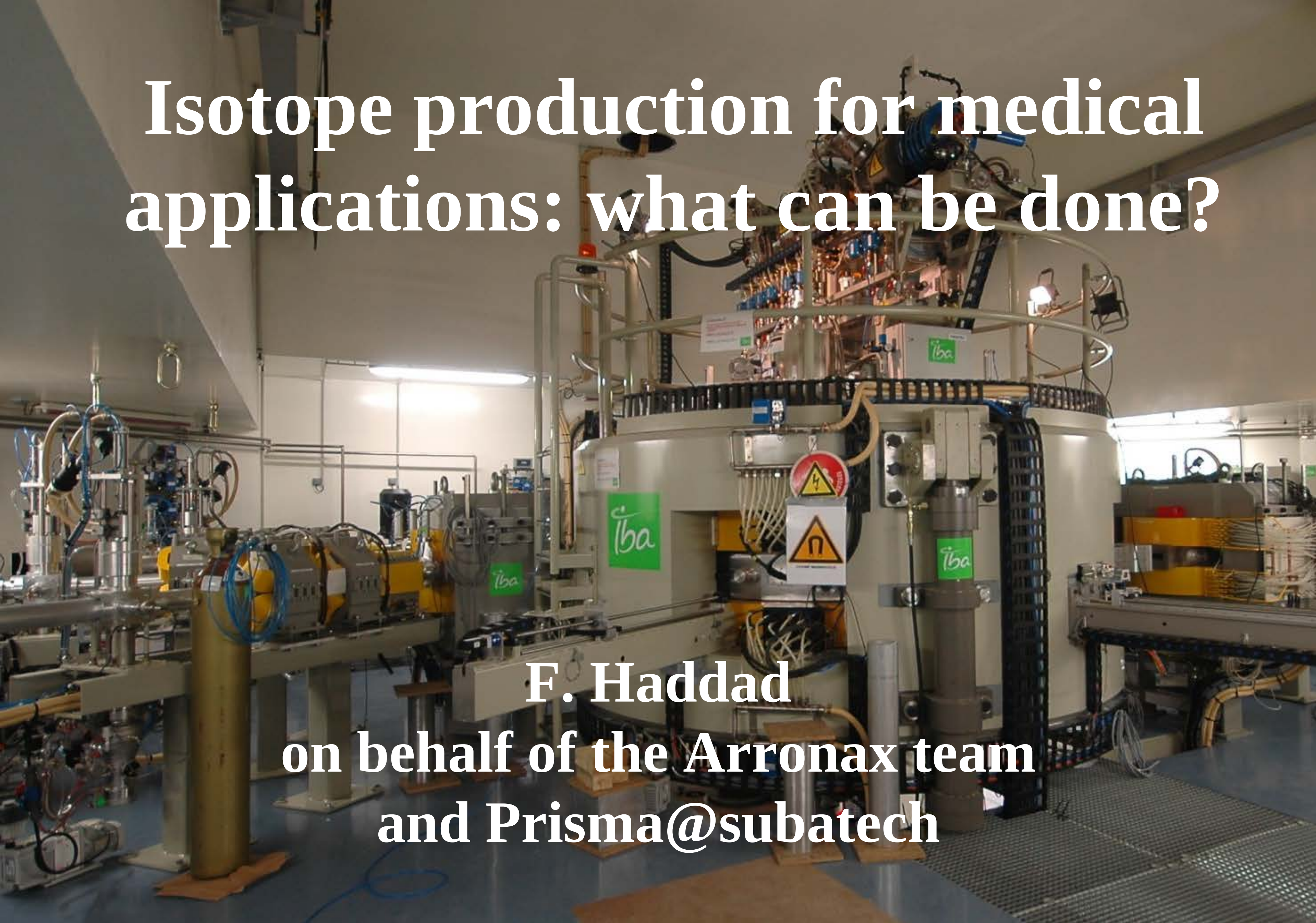

Isotope production for medical applications: what can be done?

F. Haddad
on behalf of the Arronax team
and Prisma@subatech

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Radionuclides production for nuclear medicine

Nuclear medicine is a medical specialty which deals with **radionuclide** used **as open sources** (30 Millions procedures per year - 2013).

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

In some cases, the radionuclide can be injected directly:

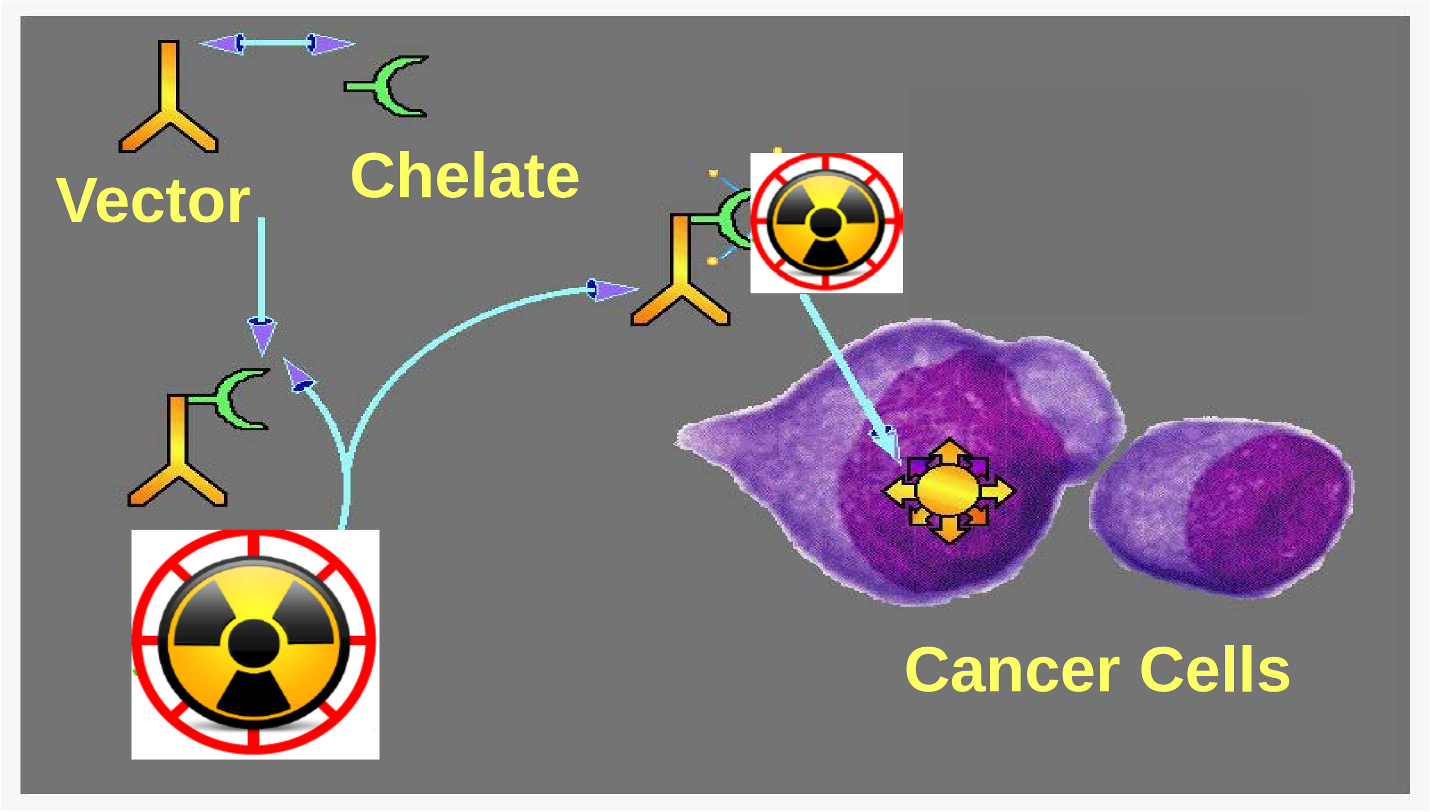
Iodine-131 goes directly to the thyroid

Rubidium-82 is accumulating in the heart

Radium-223 goes to the bones.

In most cases, a vector molecule is needed to target the cells of interest.

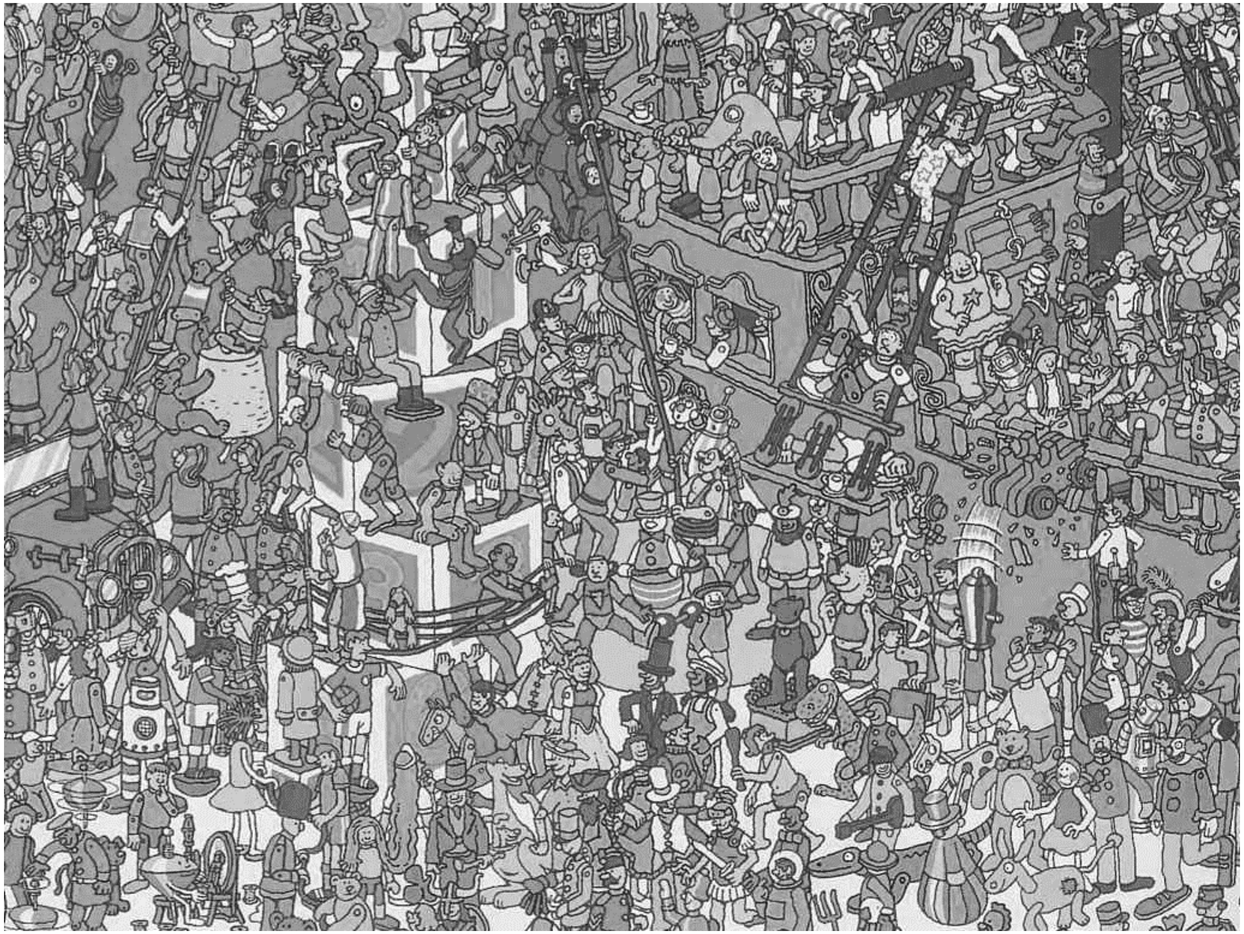
Targeting

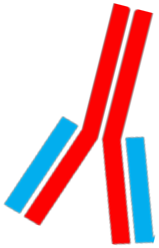


Peptides and Antibodies can be used as **vector** for either imaging and therapy

There is often a limited number of receptor sites on a cell

Targeting allows to find the right guy in a complex environment





antibody anti- « red and white strips »

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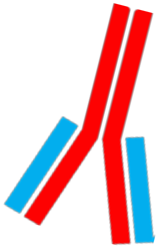
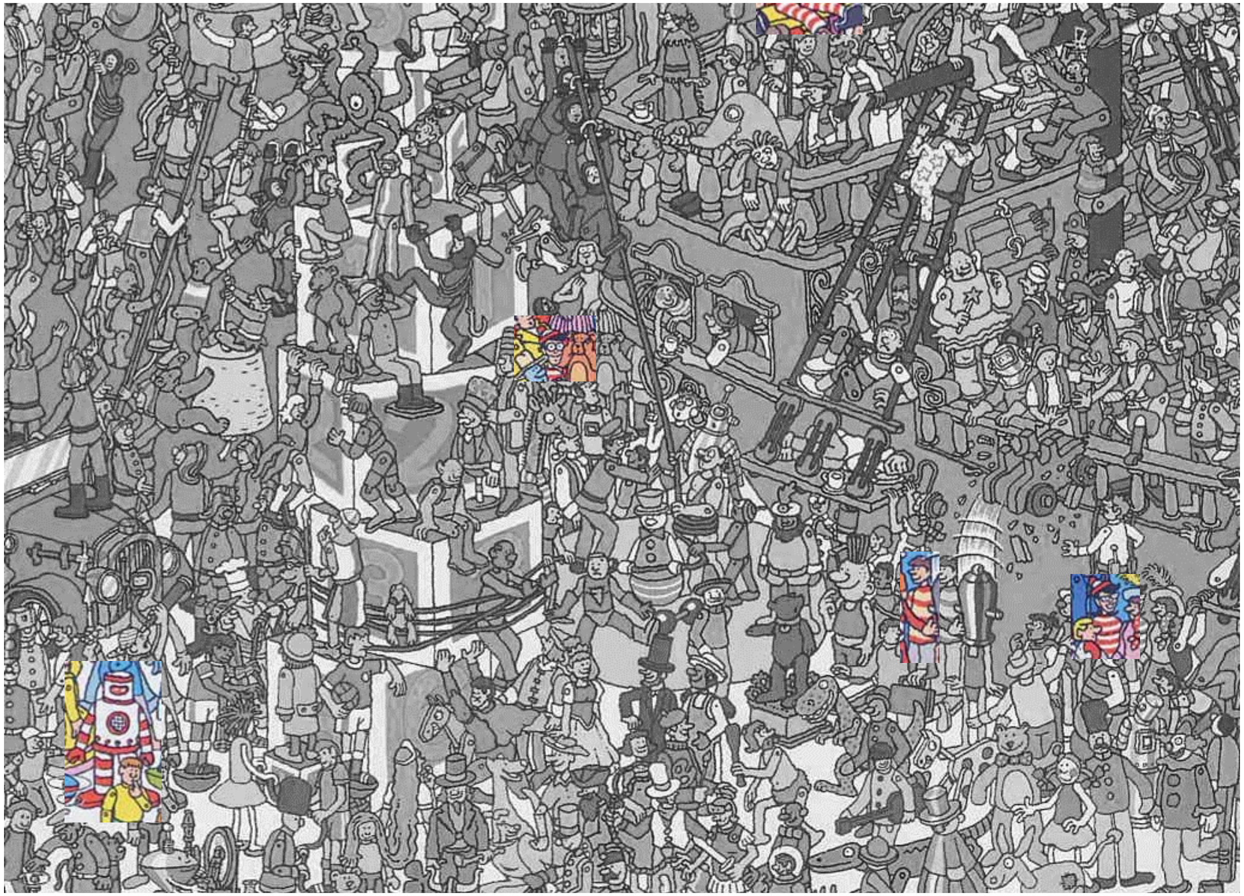
Targeting allows to find the right guy in a complex environment

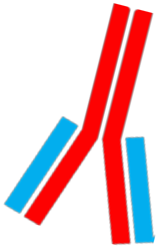


antibody anti-
« red and white
strips »



Targeting allows to find the information

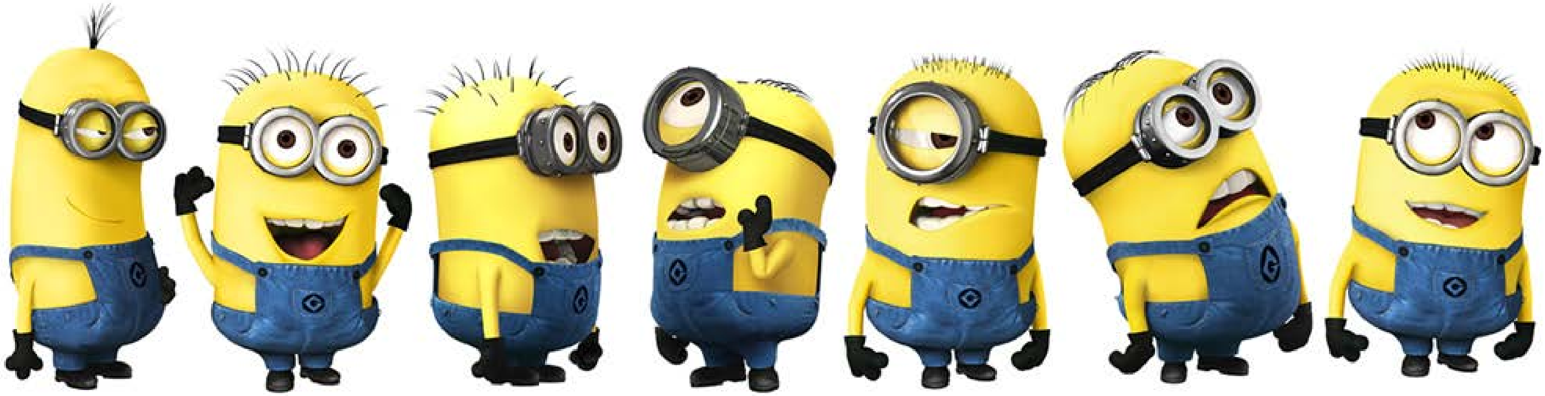
Targeting allows to find the right guy in a complex environment



Antibody
« anti-Charlie »

Changing vector, we can be more specific

Every patient is unique



There is differences between each person:

- Some are straightforward: Age, Sex, Size, Weight, …
- Some others are less simple as biological and biochemical constants, genetic characteristics, …

There is a need for personalized treatment

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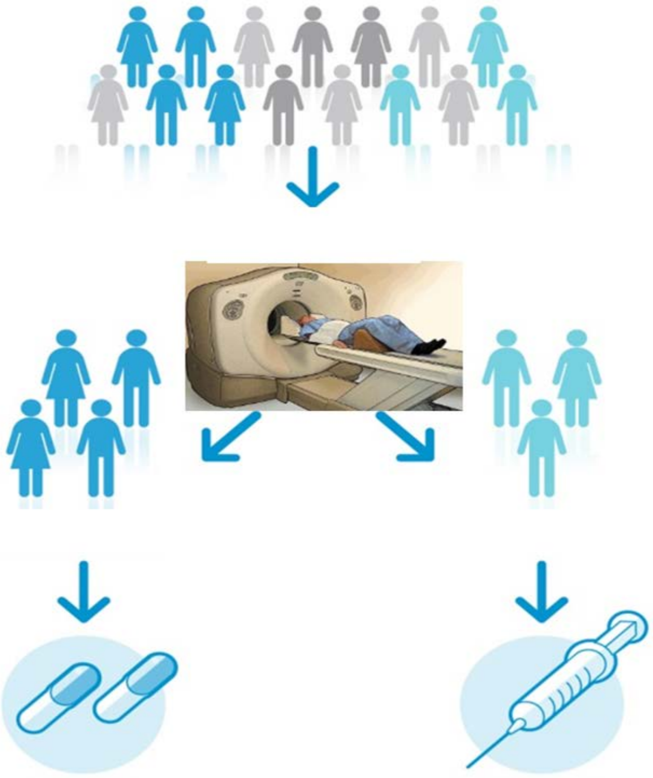
Theranostics

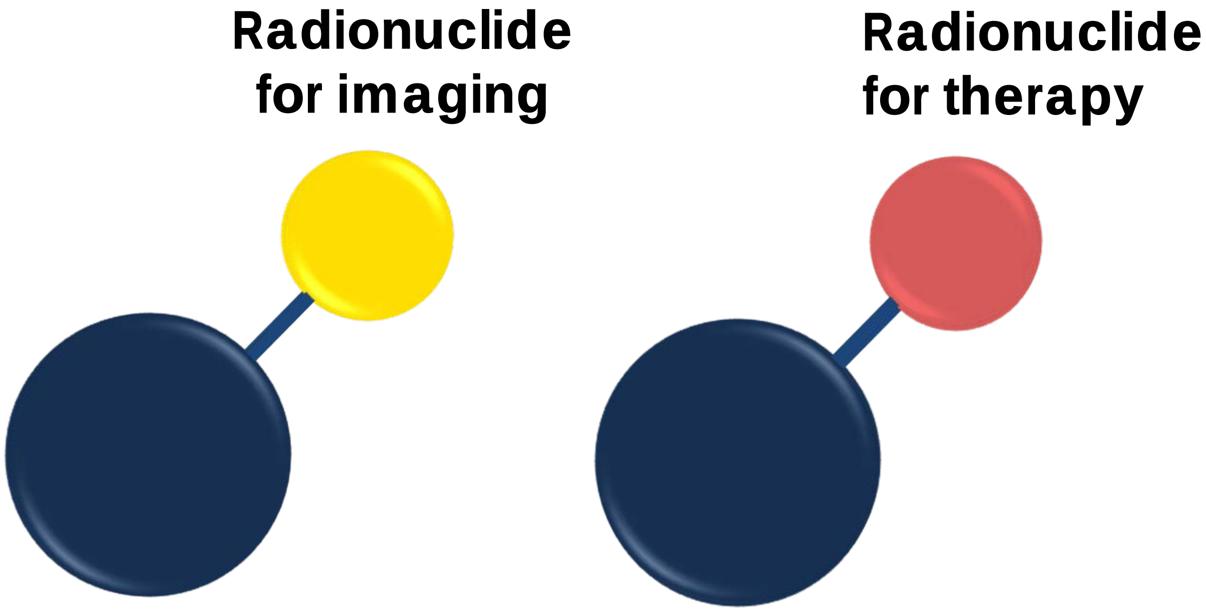
It is a **treatment strategy** that combines **thera**peutics with diag**nostics**.

- Localized lesions
- Define the **biodistribution** of a therapeutic agent to anticipate its effect
- **Select patients which are expected to response to the therapeutic agent**
- Calculate the optimal activity to be injected
- Evaluate the response after treatment



The Right Drug To The Right Patient For The Right Disease At The Right Time With The Right Dosage

Theranostics



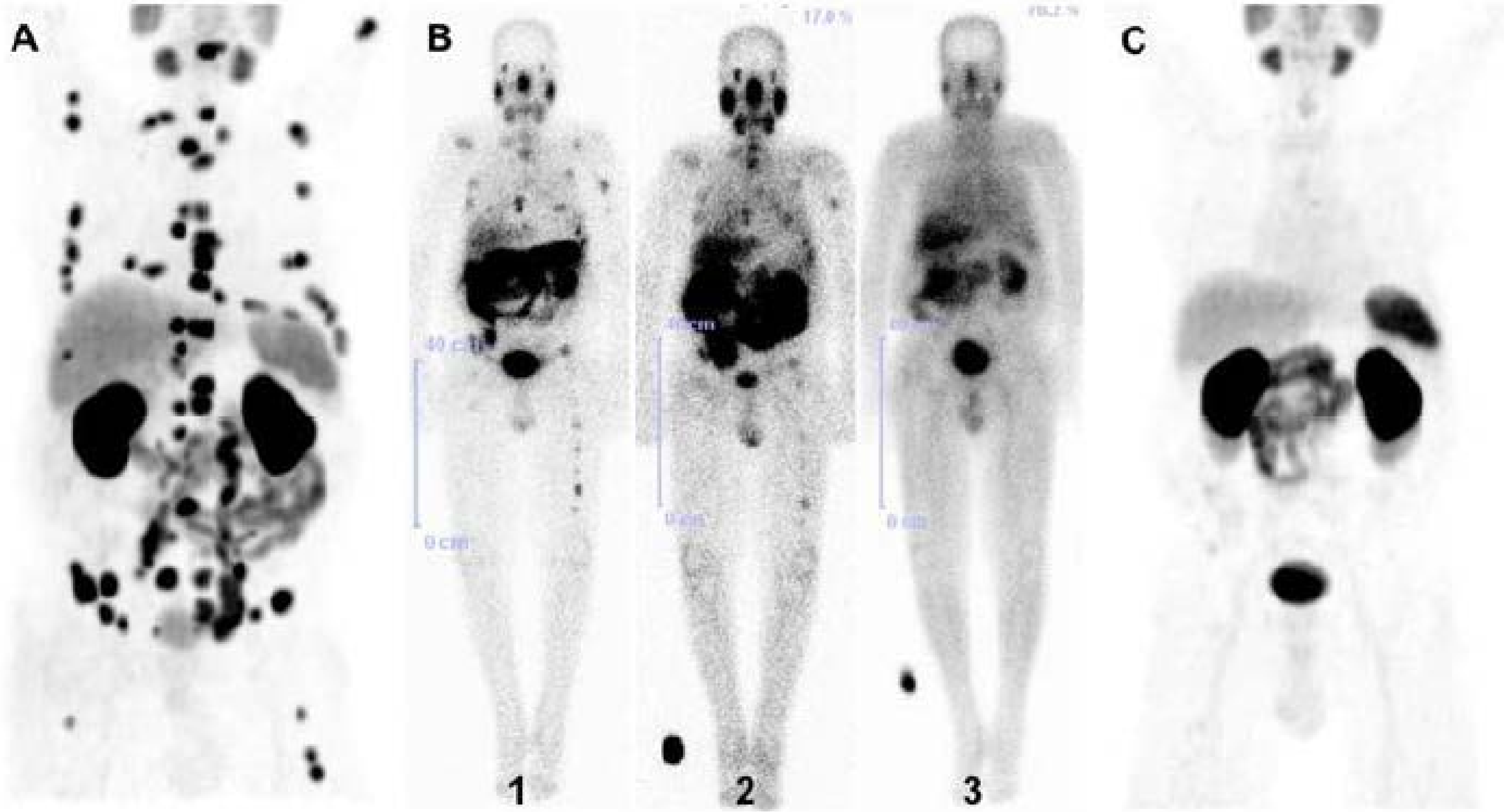
Which radionuclides?

R**adionuclides of the same element (**$^{44}Sc/^{47}Sc$, $^{64}Cu/^{67}Cu$, $^{124}I/^{131}I$, Tb …)

R**adionuclides** with comparable properties (^{68}Ga / ^{177}Lu , ^{99m}Tc / ^{188}Re)

Radionuclide with radiations for both imaging and therapy (^{117m}Sn)

^{177}Lu-radioligand therapy of advanced prostate cancer



R.P. Baum et al., J Nucl Med 2016;57:1006.
C. Kratochwil et al., J Nucl Med 2016;57:1170.
K. Rahbar et al., J Nucl Med 2017;58:85.

Courtesy U. Koster

Nuclear medicine needs radionuclides

– with different **decay radiations**:

imaging / therapy

short range High LET vs long range Low LET

– with different **Chemical properties**

– with different **Half-lives:** to match with vector distribution time in targeted therapy

– To be used for the Theranostics approach

→pair of isotopes

- With an appropriate purity

Nuclear Physics can help by developing **efficient large scale** production of **high purity** radionuclides (innovative or not)

Its unique characteristics

Main characteristics:

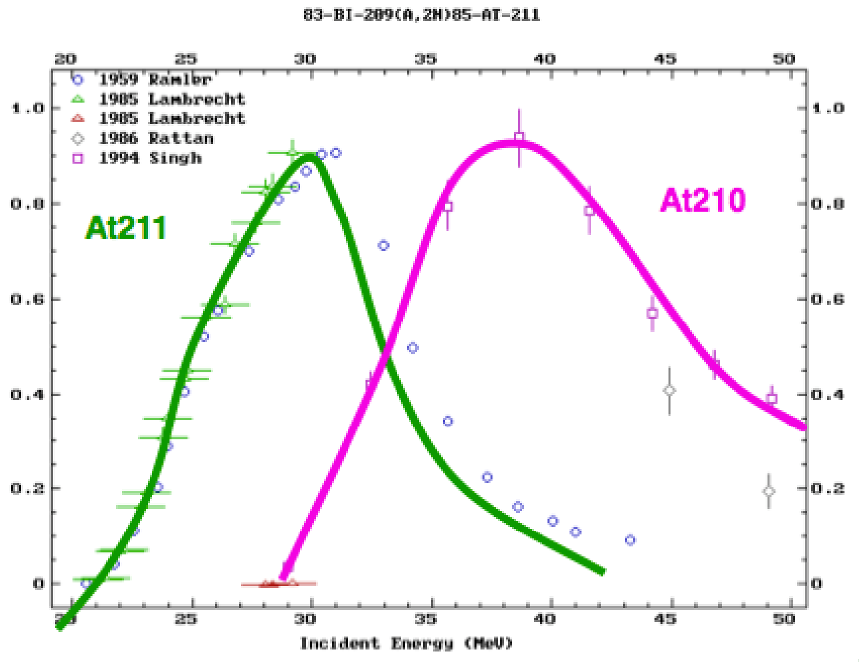
- **Multi-particles**
- **High energy**
- **High intensity**

Beam	Accelerated particles	Energy range (MeV)	Intensity (eμA)	Dual beam
Proton	H-	30-**70**	<**375**	**Yes**
	HH+	17	<50	No
Deuteron	D-	15-35	<50	Yes
Alpha	He++	**68**	<70	No

What can we do ?

High purity:

- Nuclear data
  - Allow to estimate production yield
  - Allow to define level of contaminants
  - Allow to adjust energy range of interest



Production route:

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

Energy range of interest:

[20 MeV - 28,3 MeV]

Cu-67 production

It is a β- emitter with 185 keV γ-line

$T_{1/2}$ = 61.83 h

It has a β+ emitter partners: ^{64}Cu – $T_{1/2}$ = 12.7 h

Targeted therapy with β-, SPECT imaging

Central production + continental delivery

Theranostic pair: ^{64}Cu/ ^{67}Cu

Production routes with charged particles:

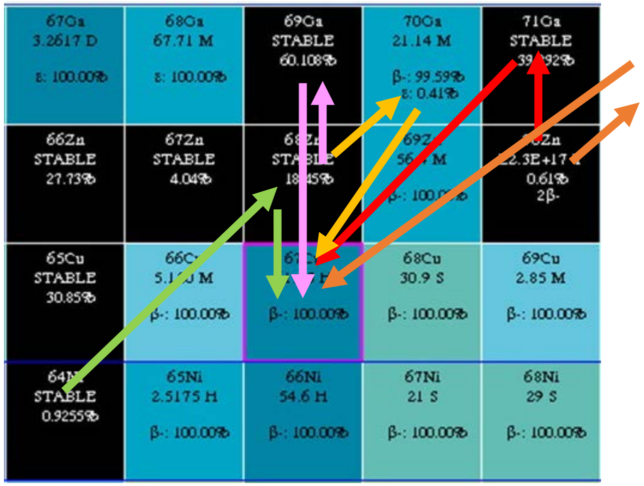
IAEA current CRP on Cu-67

- ^{68}Zn(p,2p)

  used at BNL to make ^{67}Cu available part of the year

  used at PSI in the past
- ^{70}Zn(p,α)
- ^{68}Zn(d,x)
- ^{70}Zn(d,x)
- ^{64}Ni(α,p)

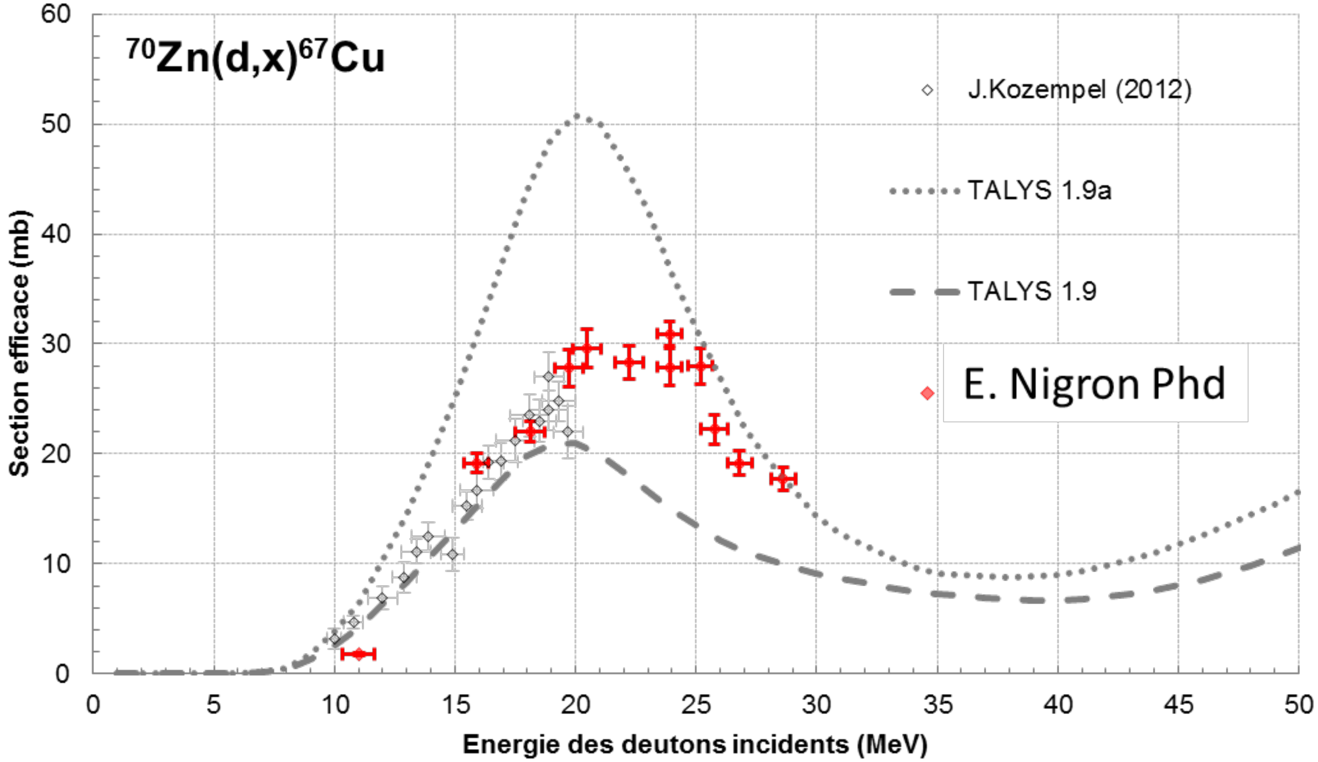
  Used in the USA



Looking to cross section will allow to determine the best ones

Cu-67 production

New cross section dataset for $^{70}Zn(d,x)^{67}Cu$



Cross section is 2 more important than with the proton route

Code calculations fail to reproduce the data

→ **Our data help improve predictions**

What can we do ?

High purity:

- ❑ Nuclear data
- ❑ Mass separation technique to get high purity products

Laser resonance ionization

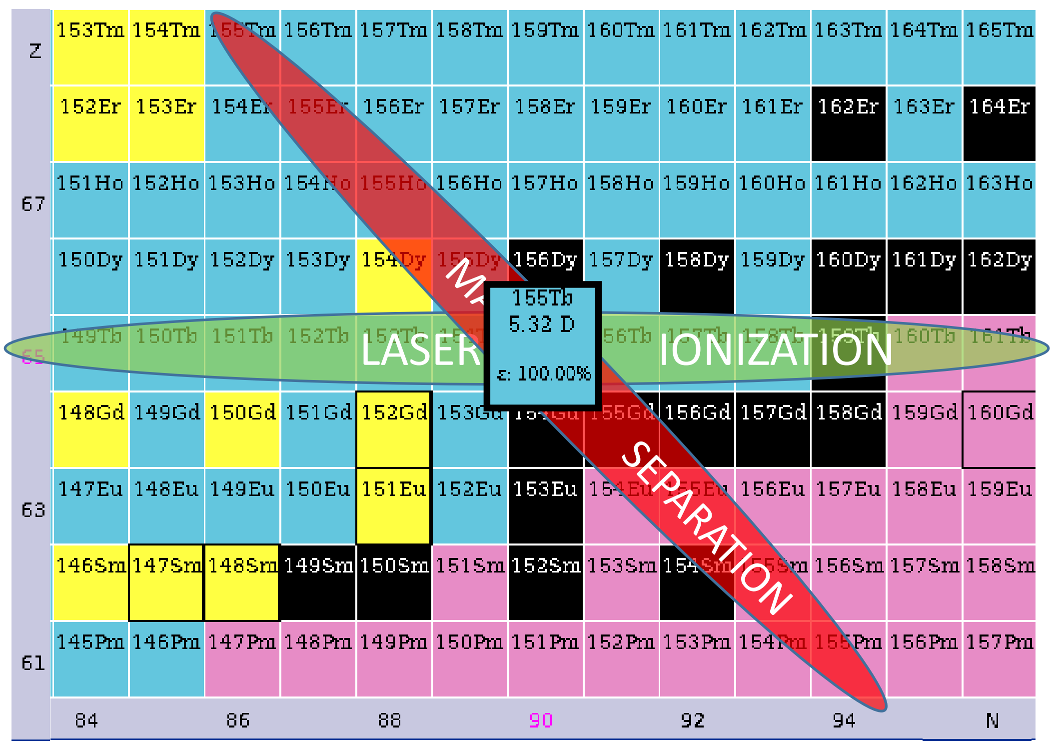
coupled to mass separation

will increase product purity

Arronax is part of the

MEDICIS collaboration

(CERN)



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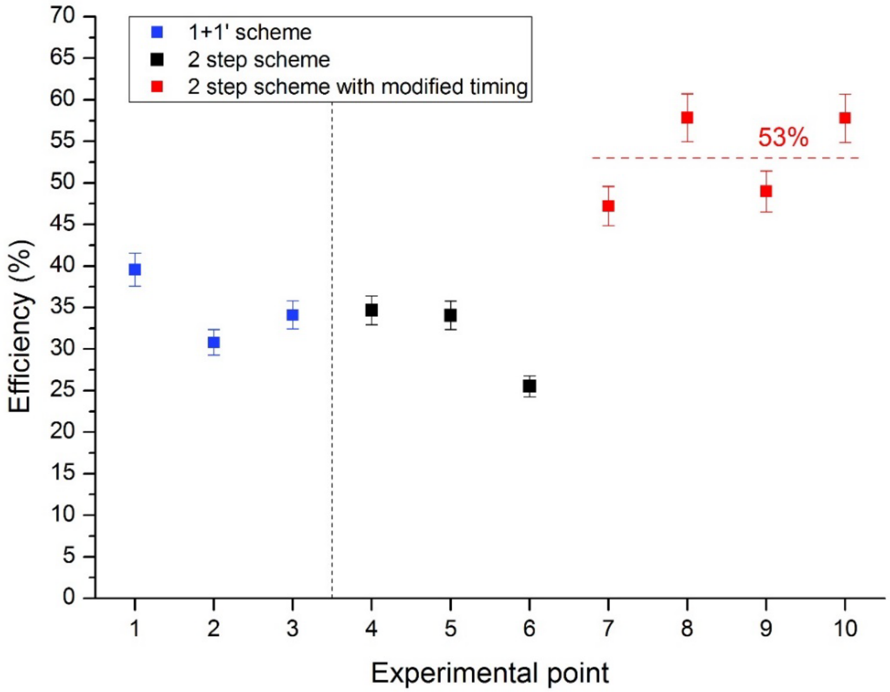
Resonant laser ionization & mass separation: cold experiments

Experiments performed for Tb and lanthanides



Experiments performed at JGU Mainz (LARISSA team)

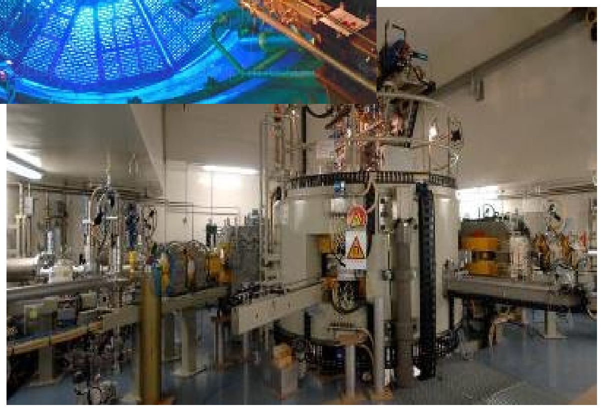
High efficiency obtained for lanthanides using resonant laser ionization

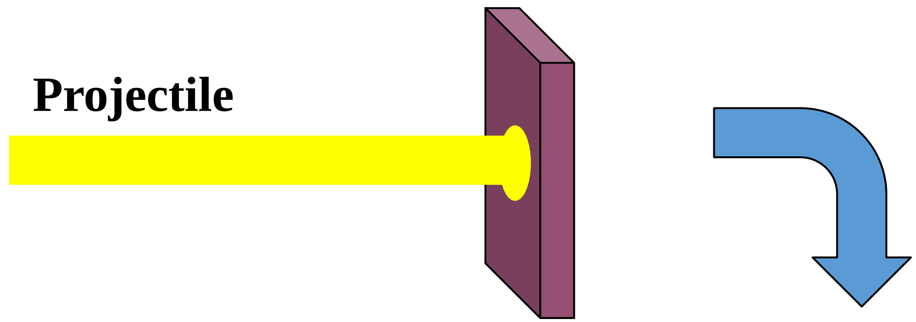
Proof of principle should be performed as soon as MELISSA laboratory@CERN will be ready

V. GADELSHIN et al, NIMB (2019)
https://doi.org/10.1016/j.nimb.2019.04.024

Radionuclides production as part of the MEDICIS@CERN project

How to survive the CERN long shutdown?





Er-169 produced @ILL
Terbium produced @Arronax

Experiment already performed without laser ionization (2018 and 2019)
Soon laser ON

R. Formento et al, NIMB (2019) ,
https://doi.org/10.1016/j.nimb.2019.04.022

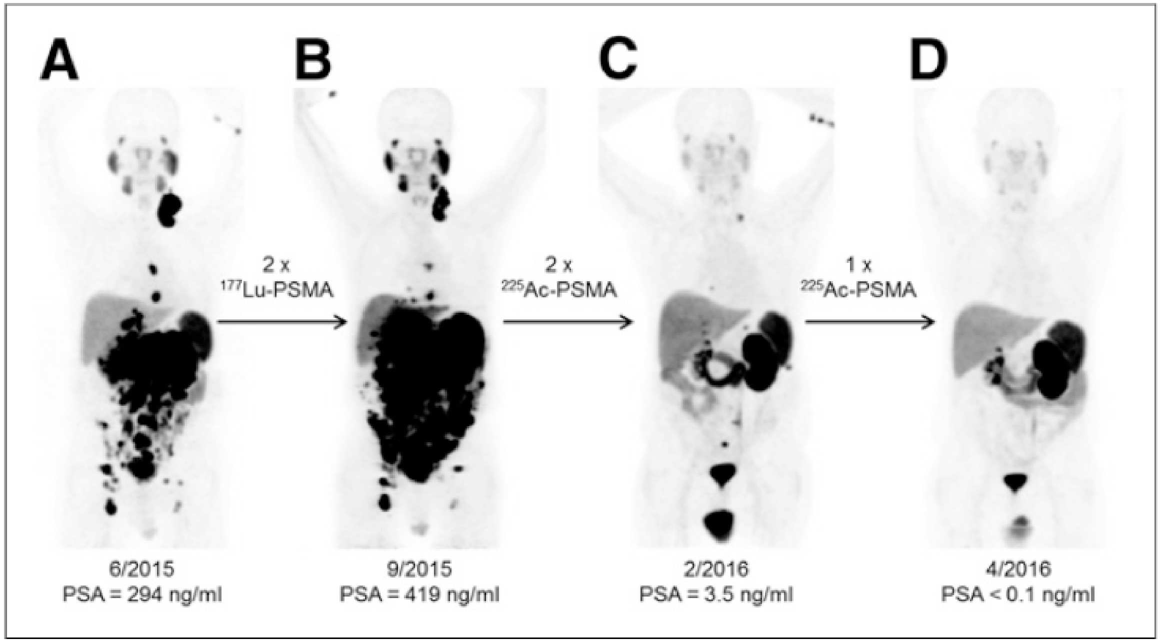
What can we do ?

High purity:

- ❑ Nuclear data
- ❑ Mass separation technique to get high purity products

Innovative radionuclides

- ❑ New isotopes for new concept (44Sc, Tb quadruplet, α emitters,…)



Kratochwil et al.
J Nucl Med 2016; 57:1-4

α-emitters are giving good results

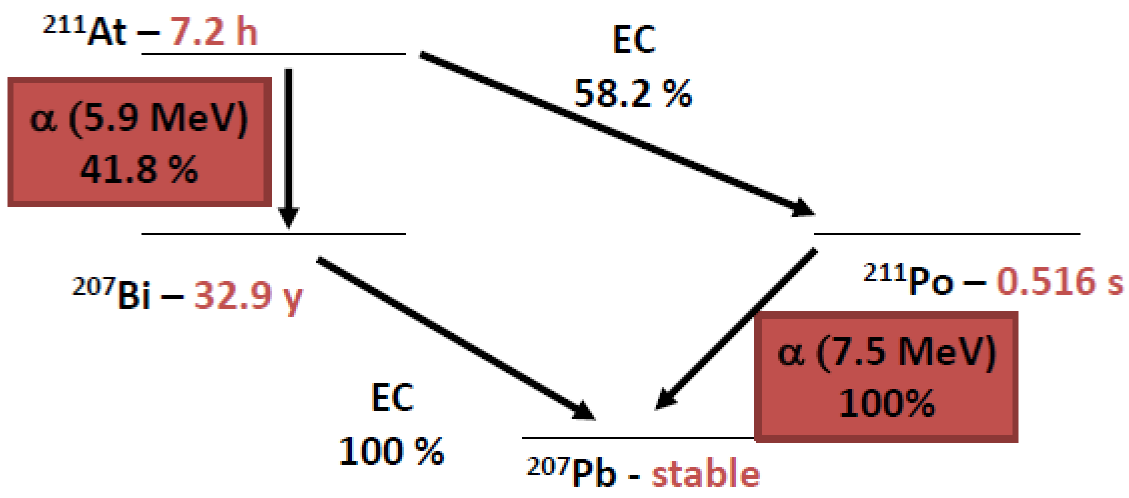
Main α-emitters of medical interest

A limited number of potential candidates

Radionuclide	Half-life (h)	# of alpha particles / decay	Eγ (keV)	Branching Ratio (%)
Tb-149	4,1 h	0,17 (β and ε)	165	26
At-211	7,2 h	1	79	21
Bi-212	1 h	1 (β)	727	7
Bi-213	45 m	1(2β)	440	26
Ra-223	11,4 d	4 (2β)	269	14
Ac-225	10 d	4(2β)	100	1
Th-226	31 m	4	111	3
Th-227	18,7 d	5(2β)	256	7

Astatine-211 is our choice

At-211 characteristics



Nearly ideal alpha emitter:

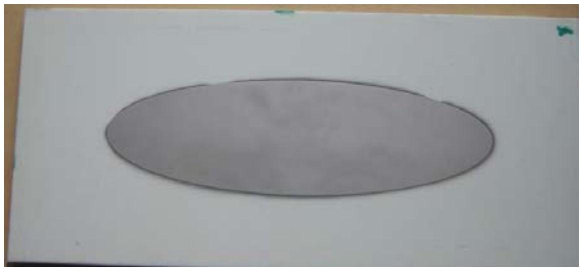
- $T_{1/2}$: not too short nor too long (7,2 h) → suitable for targeting biomolecules
- 2 decay branches leading to the emission of one alpha particle
- Available from accelerator production (28 MeV)

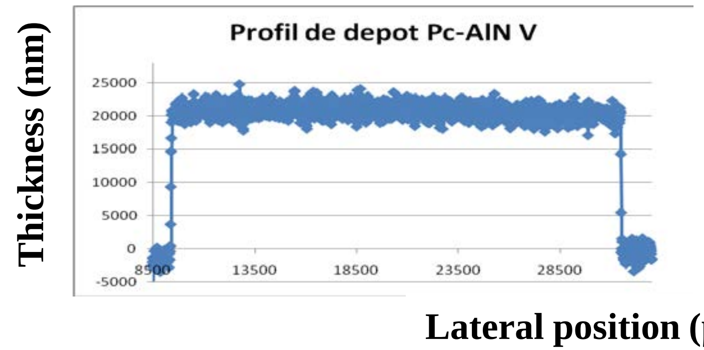
  → **easy to scale-up**

Use of high LET particles: Astine-211

Production route: $^{209}Bi + \alpha \rightarrow {}^{211}At + 2n$

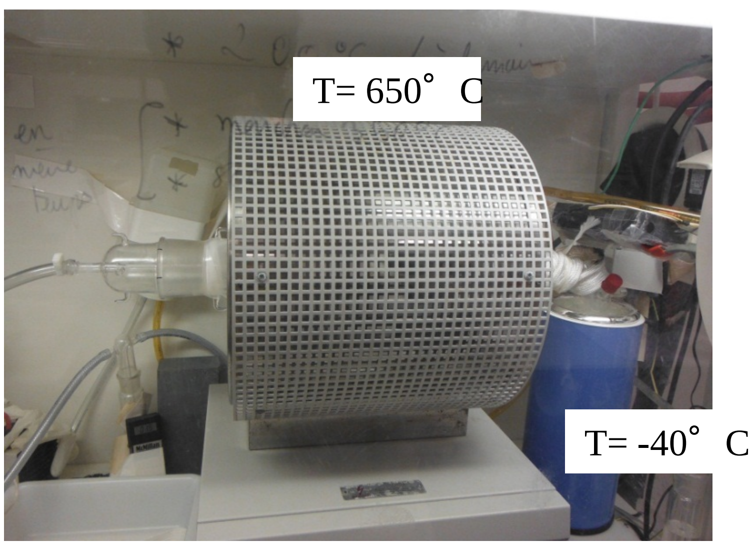
Target preparation (deposition under vacuum)

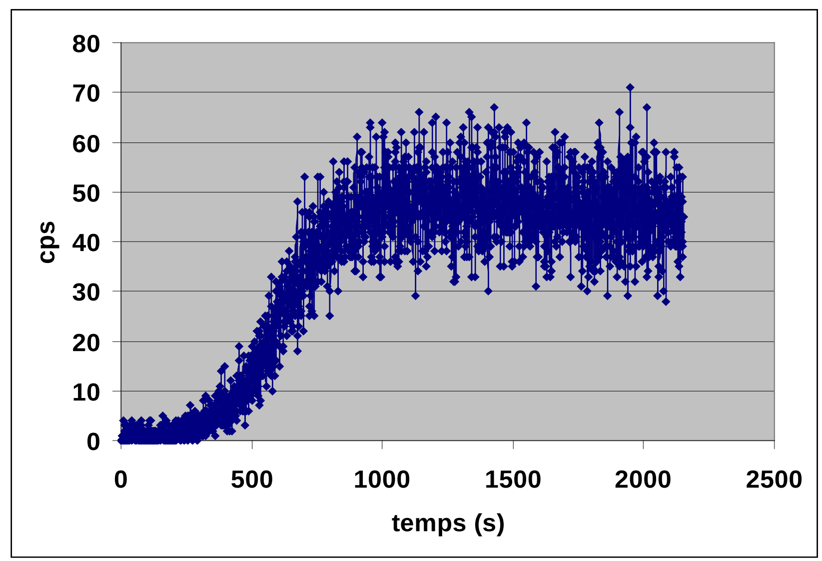




± 5 %

Dry extraction method





Astatine output: few minutes – extraction time around ≈ 2 h – Extraction yield: >80%

What can we do ?

High purity:

- Nuclear data
- Mass separation technique to get high purity products

Innovative radionuclides

- New isotopes for new concept (44Sc, Tb quadruplet, α emitters,…)

Large scale

- Highly intense beams: Targetry, beam diagnostics, activation and maintenance issues

ANR Repare (granted July 2019)

REPARE: research and developements for the Production of innovative radioelements

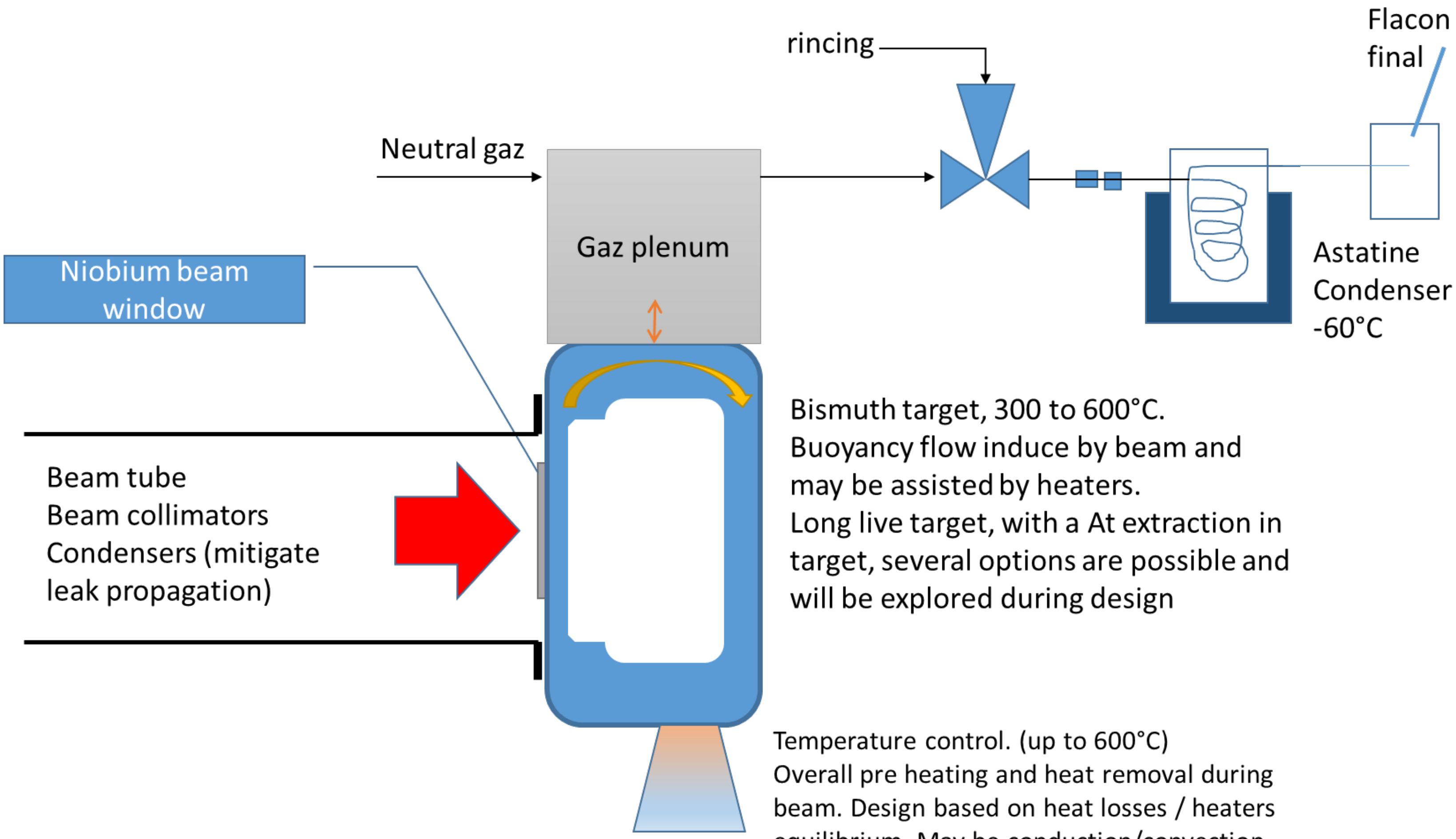
Partners: GANIL(Leader), Subatech, GIP Arronax, LDM-TEP, CERN

Duration : 4 years

Production of Astatine-211

- Cross section measurements of alpha and lithium indiuced reaction on Bi and Pb
- Solid target technology
- Liquid target with on line extraction
- Indirect production ^{211}Rn → ^{211}At using Li beam

The principle of the liquid target with on-line extraction



Bismuth target, 300 to 600°C.
Buoyancy flow induce by beam and may be assisted by heaters.
Long live target, with a At extraction in target, several options are possible and will be explored during design

Temperature control. (up to 600°C)
Overall pre heating and heat removal during beam. Design based on heat losses / heaters equilibrium. May be conduction/convection external drain

What can we do ?

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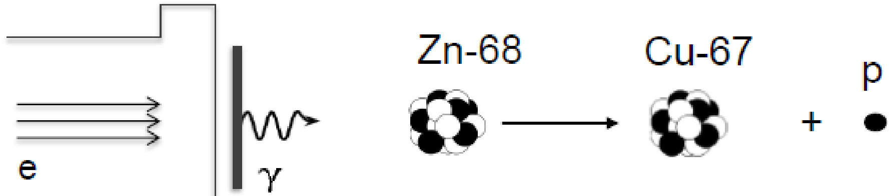
- New isotopes for new concept (44Sc, Tb quadruplet, α emitters,…)

Large scale

- Highly intense beams: Targetry, beam diagnostics, activation and maintenance issues
- New developments in accelerator : electron Linac and photoreaction

Photo-production of Isotopes

NIOWAVE
www.niowaveinc.com



Electrons are accelerated

Electrons brake and produce photons

Photons knock out neutrons (or protons) and new isotopes are formed

$$Y = N \int_{E_{th}}^{E_{max}} \varphi(E) \cdot \sigma(E) dE$$

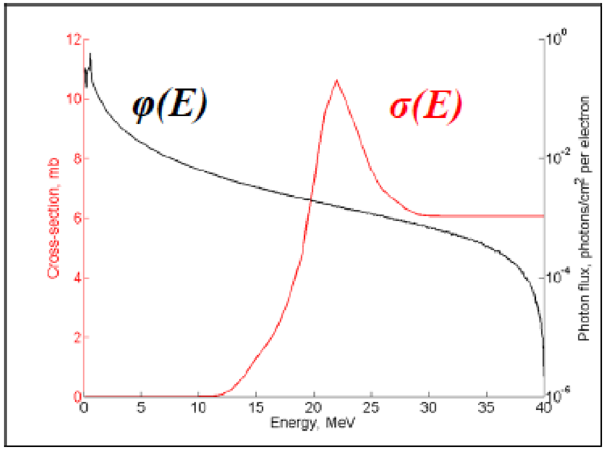


Figure 2. A compact superconducting accelerator used for radioisotope production

Isotopes of interest:
^{99}Mo, ^{67}Cu, ^{225}Ac, …

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What can we do ?

High purity:

- Nuclear data
- Mass separation technique to get high purity products

Innovative radionuclides

- New isotopes for new concept (44Sc, Tb quadruplet, α emitters,…)

Large scale

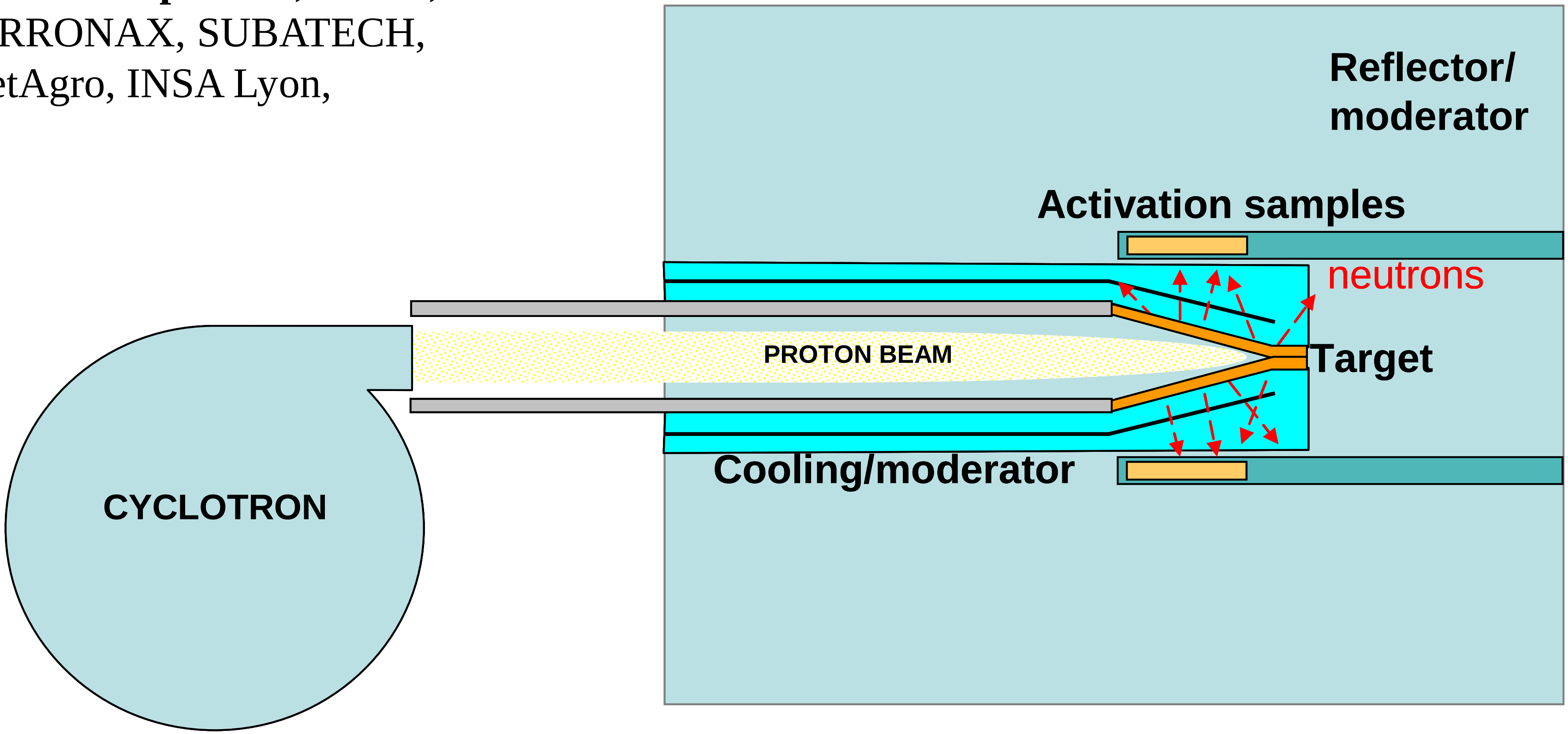
- Highly intense beams: Targetry, beam diagnostics, activation and maintenance issues
- New developments in accelerator: linac or compact cyclotrons

Efficient

- Neutron production without reactor

A Neutron source with industrial capabilities @ Arronax

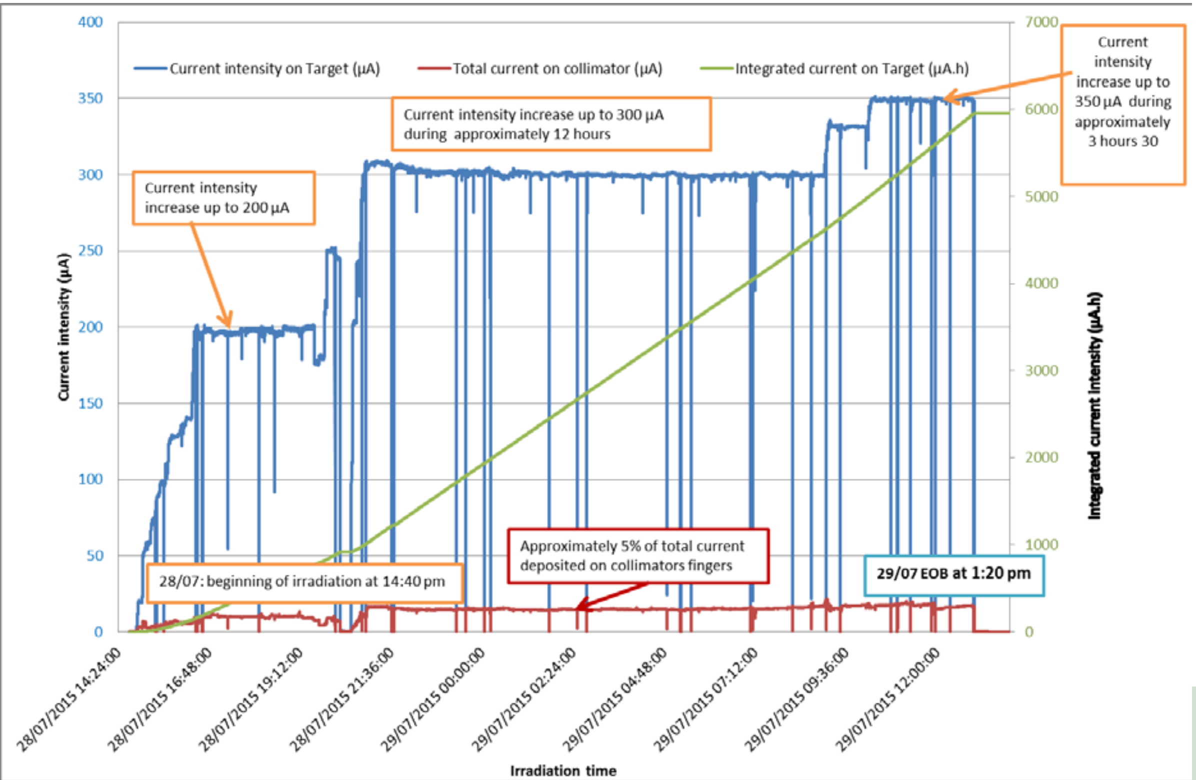
Partnership: AAA, Nanoh, ARRONAX, SUBATECH, vetAgro, INSA Lyon,



350µA , 70 MeV protons → 10^{12} n/s

Our neutron Activator

Loading/unloading station



Partnership: AAA, Nanoh, ARRONAX, SUBATECH, vetAgro, INSA Lyon,

What can we do ?

High purity:

- Nuclear data
- Mass separation technique to get high purity products

Innovative radionuclides

- New isotopes for new concept (44Sc, Tb quadruplet, α emitters,…)

Large scale

- Highly intense beams: Targetry, beam diagnostics, activation and maintenance issues
- New developments in accelerator: linac or compact cyclotrons

Efficient

- Neutron production without reactor
- Alternative production route for established radionuclides

Re-186 ($T_{1/2}$ = 3.7 d - β- emitter)

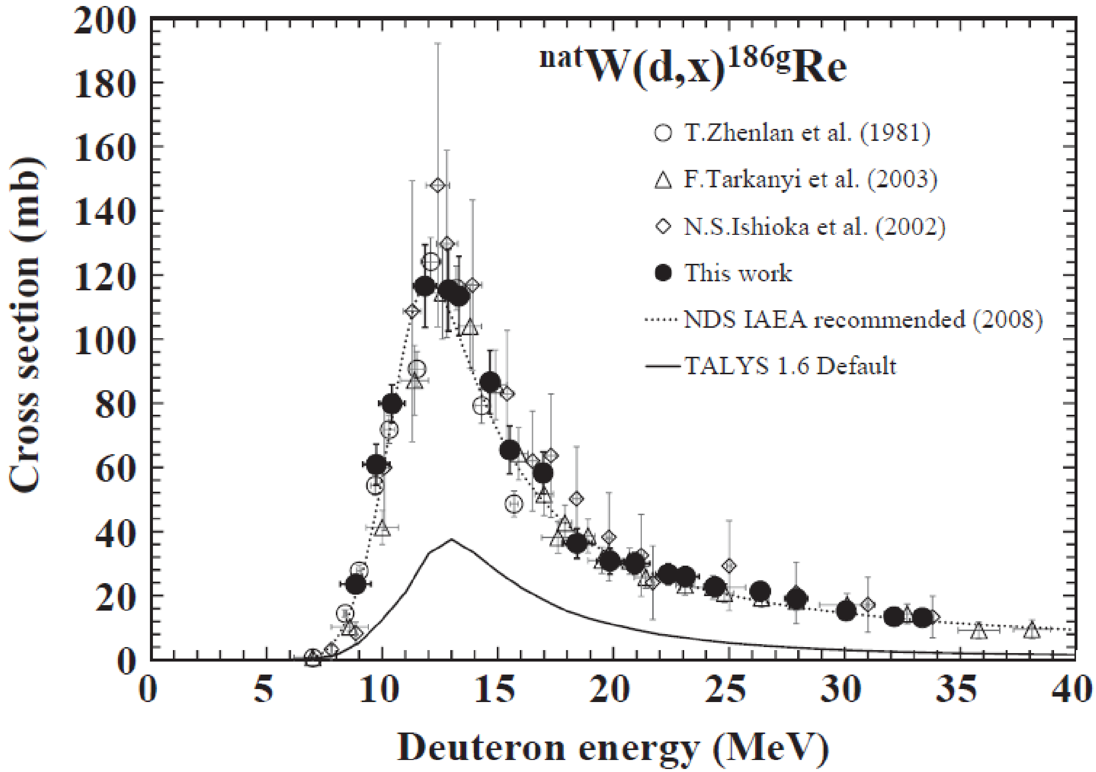


Fig. 1. $^{nat}W(d,x)^{186g}Re$ production cross section.

Deuteron is 3 times more efficient than proton

Conclusions

Nuclear Physics can do a lot for radionuclide production

However, **producing the radionuclide is just the first step**, someone has to use it. For that you need:

1. Produce it on a **regular basis** with the appropriate **quality** and **quantity**

2. Insure that this production capability will stay **available for several years (**small animals studies and clinical trials take time)

3. Produce it as an **Active Pharmaceutical Ingredient**
   → A quality assurance program helps

Thank you for your attention

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the **Université de Nantes**
the **French government** (CNRS, INSERM)
the **European Union**.

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