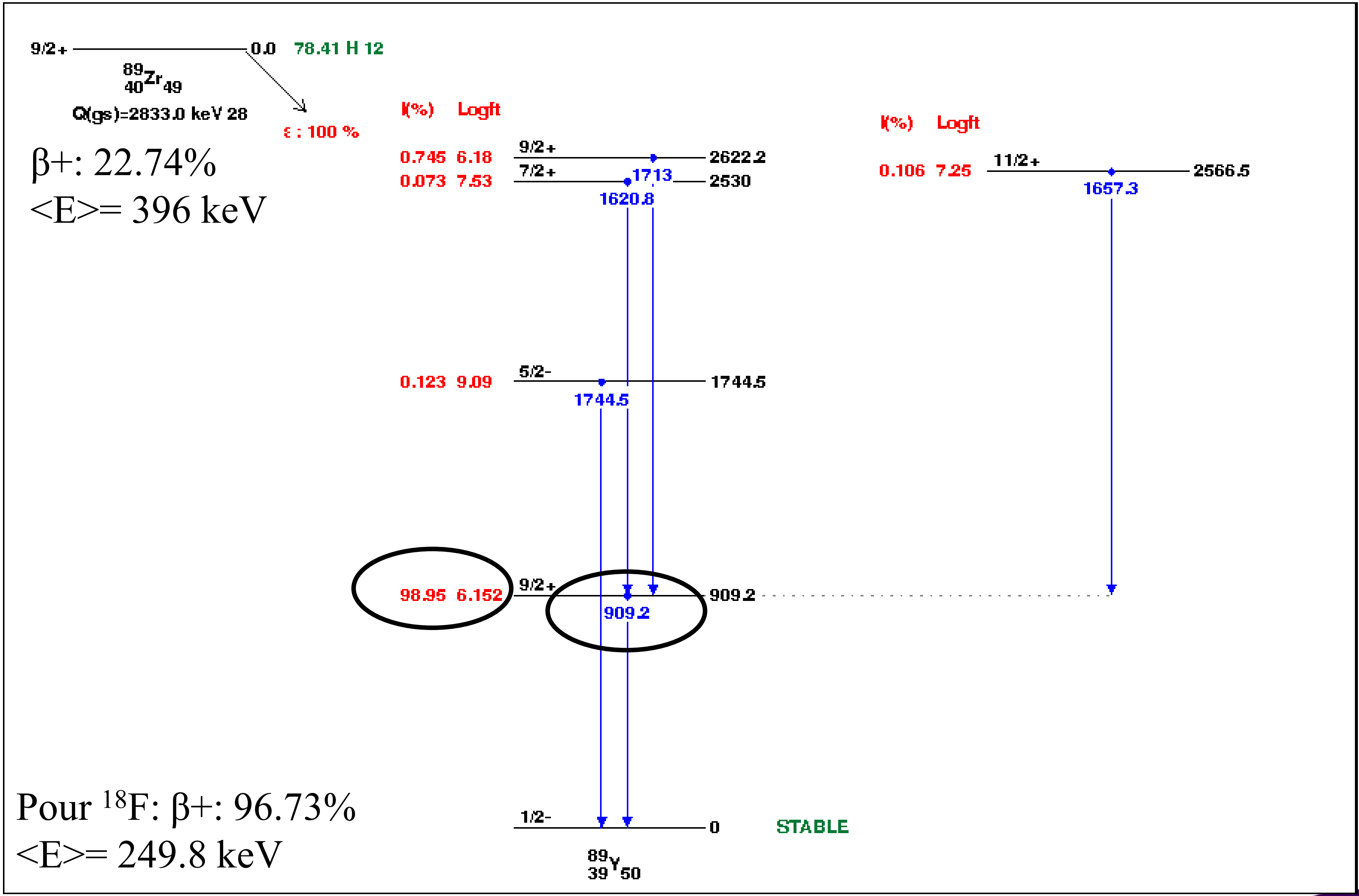
The most used one is ^{18}**F** with ***Fluorodeoxyglucose***

Other can be selected with respect to:

- $T_{1/2}$ → to adapt to vector transit time
- branching ratio → to optimize the contrast on the image
- associated radiation → potential radioprotection issues
- positron energy → to get the best image resolution
- Generator produced,… → to reduce logistics

Sc-44, Cu-64, Zr-89, I-124, Tb-152, …

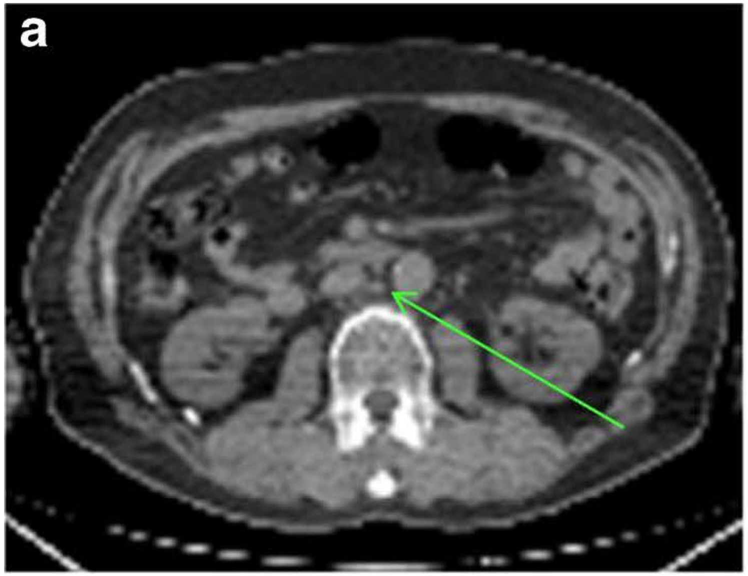
Radionuclide of interest for PET : ^{89}Zr

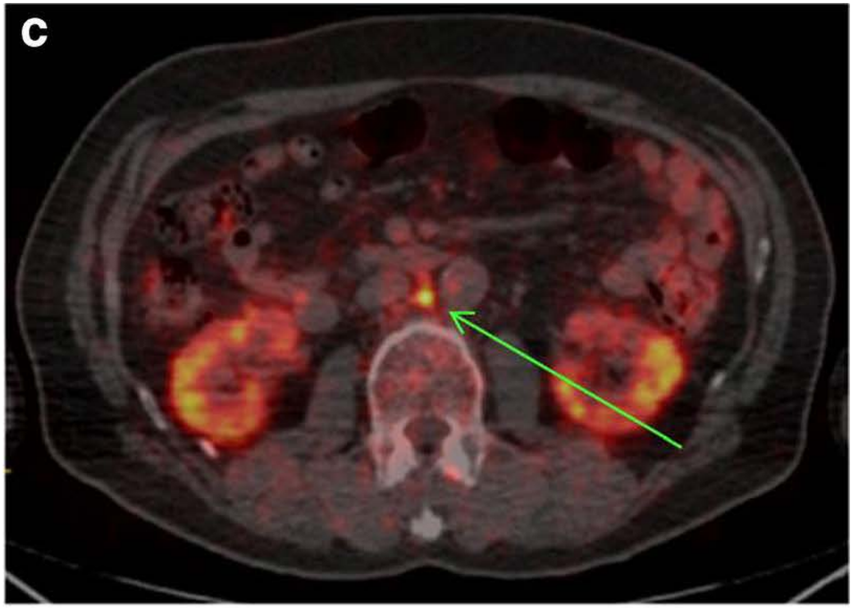


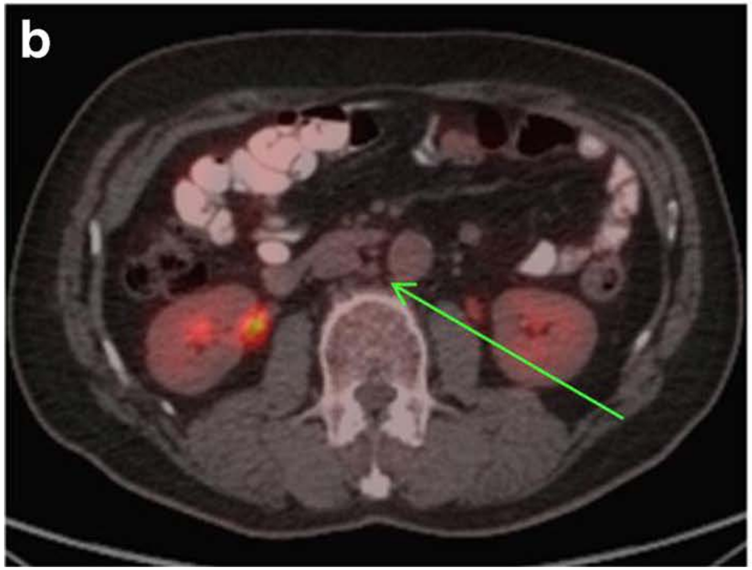
β+: 22.74%
<E>= 396 keV

Pour ^{18}F: β+: 96.73%
<E>= 249.8 keV

An example of the Added value of PET nodule in the prostate







An antibody coupled to Zr-89

Nodule diameter <1cm
→No suspicion in CT Scan

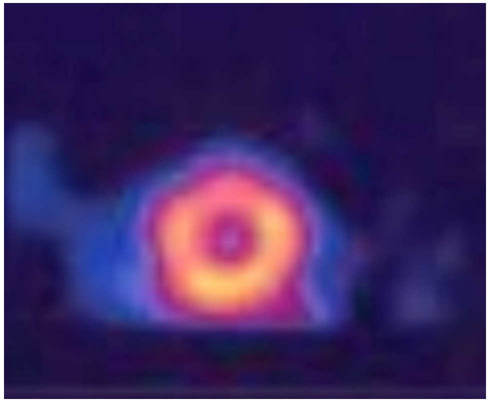
PET exam shows the nodule uptake is high
→ cancerous

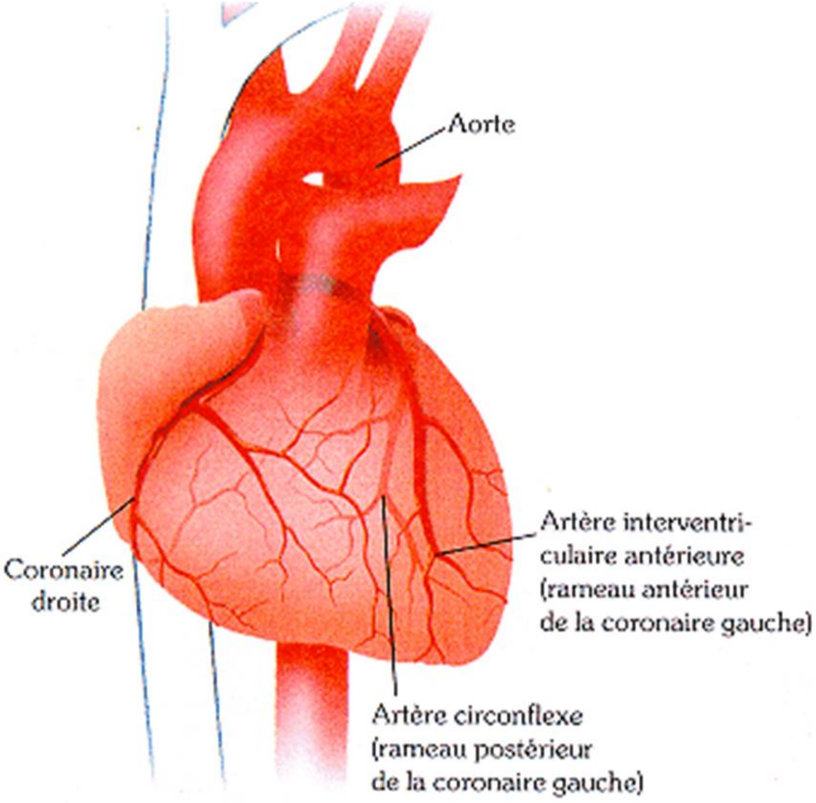
Rubidium-82 (^{82}Rb)

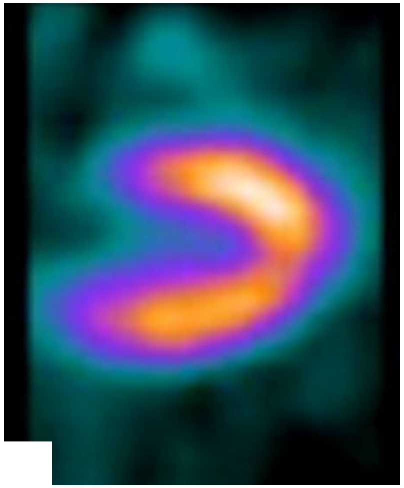
PET imaging in cardiology

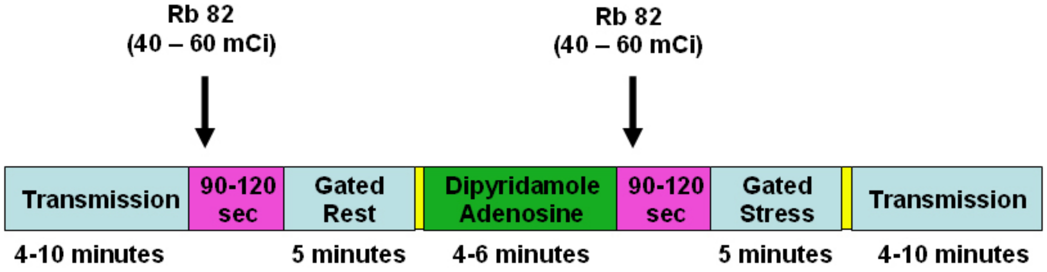
An exemple of PET production using a solid target

Rubidium-82 (^{82}Rb): PET imaging in cardiology









Rb 82 (40 – 60 mCi)

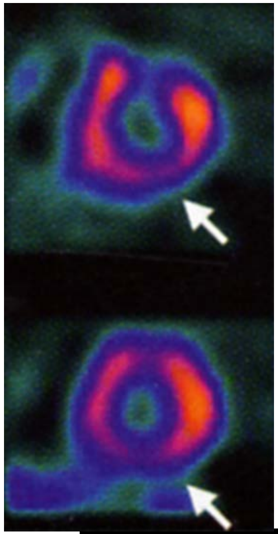
Rb 82 (40 – 60 mCi)

Transmission	90-120 sec	Gated Rest	Dipyridamole Adenosine	90-120 sec	Gated Stress	Transmission
4-10 minutes		5 minutes	4-6 minutes		5 minutes	4-10 minutes

Di Carli MF. Major achievements in nuclear cardiology:XI. Advances in positron emission tomography. J Nucl Cardiol. 2004;11:719-732

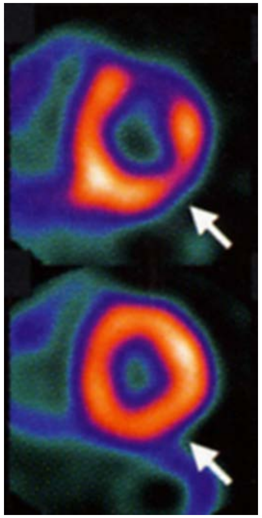
Rubidium-82 (^{82}Rb): PET imaging in cardiology

^{99m}Tc-MIBI
SPECT



Bad corrections

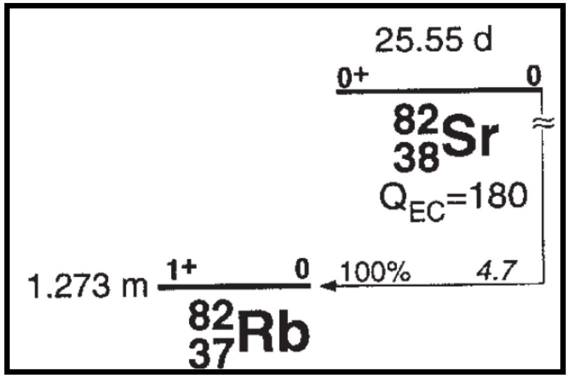
^{82}Rb-PET



D. Le Guludec et al, Eur J Nucl Med Mol Imaging 2008; 35: 1709-24

Several advantages:

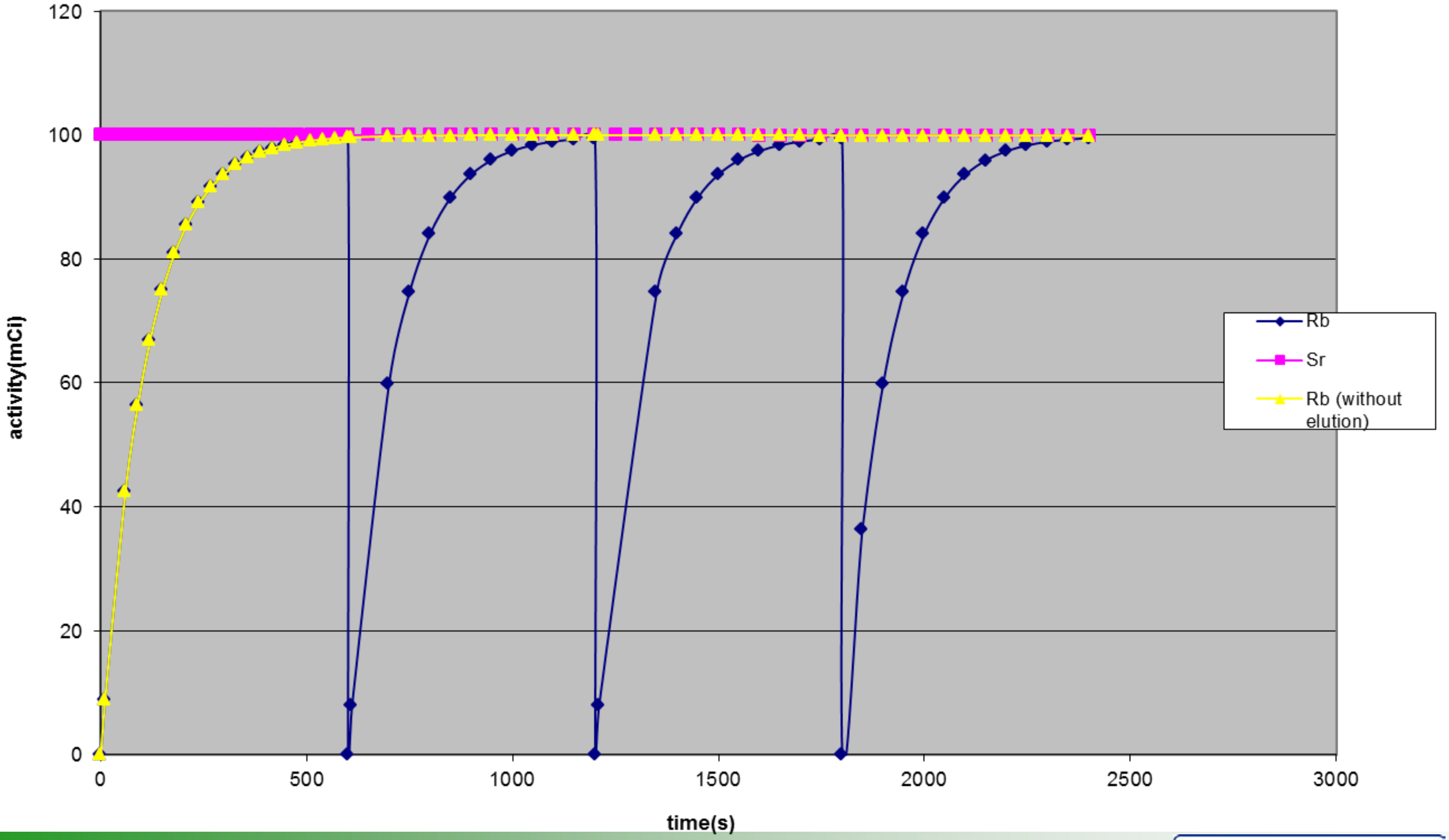
- Better corrections
- Quantification
- Shorter duration of the exam
- Lower dose to patient



^{82}Sr/^{82}Rb generator

Rubidium-82 (^{82}Rb): PET imaging in cardiology

$$^{82}\mathrm{Sr} \xrightarrow{\lambda_1} {}^{82}\mathrm{Rb} \xrightarrow{\lambda_2} {}^{82}\mathrm{Kr}\ \text{(stable)}$$



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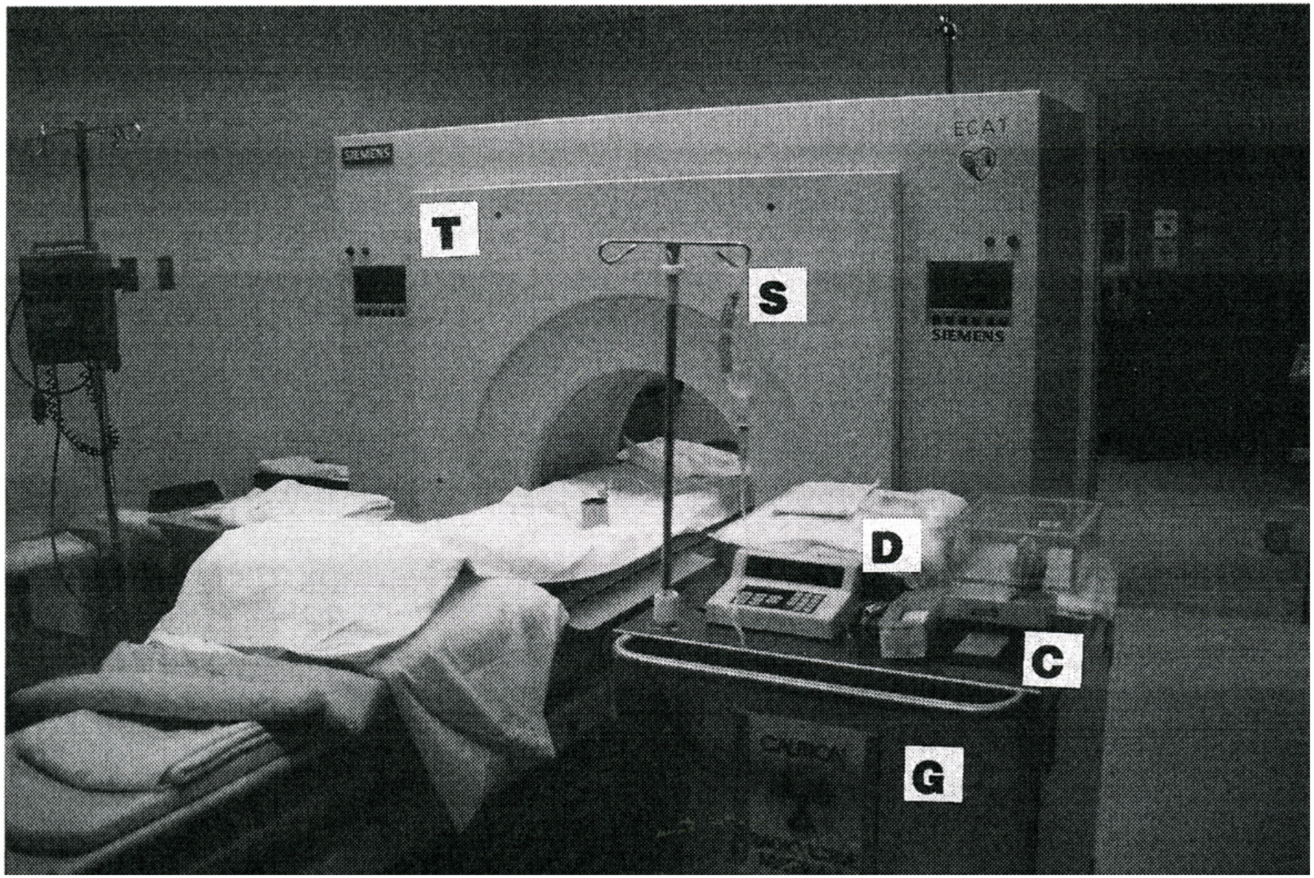


T = PET Scanner
S = NaCl solution
G = Chart containing the Sr82/Rb82 generator

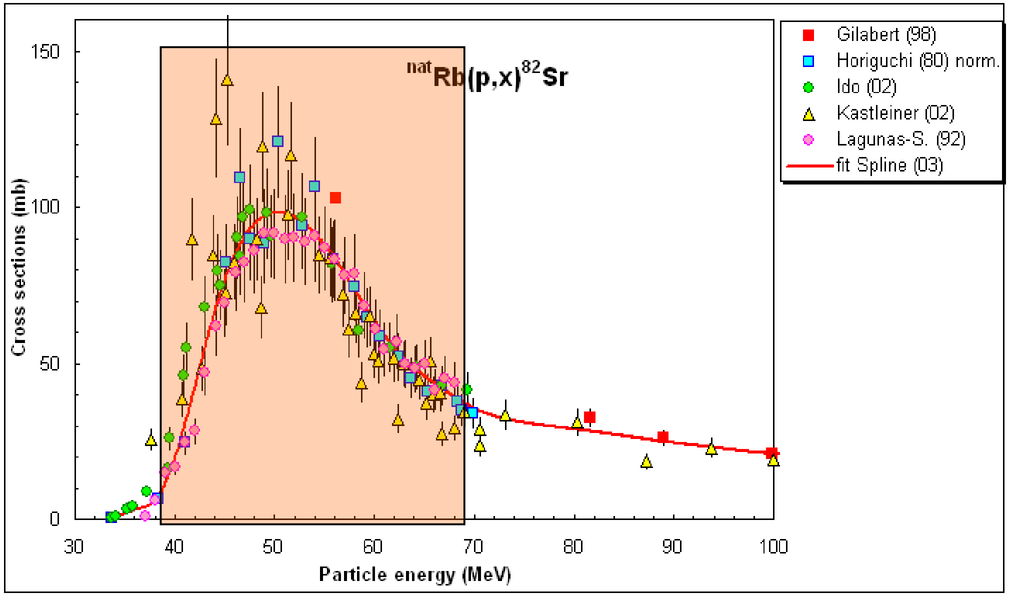
D = Automatic infusion system
C = Control computer

Generator ^{82}Sr/^{82}Rb

Infusion system

^{82}Sr production

- Reaction and Cross section **$^{nat}Rb + p \rightarrow {}^{82}Sr + x$**



Low cross section

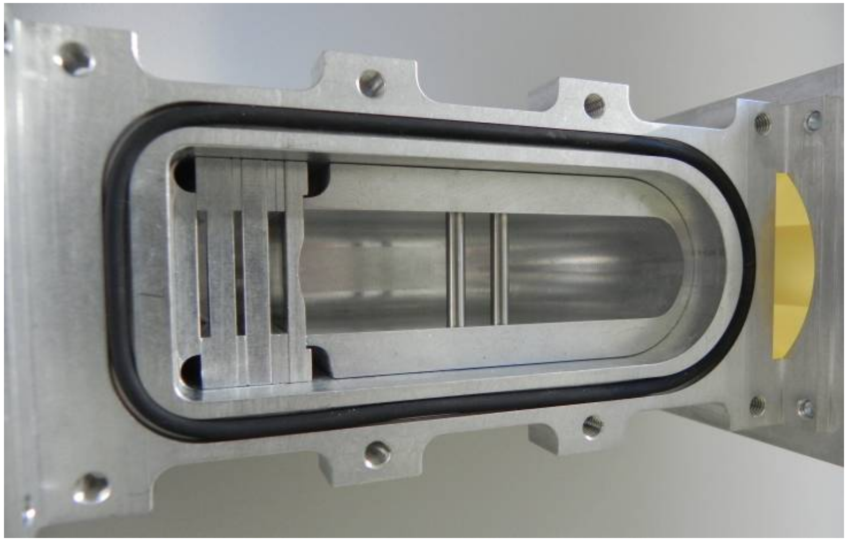
Energy range of interest
40 MeV-70 MeV

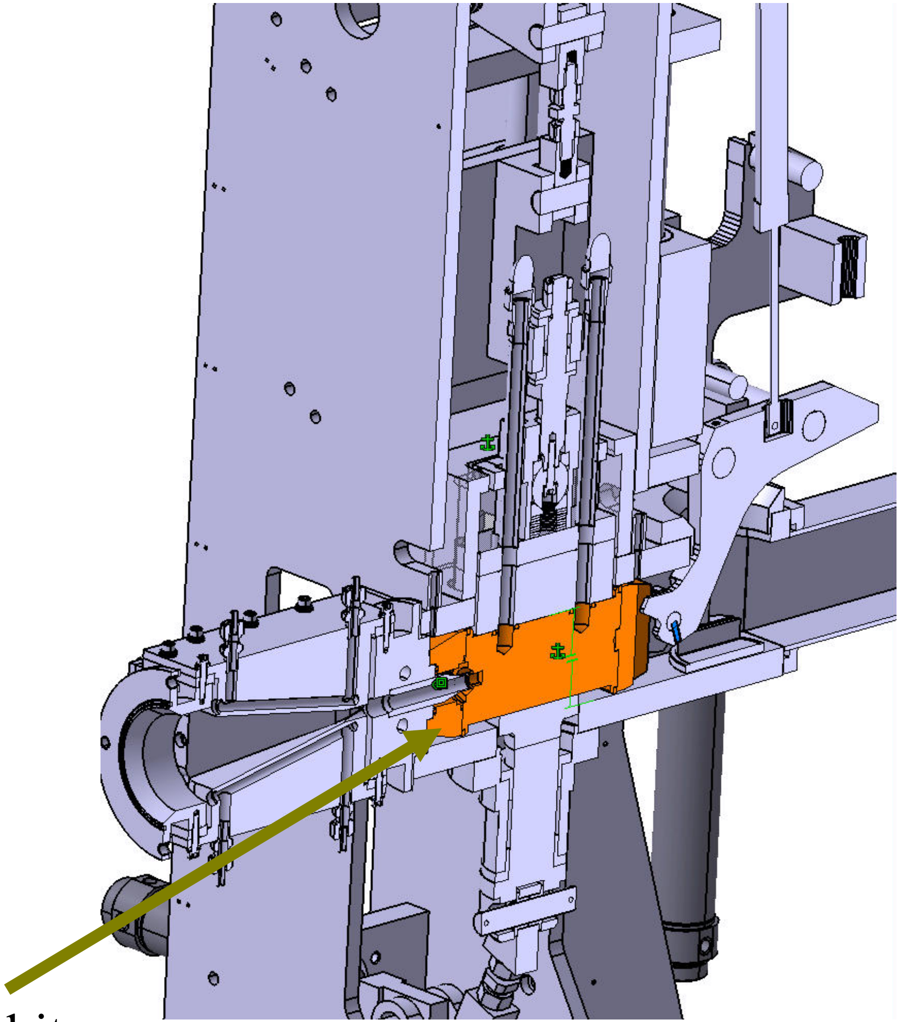
Production needs high energy machines and high intensity beams

ARRONAX irradiation station

Pressed pellet of RbCl

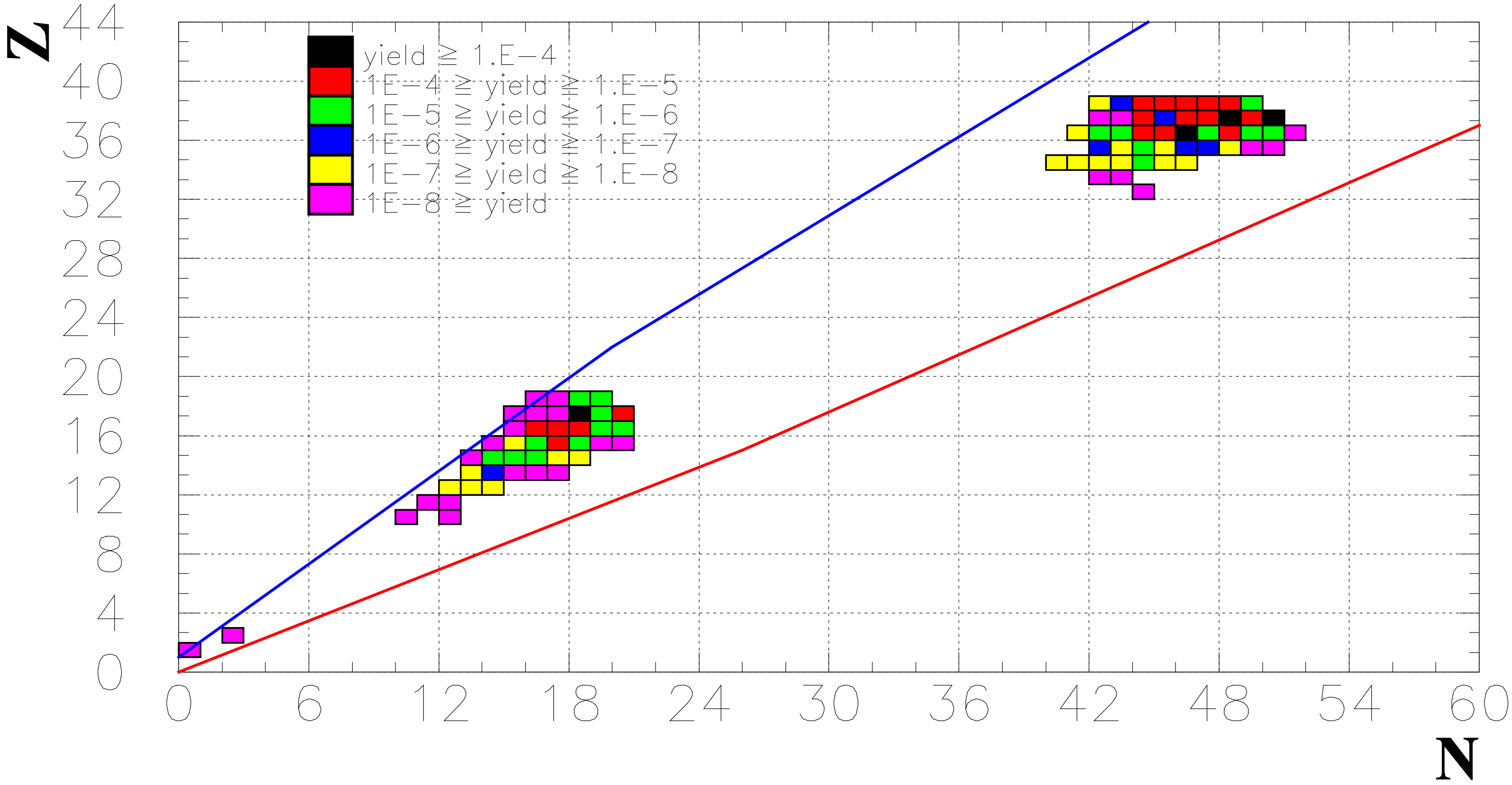
Encapsulated RbCl



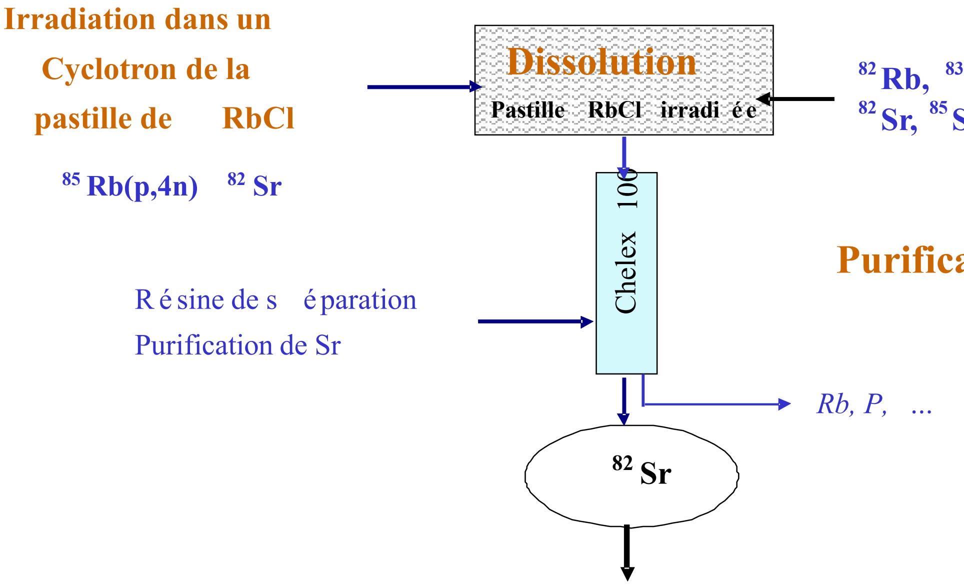


Rabbit

RbCl inventory (simulation using MCNPX)



Extraction and purification



Irradiation dans un Cyclotron de la pastille de RbCl

^{85}Rb(p,4n) ^{82}Sr

Dissolution

Pastille RbCl irradiée

^{82}Rb, ^{83}Rb, ^{83m}Rb, ^{84}Rb, ^{86}Rb
^{82}Sr, ^{85}Sr, ^{32}P, ^{83m}Kr…

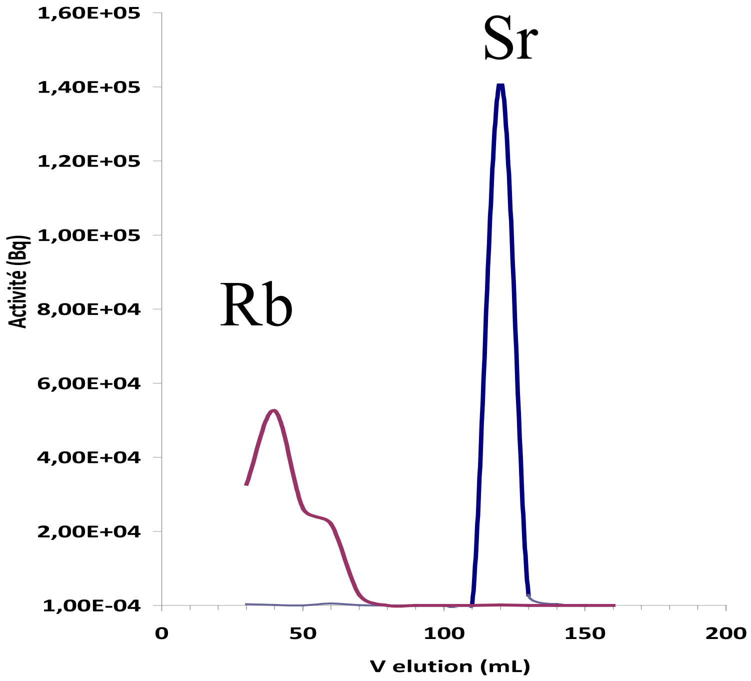
Chelex 100

Résine de séparation
Purification de Sr

Rb, P, …

^{82}Sr

Purification de Sr



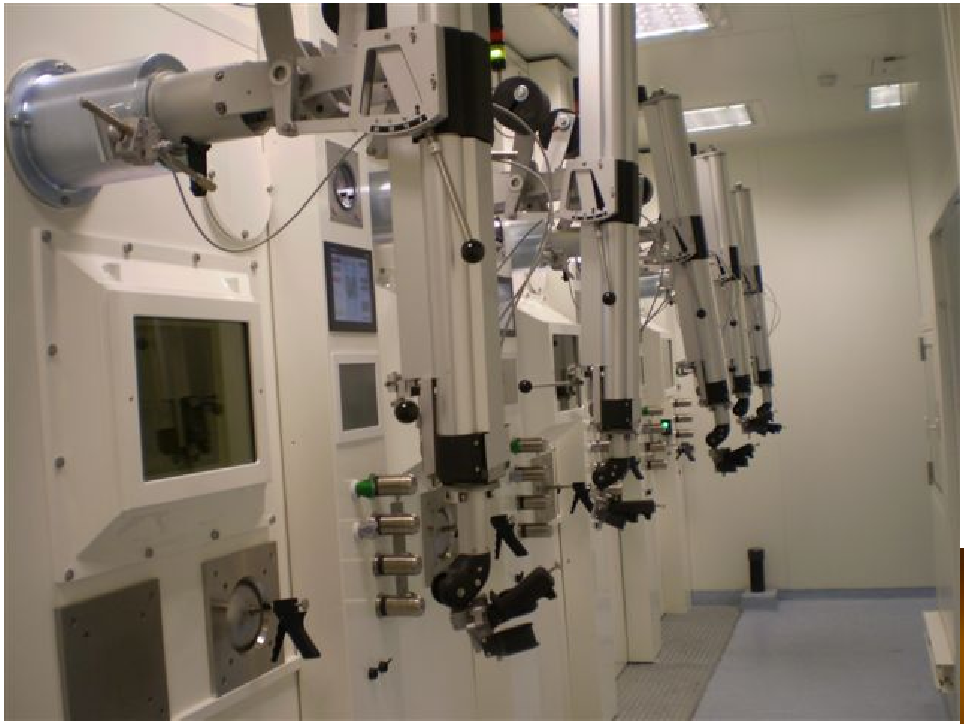
Good separation

Reproducibility verified

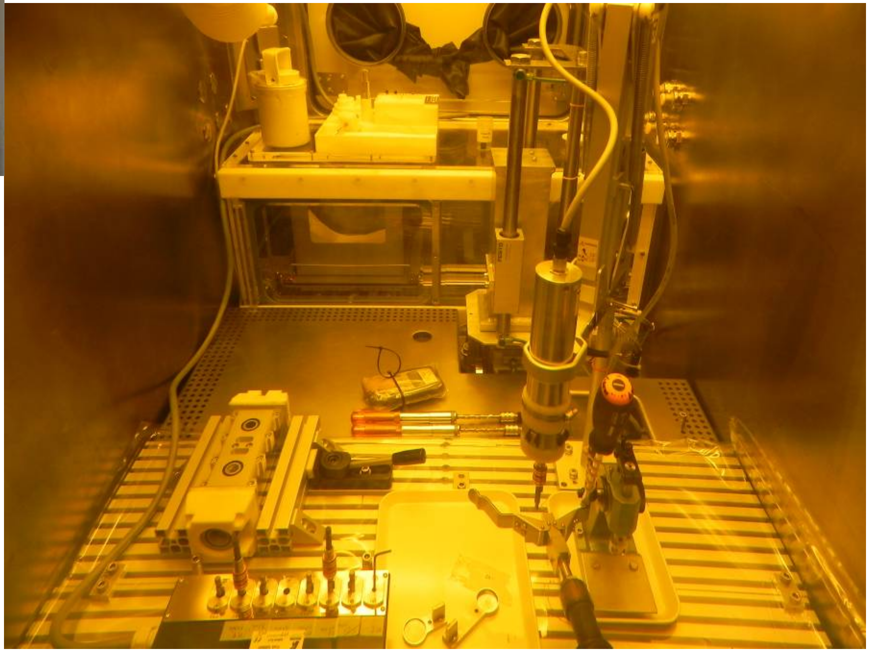
Extraction yield = 92.9 % ± 3.7% (k=2)

Purity of the product fulfills regulatory requirements.

Processing in hot cells

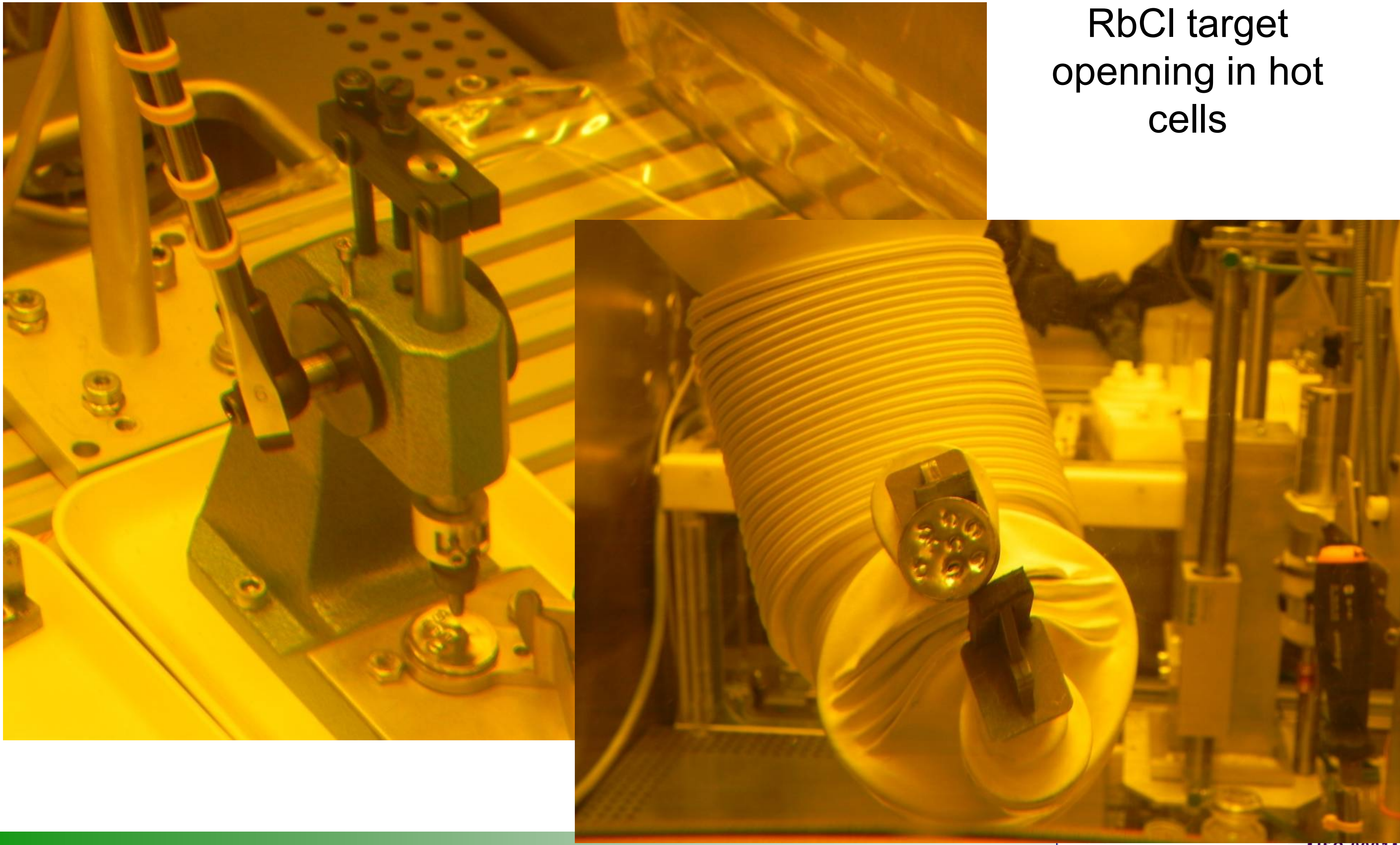


Hot cells



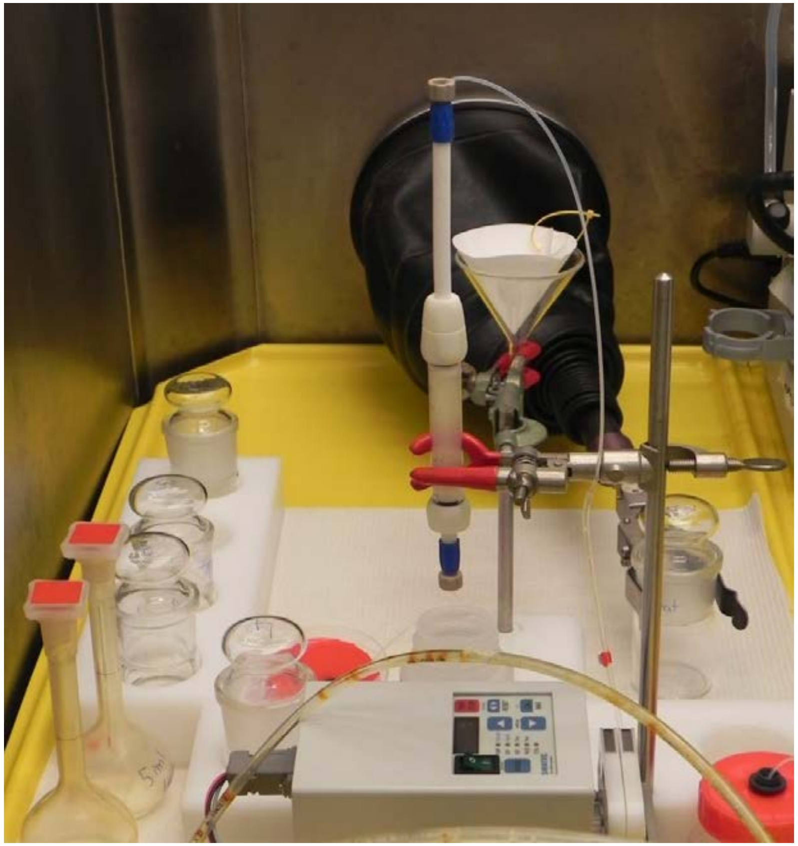
Dismounting the rabbit

Processing in hot cells



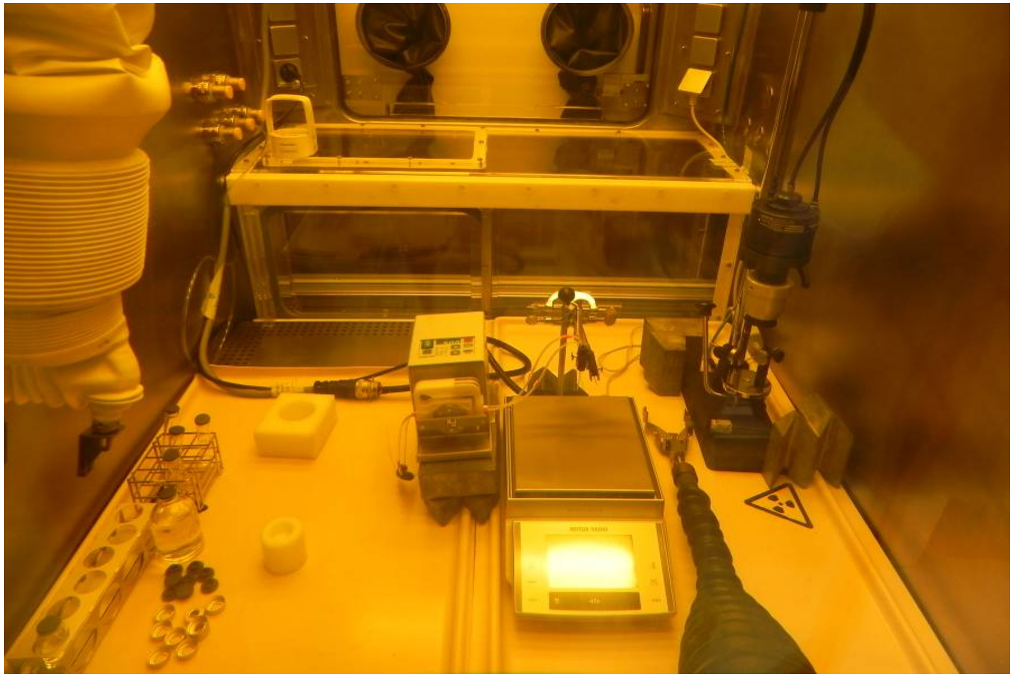
RbCl target
openning in hot
cells

Processing in hot cells



Chemical separation

Dispensing and quality control



Quality control:

- γ -Spectroscopy
- ICP-OES

Shipment

afaq
ISO 9001
Qualité
AFNOR CERTIFICATION

Conclusions

- Many different constraints have to be taken into account to develop radionuclide production

- The weight to put on different parameters depends on the application

- These rules are the same for therapeutic radionuclides

- Medical applications drive the field neither physics nor chemistry.

- Exciting fields with new techniques and new isotopes

Thank you for your attention

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