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La production de radio-isotopes avec des cyclotrons

Arnaud Guertin, Ferid Haddad

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GUERTIN Arnaud

Subatech Laboratory – UMR 6457
CNRS Research Officer



IN2P3

Institut national de **physique nucléaire**
et de **physique des particules**

La production de radio-isotopes avec des cyclotrons

A. Guertin and F. Haddad

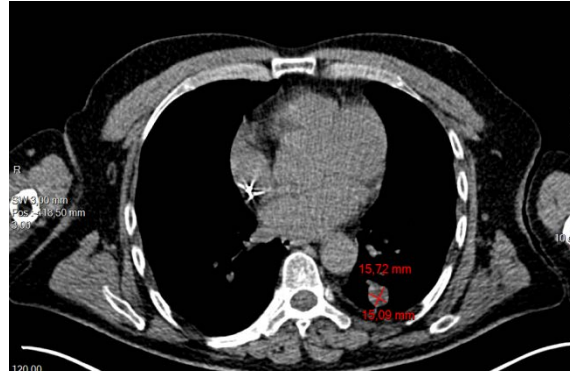
Conventional imaging in oncology

**Visualize and localize tumors, measure them
and evaluate the response to treatments**



Centre François Baclesse

Radiography



Centre René Gauducheau

Computerized Tomography
Scanner



Institut Roi Albert II

Magnetic Resonance
Imaging

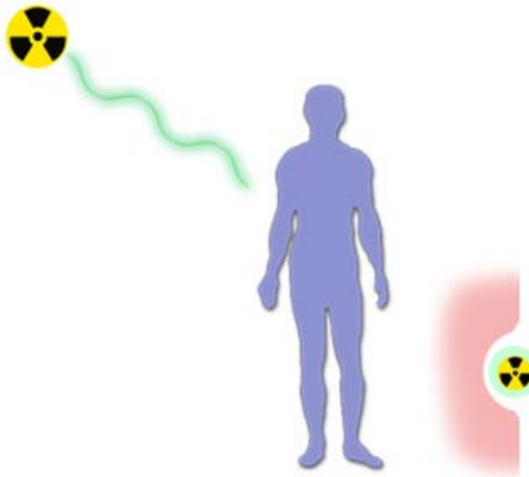
These techniques allow to get accurate information on the morphology but give limited information on the metabolism

A gain can be obtain by coupling them with nuclear medicine technique (SPECT or PET) which gives these information

Conventional radiotherapy

External beam radiotherapy:

- X rays, gamma, electrons
- Hadrontherapy



Brachytherapy
 Curietherapy



Institut de cancérologie de l'Ouest



ProteusOne, IBA



Institut de cancérologie de l'Ouest

These techniques are very efficient to treat a localized disease

Limit: does not target disseminated disease or residual disease

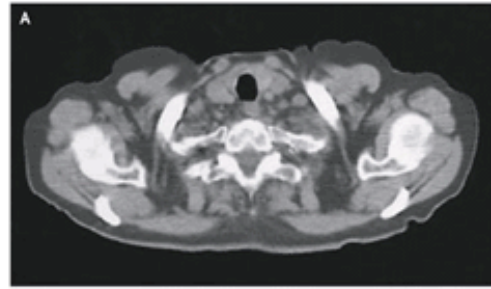
This can be address by nuclear medicine techniques

Great progress in the last ten years

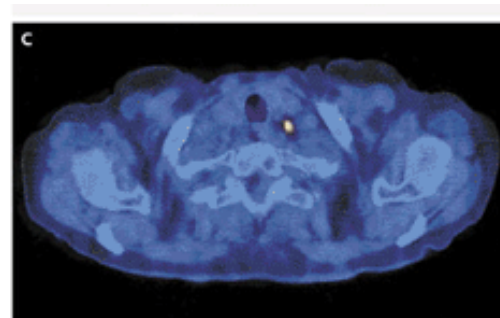
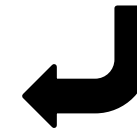
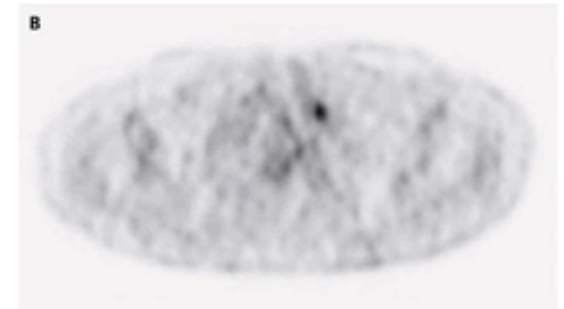
¹⁸F-FDG PET: whole body 3D mapping of a biomarker, non invasive

Multimodality: SPECT/CT, PET/CT then PET/MR

Morphology

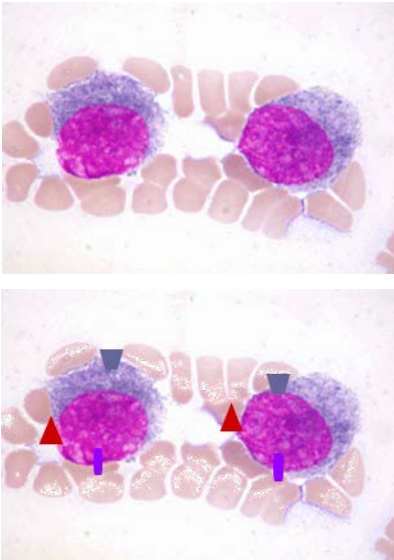


Metabolism



New targets, tracers and radionuclides (béta+, béta-, Auger and alpha)

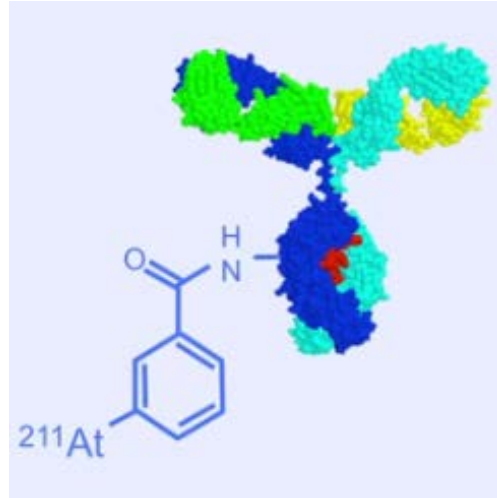
Molecular targeting



From Pr Kraeber-Bodéré

- Receiver: SMS
- Antigen: CEA
- Carrier: GLUT1
- ...

Radiopharmaceutical



GIP ARRONAX

- Peptide
- Antibody
- NorA analog
- Glucose
- ...



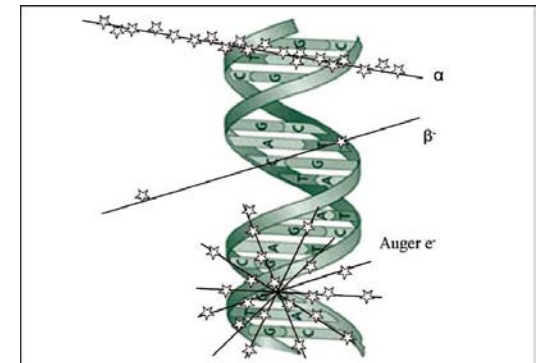
Siemens

Gamma: scint, SPECT/CT



General Electric

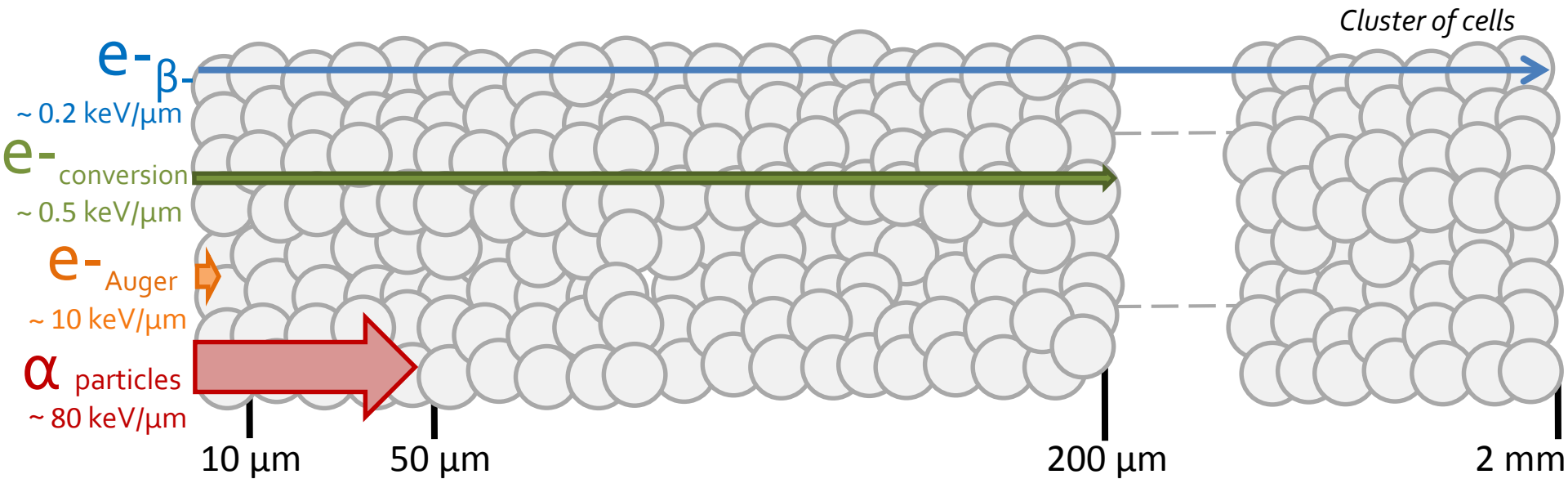
Béta +: PET, PET/CT



JCRT 6, 3, p. 239

Alpha, béta-, Auger e-: therapy

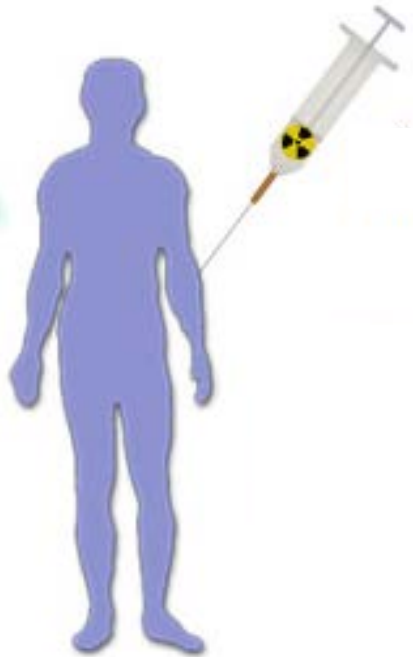
Targeted therapy and LET



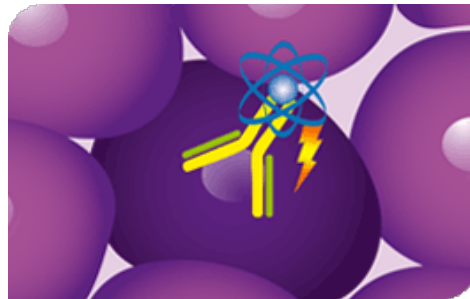
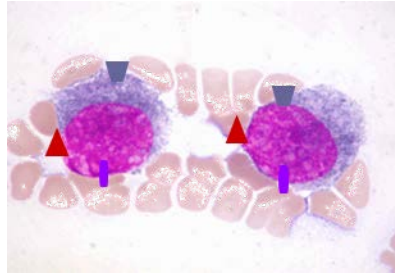
From C. Duchemin PhD defense

Imaging and molecular radiotherapies

Inject a tracer



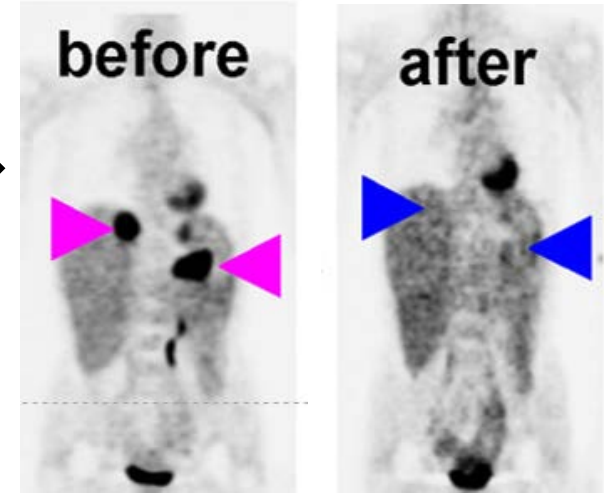
Target a tumor marker



AREVA Med

Detect the disease

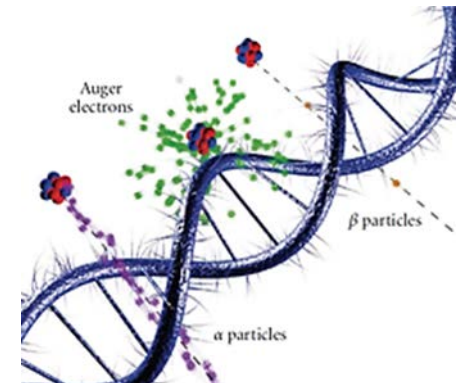
γ, β^+ →



NIRS, Shiba, MIC

Treat the disease

$\beta^-, \alpha,$
 e_{Auger} →



B.Q. LEE et al.

Theranostic radiopharmaceuticals



Predictive imaging,
companion diagnostic



Targeted therapy

THERANOSTICS

M



L

E

C

U

L

E

WANTED

An adequate therapeutic nuclide

A corresponding positron emitter

= (Available matched) pair
of therapeutic and PET nuclides

WANTED

Molecules = targeting vectors

Identical or similar
radiolabelling chemistry

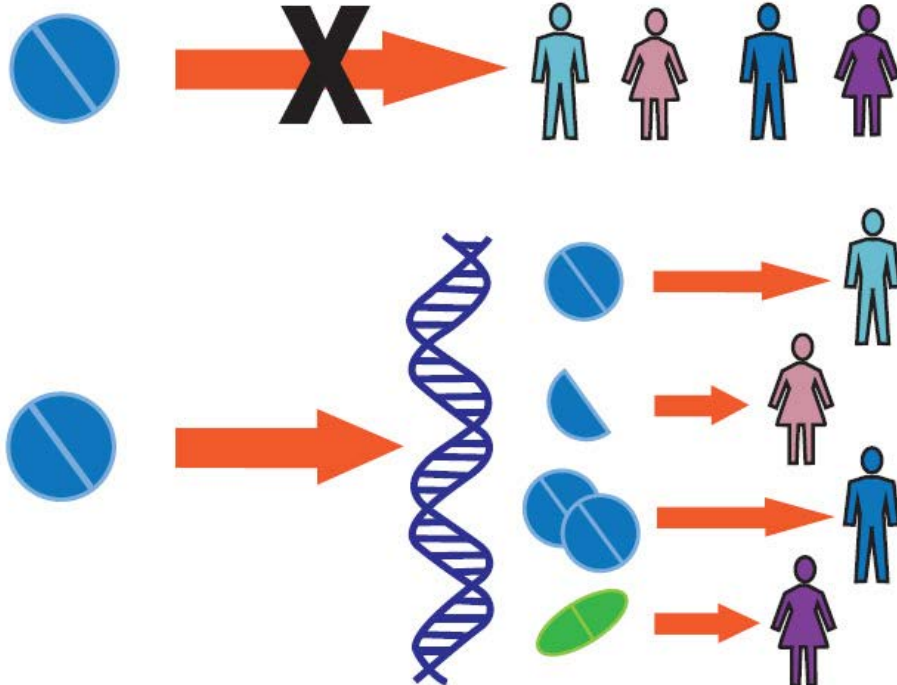
Pharmaceuticals 2017, 10(2), 56

Personalized nuclear medicine

Imaging and diagnosis

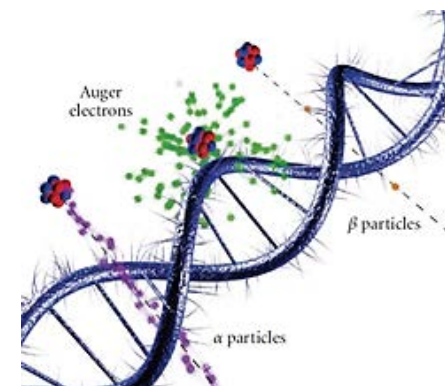
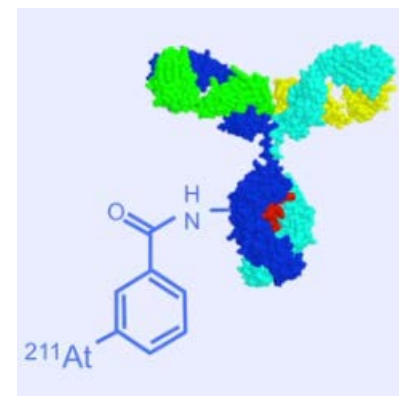
Choose the best treatment

Evaluate its efficacy



Therapy

Destroy tumor cells



The Right Drug

At The Right Time

To The Right Patient

For The Right Disease

With The Right Dosage

Imagery

For SPECT

γ emitters (100 – 250 keV)

^{99m}Tc , ^{123}I , ^{201}Tl

For PET

β^+ emitters

^{11}C , ^{13}N , ^{15}O , ^{18}F ,

^{68}Ge (^{68}Ga), ^{82}Sr (^{82}Rb)

^{64}Cu , ^{124}I

Therapy

β^- emitters (^{32}P , ^{90}Y , ^{131}I , ^{153}Sm , ^{177}Lu)

α emitter (^{211}At)

Auger electron emitters (^{67}Ga , ^{111}In , ^{125}I)

X-ray emitter (^{103}Pd)



^{18}F FDG PET: whole body 3D mapping of a biomarker

Multimodality: SPECT/CT, PET/CT then PET/MR

In biology, **new vectors:** peptides, humanized antibodies, nanobodies ...

New radionuclides are needed to match with these new vectors

A large set of radioisotopes with very different characteristics is suitable:

- **Radiation type** for the different applications
- Half-life – to match the **bio-distribution** time
- Chemical properties – to attach to the **vector molecule**
- Production yields – to get the **purest product**
- Production capacities – to envisaged **large scale use**

The nuclear physicist could have crucial contribution:

- Identify production route and define production process even large scale production (reactors, accelerators by spallation, fission or activation)
- Identify and quantify contaminants
- Define waste management process
- Discuss with physicians to promote its use

Over the last years, several radionuclides have emerged:

- Béta+: Cu-64, Ga-68, Zr-89 ...
- Gamma: Sn-117m ...
- Béta- : Ho-166, Lu-177 ...
- Alpha: At-211, Bi-212, Bi-213, Ra-223, Ac-225 ...
- Theranostic: Sc-44/Sc-47, Cu-64/Cu-67, Ga-68/Lu-177 ...
Terbium quadruplet Tb-149, 152, 155, 161
- Auger: Sn-117m, Tb-155 (at the research level for the moment)

To do so, we possess facility (will possess) available for irradiations equipped with experimental techniques

Production in a nuclear reactor

Examples:

(n,γ) , (n,f) and (n,p) reactions

Production at an accelerator via photonuclear reactions

Examples:

(γ,n) and (γ,p) reactions

Production at a cyclotron

Examples:

p , d , ${}^3\text{He}$ - and α -particle induced reactions

*Nuclear reaction data are needed
for optimisation of production procedure*



IN2P3
Les deux Infinis

A high intensity cyclotron for medical applications



dépasser les frontières

Inserm

Institut national
de la santé et de la recherche médicale



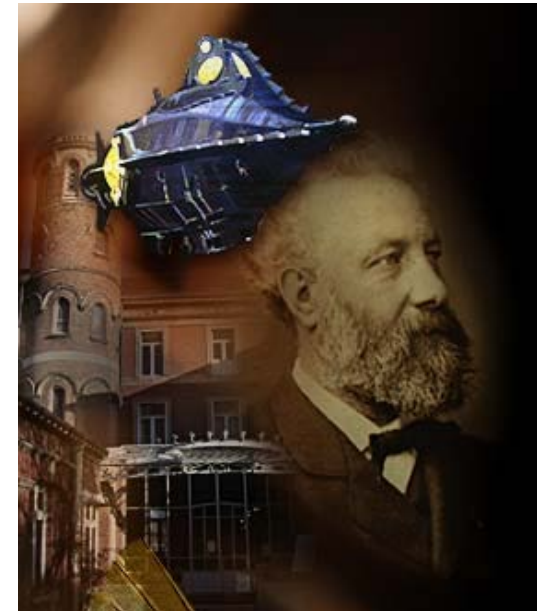
What is ARRONAX ?

ARRONAX is the acronym for

“Accelerator for **R**esearch in **R**adiochemistry and **O**ncology at **N**antes **A**tlantique”

It is both the name of the accelerator and of the facility (GIP ARRONAX)

The name ARRONAX is a tribute to the famous novel writer **Jules Verne** which was born in Nantes in 1828. **Aronnax** is the name of the Professor in the novel « *Twenty Thousand Leagues Under the Sea: A Tour of the Underwater World* » published in 1870



What is ARRONAX ?

Arronax is a “Groupement d'Intérêt Public (GIP)”. It is a mixed economy organization*

Stakeholders are :

– **Research organizations:**

- Centre national de la recherche scientifique (CNRS)
- Institut national de la santé et de la recherche médicale (Inserm)

– **Health institutions:**

- Nantes University Hospital
- Institut de Cancérologie de l'Ouest (ICO), Saint-Herblain

– **Educational institutions:**

- Nantes University
- Mines-Telecom Atlantique

– **Other institutions:**

- The State (Ministère de la Recherche et de l'Enseignement Supérieur)
- Pays de la Loire Regional Council

*legally a governmental entity allowing personnel procurement by the GIP members runs as a company with a private accounting system and private contracts for additional hired staff members

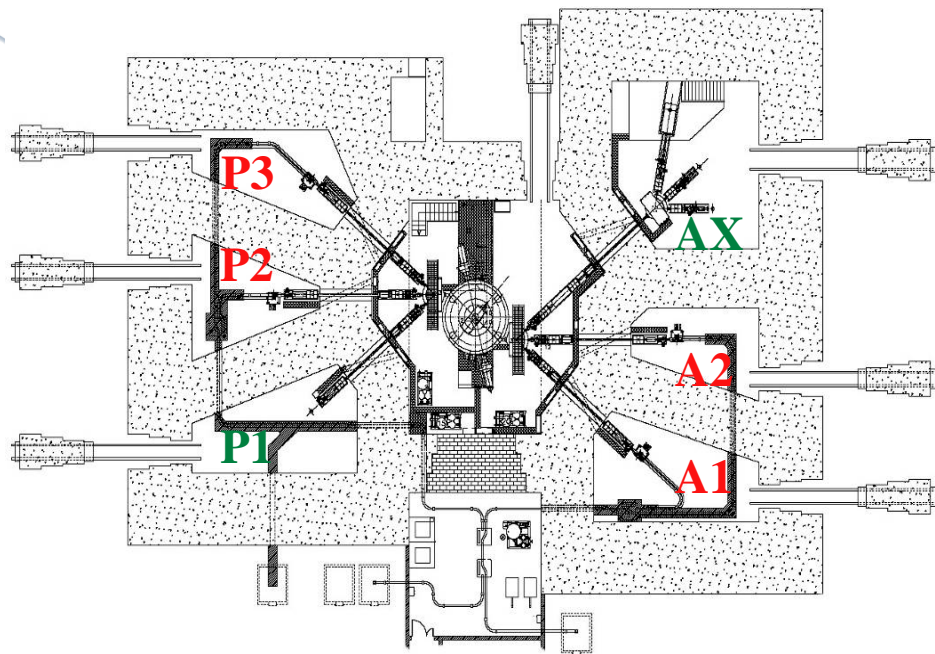
Since 2010 Subatech & ARRONAX launched a program on production of innovative radionuclides



C70 Cyclotron build by IBA:

- 4 sectors isochron cyclotron
- 2 multi-particle sources:
 - H⁻, D⁻: multicusp
 - He²⁺, HH⁺: supernanogan ECR
- 2 extraction lines:
 - stripper or electrostatic deflector

| Extracted | Energy (MeV) | Max. current (μA) |
|------------------|--------------|-------------------|
| H ⁺ | 30 – 70 | 2 x 375 |
| D ⁺ | 15 – 35 | 2 x 50 |
| He ²⁺ | 68 | 70 |
| HH ⁺ | 17 | 50 |

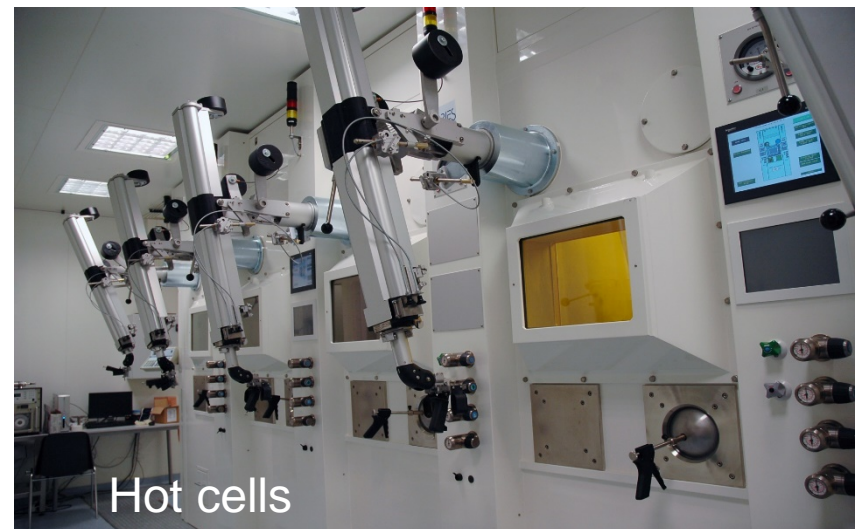


6 experimental vaults

4 vaults connected through a **pneumatic system** to the hot-cells

5 lines of hot cells

2 lines in a sterile environment



– **Radionuclide targeted therapy:**

^{211}At (α emitter)

^{67}Cu , ^{47}Sc (β^- emitters)

– **Theranostic radionuclides:**

Radionuclide pairs β^+/β^- : $^{64/67}\text{Cu}$, $^{44/47}\text{Sc}$

– **Imaging:**

Cardiology: $^{82}\text{Sr}/^{82}\text{Rb}$

Oncology: $^{68}\text{Ge}/^{68}\text{Ga}$

Hypoxia : ^{64}Cu + ATSM

Immuno-PET (^{64}Cu , ^{44}Sc , ...)

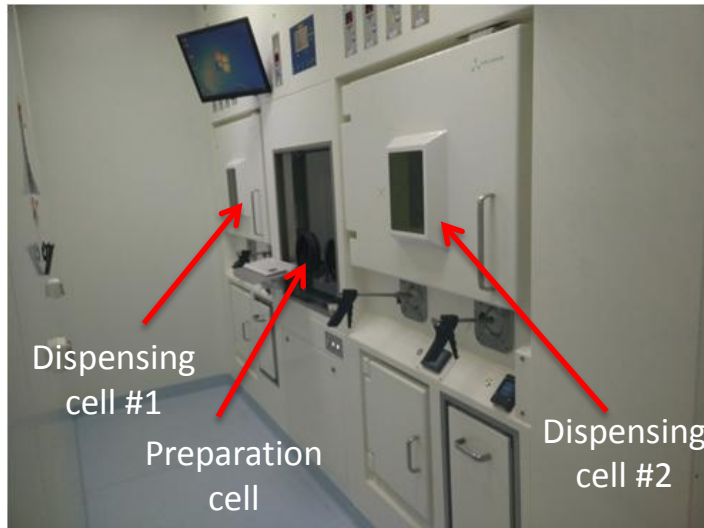
**GMP production
Approved by FDA & ANSM**

– **Neutron production for particle activation:**

^{166}Ho

Goal: produce radiopharmaceuticals for clinical trials (with the Nantes CHU)

- **New hot cells in a sterile environment**



Authorization obtained **from ARS: Feb. 2017**

Funding obtained for 4 clinical trials: 2 with Lu-177, 2 with Cu-64

other under studies with both At-211 and Cu-64

Investigational Medicinal Product Dossiers (IMPD) ongoing.

→ First patient expected May 2018

Targeted alpha-particle radiotherapy

Direct production with alpha particles

Bi-209($\alpha,2n$)At-211, 20.7 MeV

Bi-209($\alpha,3n$)At-210, 28.6 MeV \triangle

At-211 α particles

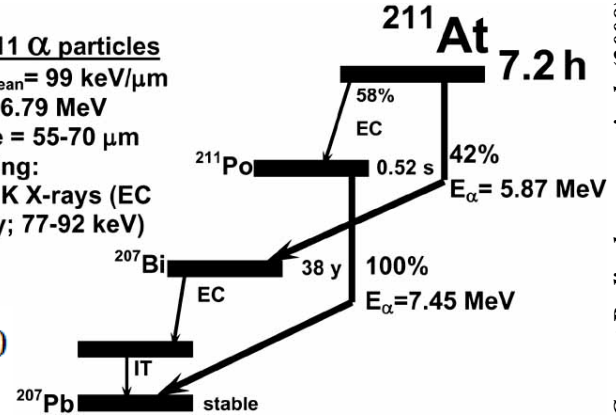
LET_{mean} = 99 keV/ μ m

E_{ave} = 6.79 MeV

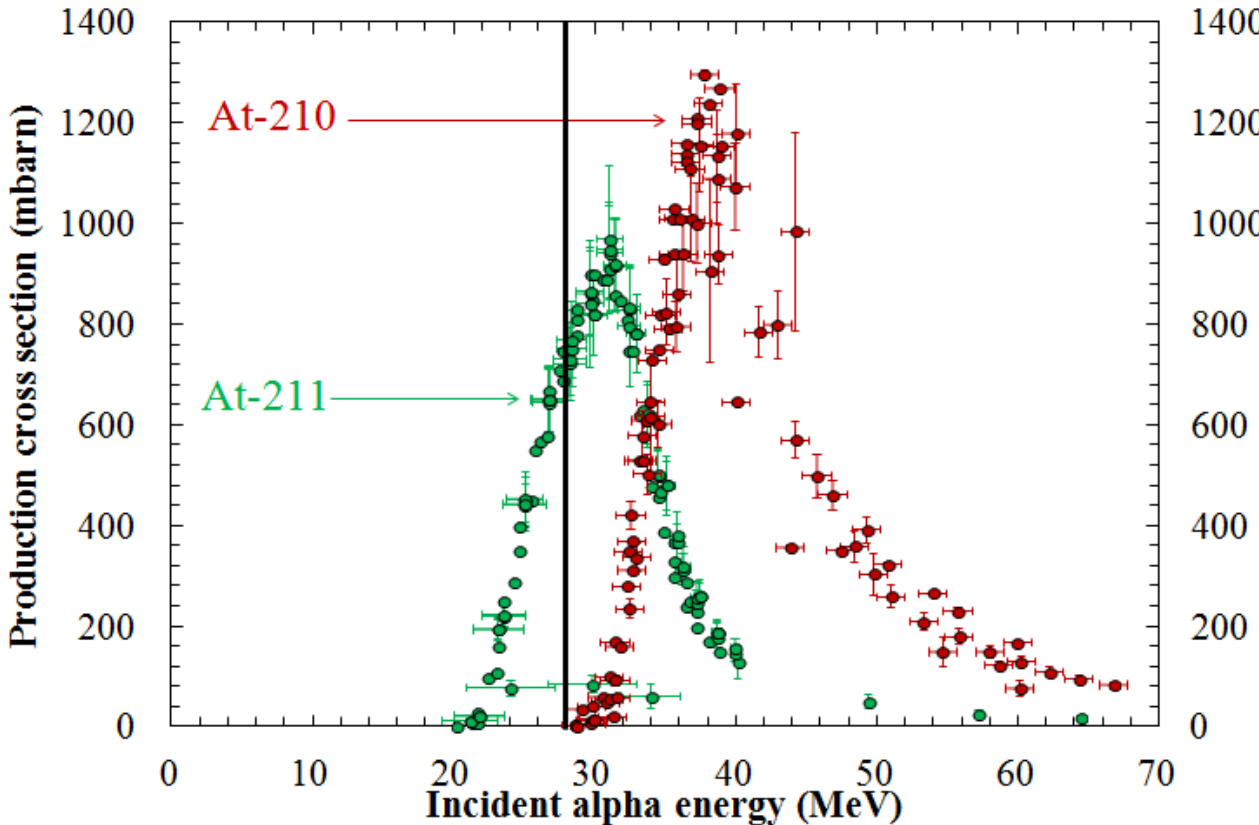
range = 55-70 μ m

Imaging:

²¹¹Po K X-rays (EC decay; 77-92 keV)



Current Radiopharmaceuticals (2008) 1. 177-196.



At-210, T_{1/2} 8.1 h
 decays at 99.8% by EC
 to **Po-210** (138.4 days)
 and at 0.2% by α emission
 to Bi-206 (6.2 days)

Have a good knowledge of the **target isotopic composition**

Control of the **energy dispersion**

Otherwise

Use low energy in order to **limit parasitic reactions**:

- (p,n) reaction to produce ^{11}C , ^{13}Na , ^{18}F

Use **indirect activation modes**:

- secondary neutrons and moderation
- electrons for photonuclear production

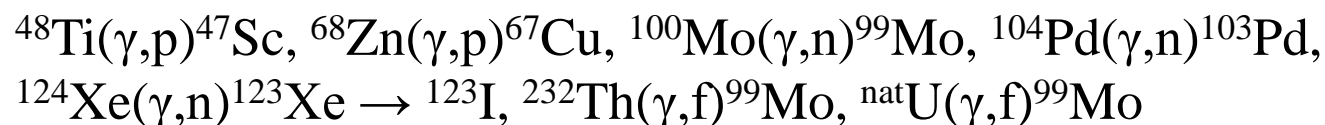
*present day photon sources could not produce radionuclides
in quantities sufficient for medical application*

In the near future, radionuclide production technology will strongly depend on:

- Research reactors
- Small and medium-sized cyclotrons, often accelerating multiple particles, to energies up to about 30 MeV

In the medium to long term range, however, newer irradiation facilities are expected to be developed:

- Intermediate energy proton accelerators
- Spallation neutron sources
- High-energy and high-intensity photon sources [to compensate for the low cross section]



Photoproduction

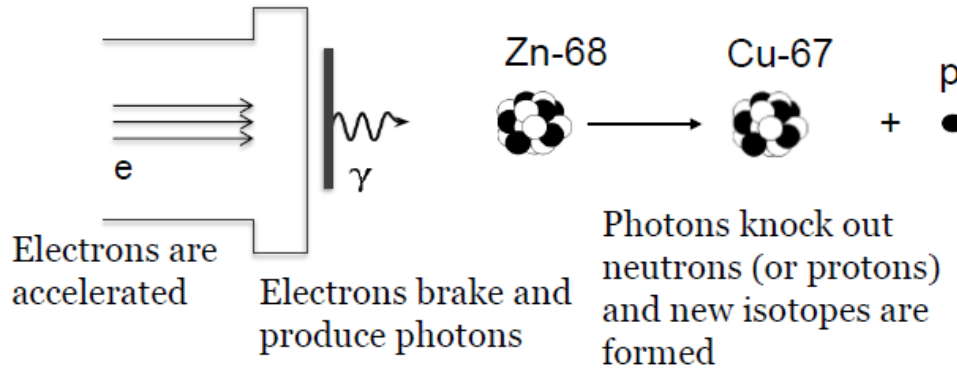
(γ, n) threshold 8 MeV maximum σ at about 15 MeV around 150 mb

(γ, p) threshold 10 MeV, maximum σ between 20 and 30 MeV around 10 mb



Photo-production of Isotopes

NIOWAVE
 www.niowaveinc.com

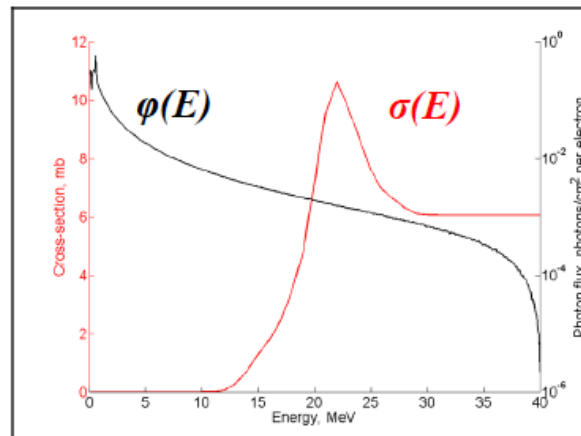


Two major advantages of the photon-induced reactions as compared to the charged particle induced reactions:

large thick samples can be irradiated

heat dissipation is no problem

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



Nuclear medicine

Cyclotrons and accelerators being used in an increasing number of countries along with reactors

- Diagnosis (γ , β^+)
- Therapy (β^- , α , e_{Auger})

Many useful / potentially useful isotopes identified for applications in nuclear medicine

- Personalized medicine

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

Nuclear data

- **Accurate and reliable** sets of data
Statistical + systematic errors < 10%
- Well defined **production routes and decay properties**
neutron, light charged particles, ions and photons
- **Optimum production of specific radionuclides**, minimization / elimination of **impurities**, realistic dose calculations, monitor reactions

In the medium to long term range

Newer irradiation facilities are expected to be developed:

intermediate energy accelerators, spallation neutron sources, high intensity photon sources

Thank you for your attention

Acknowledgments to the Workshop organization committee

“La production de radio-isotopes avec des cyclotrons”

Guertin A.¹, Haddad F.^{1,2}

1 SUBATECH, IMT Atlantique, Université de Nantes, CNRS/IN2P3, Nantes, France

2 GIP ARRONAX, 1 rue Aronnax, 44817 Saint-Herblain cedex – France