La production de radio-isotopes avec des cyclotrons

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CNRS Research Officer

La production de radio-isotopes avec des cyclotrons

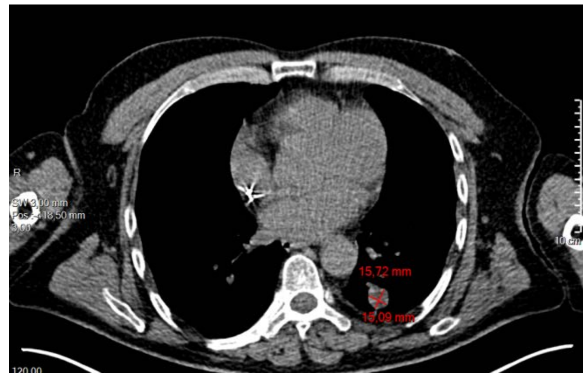
A. Guertin and F. Haddad

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

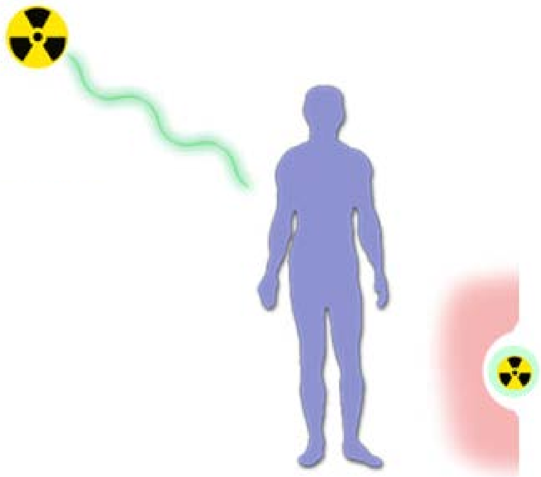
Magnetic Resonance Imaging

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

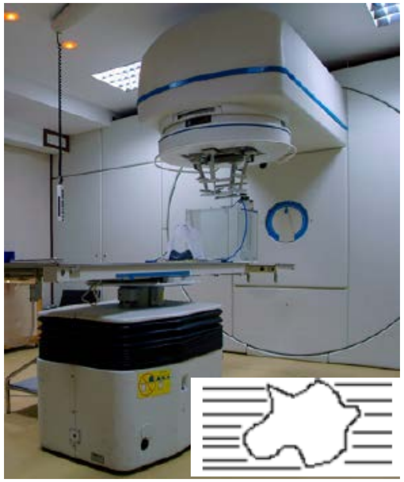
A gain can be obtain by coupling them with nuclear medicine technique (SPECT or PET) which gives these information

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

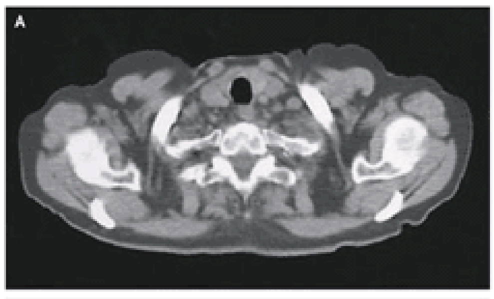
This can be address by nuclear medicine techniques

Great progress in the last ten years

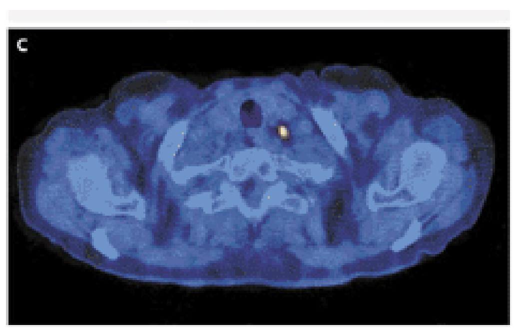
18FDG PET: whole body 3D mapping of a biomarker, non invasive

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

Morphology



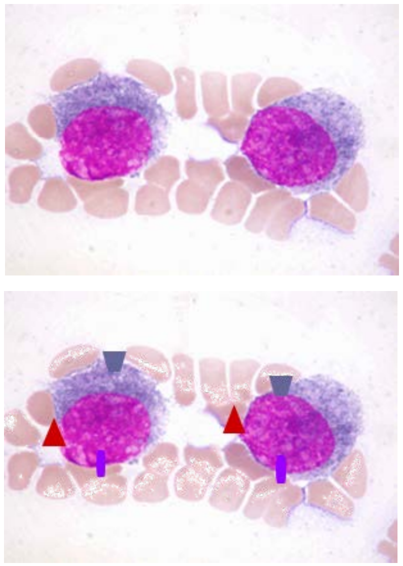
Metabolism



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

Nuclear medicine

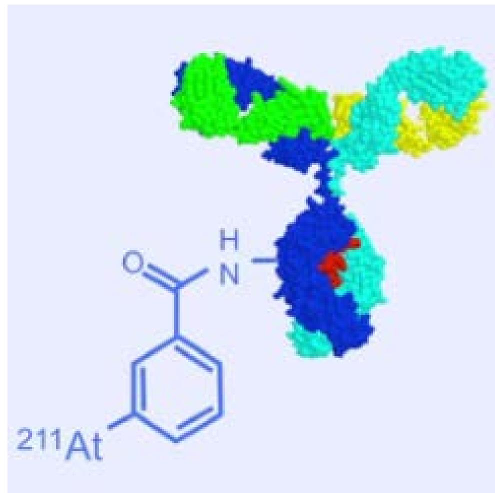
Molecular targeting



From Pr Kraeber-Bodéré

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

Radiopharmaceutical



GIP ARRONAX

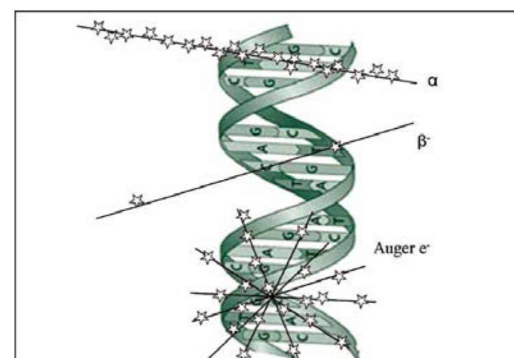
- Peptide
- Antibody
- NorA analog
- Glucose
- …

Gamma: scint, SPECT/CT

Siemens

Béta +: PET, PET/CT

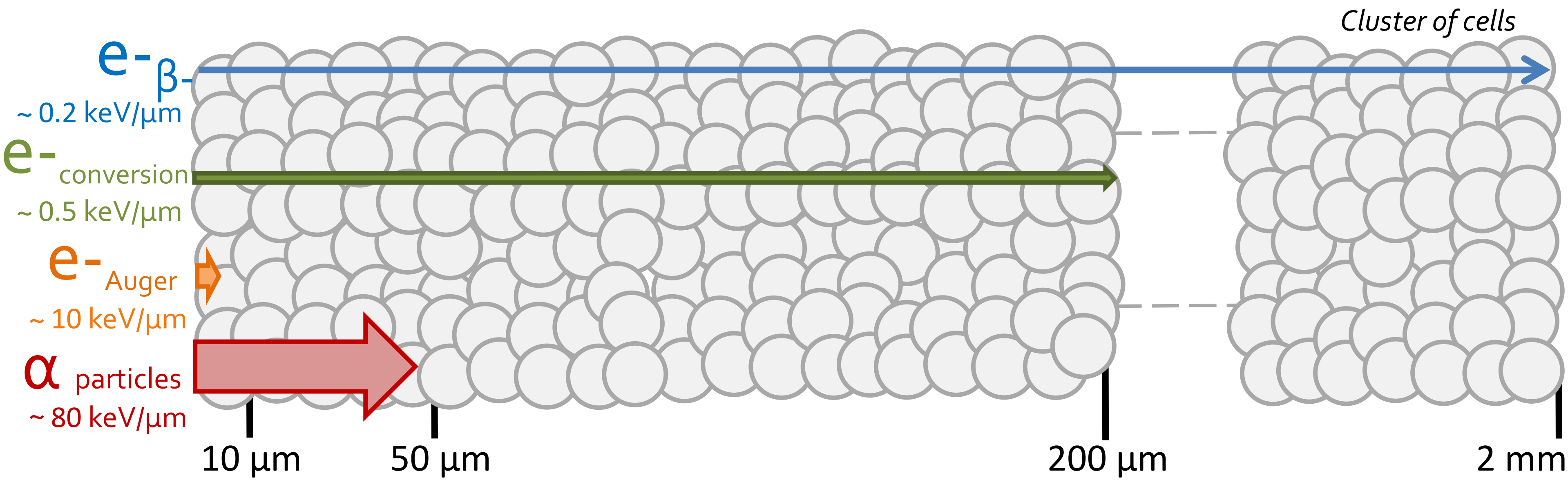
General Electrics



Alpha, béta-, Auger e-: therapy

JCRT 6, 3, p. 239

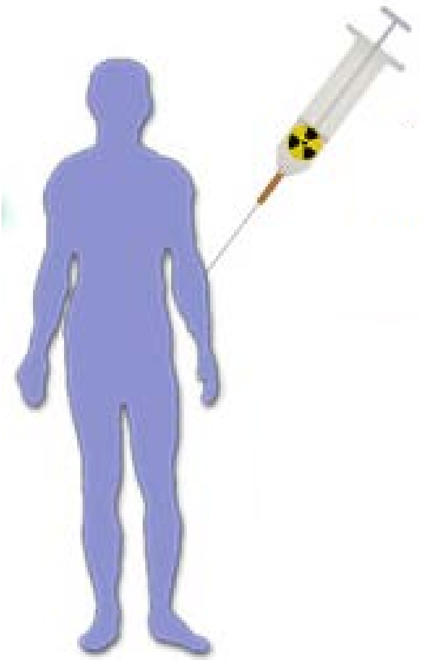
Targeted therapy and LET



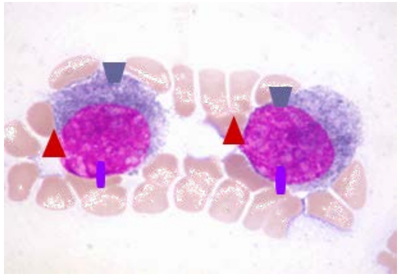
From C. Duchemin PhD defense

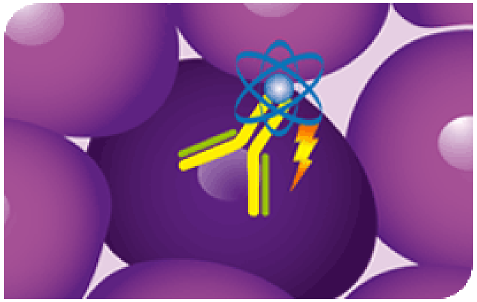
Imaging and molecular radiotherapies

Inject a tracer



Target a tumor marker



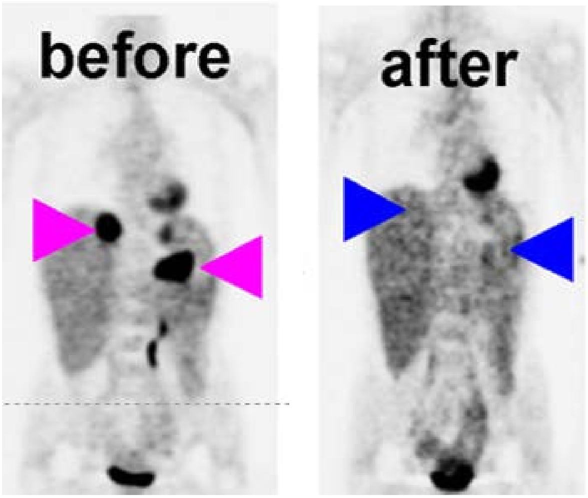


AREVA Med

γ, β+ ➡

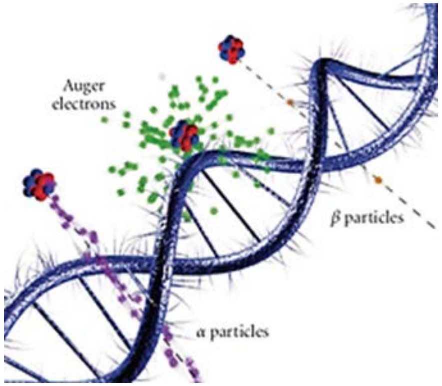
β-, α, e_{Auger} ➡

Detect the disease



NIRS, Shiba, MIC

Treat the disease

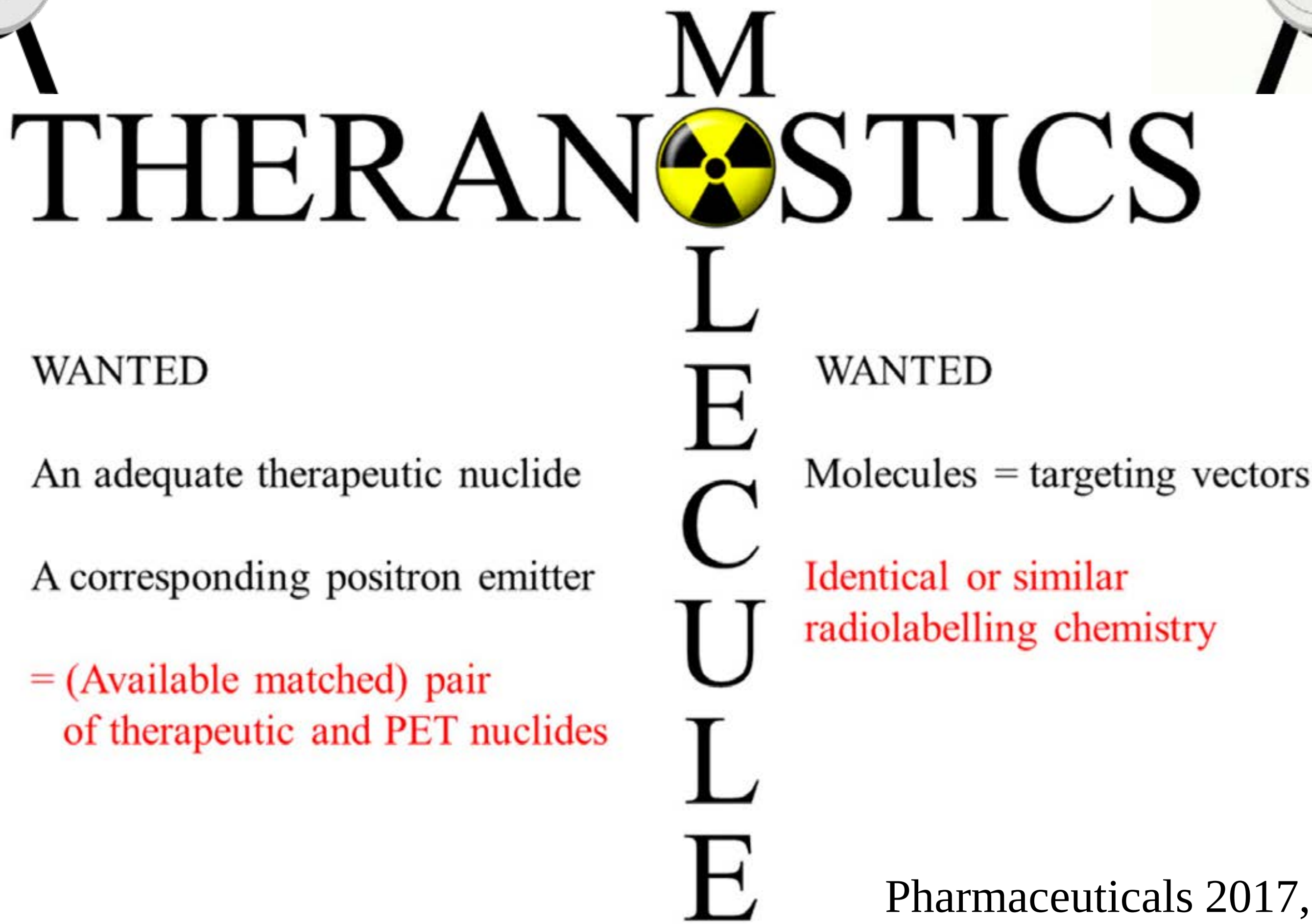


B.Q. LEE et al.

Theranostic radiopharmaceuticals

Predictive imaging,
companion diagnostic

Targeted therapy



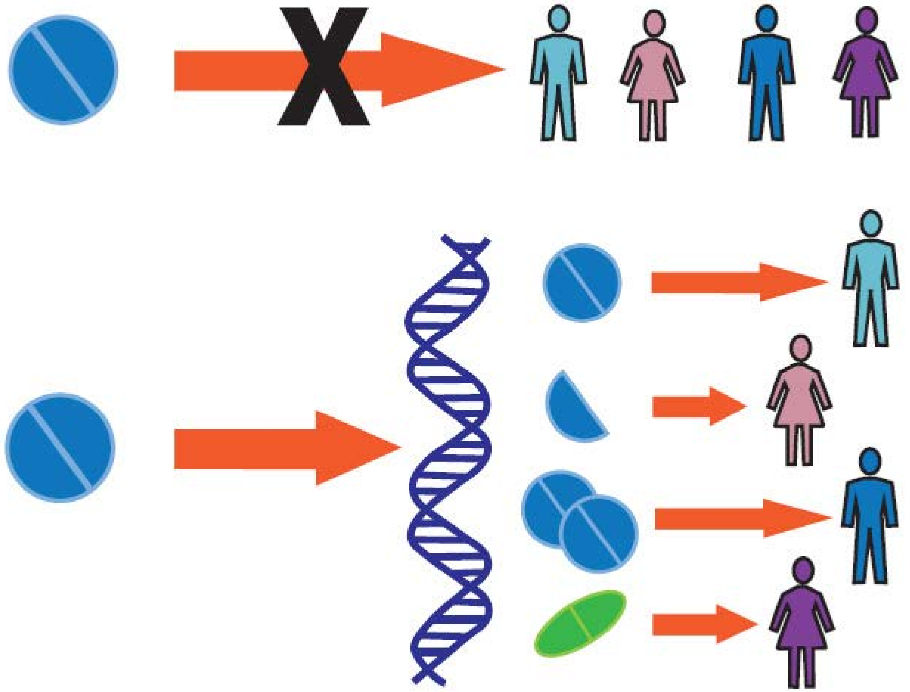
Pharmaceuticals 2017, 10(2), 56

Personalized nuclear medicine

Imaging and diagnosis

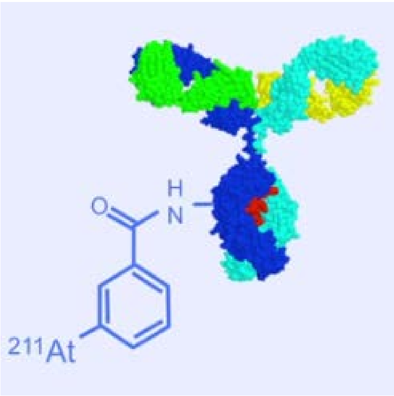
Choose the best treatment

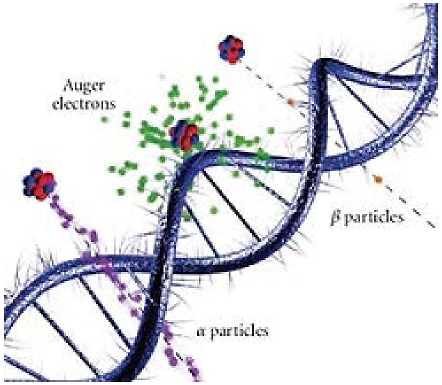
Evaluate its efficacy



Therapy

Destroy tumor cells





The Right Drug   To The Right Patient   For The Right Disease

At The Right Time   With The Right Dosage

Radionuclides commonly used in nuclear medicine

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)

Challenges address to nuclear physicists

^{18}**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**

Role of the physicist

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

Main production modes

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}He- and α-particle induced reactions

Nuclear reaction data are needed
for optimisation of production procedure

A high intensity cyclotron for medical applications

CNRS IN2P3 Les deux infinis

Région Bretagne

Région Pays de la Loire

Région Poitou Charentes la démocratie participative

Université de Nantes

Agence Nationale de la Recherche ANR

République Française — Préfecture de la région Pays de la Loire — Préfecture de la Loire-Atlantique

angers loire métropole communauté d'agglomération

Académie Nantes — Ministère de l'Éducation Nationale — Ministère de l'Enseignement Supérieur et de la Recherche

Nantes Métropole communauté urbaine

Loire Atlantique Conseil général

Anjou Conseil Général Département de Maine-et-Loire

CNRS dépasser les frontières

Inserm Institut national de la santé et de la recherche médicale

Mines Nantes

Centre Hospitalier Universitaire de Nantes

Institut de Cancérologie de l'Ouest

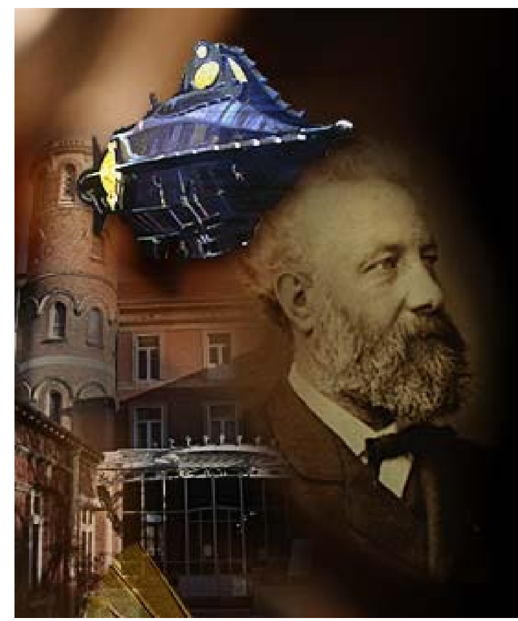
What is ARRONAX ?

ARRONAX is the acronym for

“**A**ccelerator 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

Experimental facility

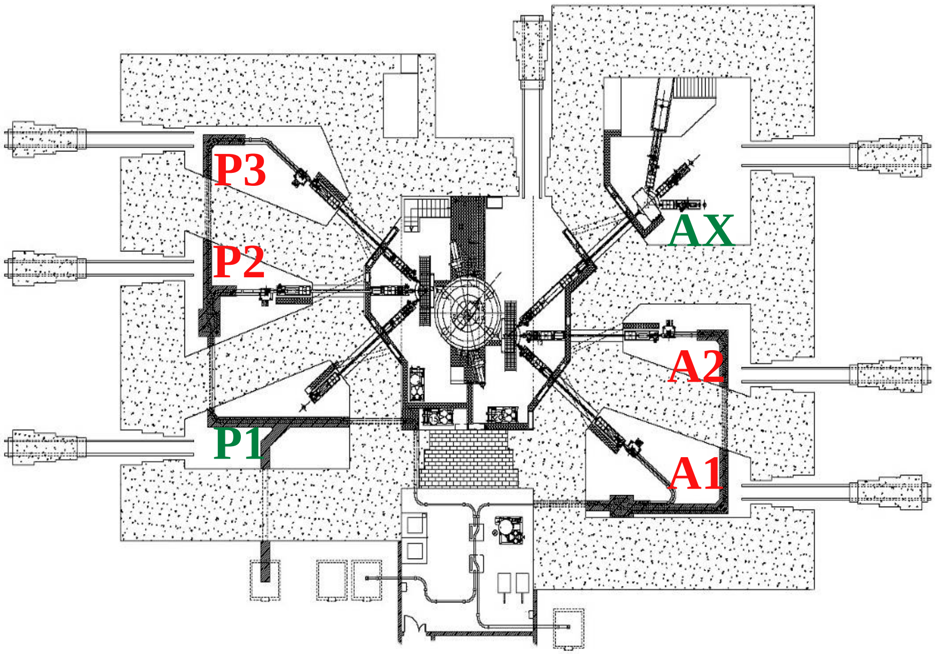
Since 2010 Subatech & ARRONAX launched a program on production of innovative radionuclides

C70 Cyclotron build by IBA:

- **4 sectors** isochron **cyclotron**
- **2 multi-particle sources**:
  - H^-,D^-: multicusp
  - He^{2+},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

ARRONAX facility

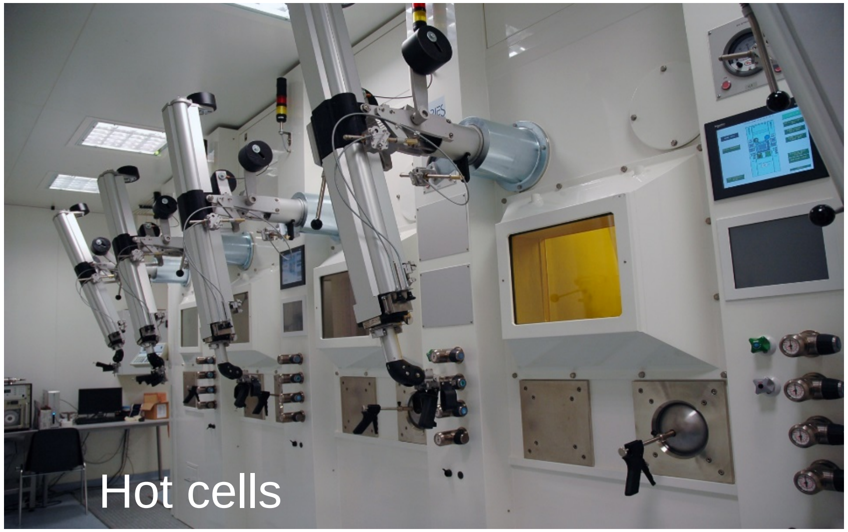


6 experimental vaults

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

5 lines of hot cells

2 lines in a sterile environment



Radionuclides production : ARRONAX priority list

- **Radionuclide targeted therapy**:

  ^{211}**At** (α emitter)

  ^{67}Cu, ^{47}Sc (β^- emitters)

- **Theranostic radionuclides**:

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

- **Imaging**:

  Cardiology: ^{82}**Sr**/^{82}**Rb**

  GMP production
  Approved by FDA & ANSM

  Oncology: ^{68}Ge/^{68}Ga

  Hypoxia : ^{64}**Cu + ATSM**

  Immuno–PET (^{64}**Cu**, ^{44}Sc, …)

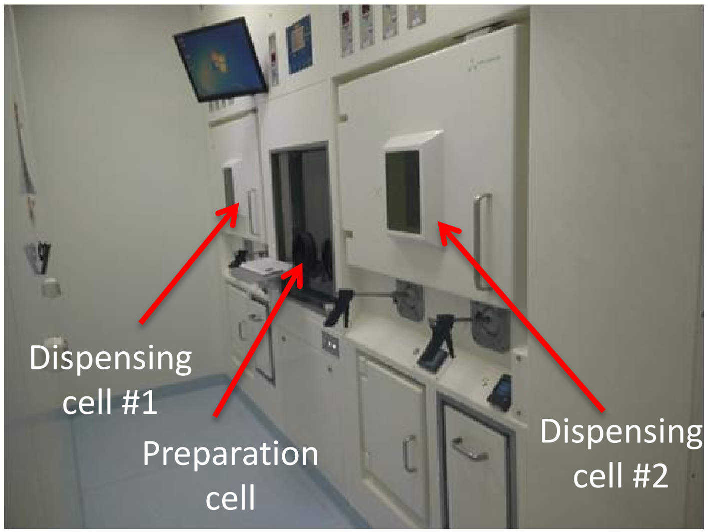
- **Neutron production for particle activation**:

  ^{166}Ho

ARRONAX radiopharmacy

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

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



Automates for radio-synthesis and aseptic dispensing

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

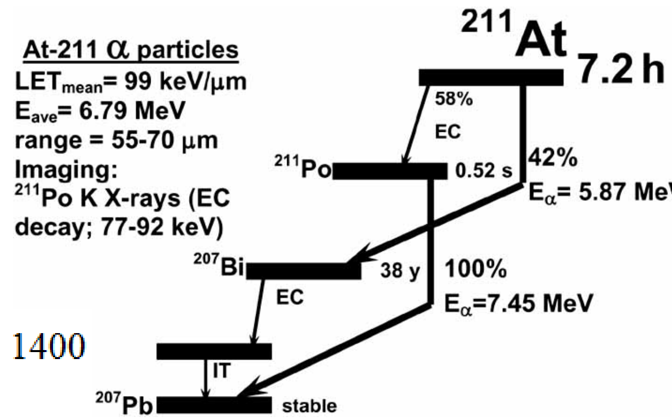
Focus on contaminants: At-211 production

Targeted alpha-particle radiotherapy

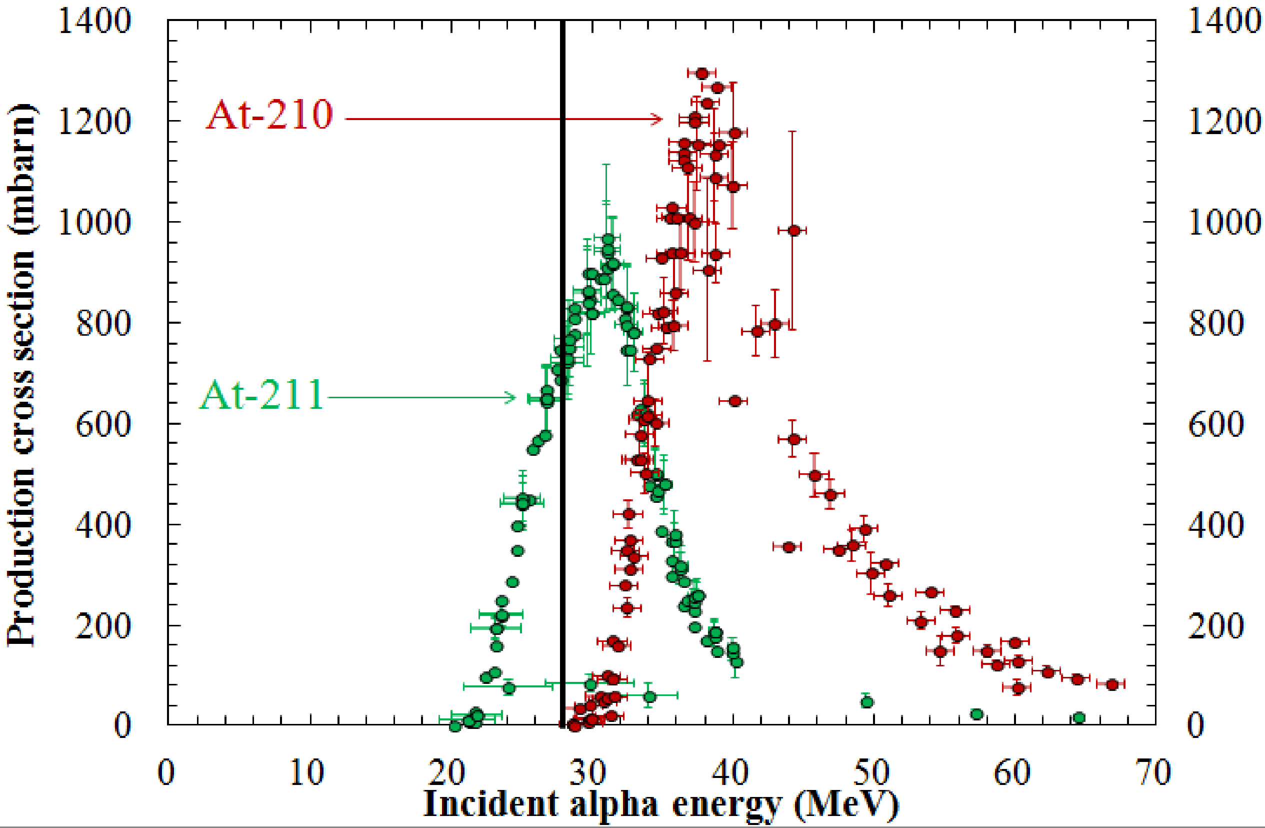
Direct production with alpha particles

Bi-209(α,2n)At-211, 20.7 MeV

Bi-209(α,3n)At-210, 28.6 MeV ⚠



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)

Comments

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

Development of newer irradiation technologies

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]

^{48}Ti(γ,p)^{47}Sc, ^{68}Zn(γ,p)^{67}Cu, ^{100}Mo(γ,n)^{99}Mo, ^{104}Pd(γ,n)^{103}Pd,
^{124}Xe(γ,n)^{123}Xe $\rightarrow$ ^{123}I, ^{232}Th(γ,f)^{99}Mo, ^{nat}U(γ,f)^{99}Mo

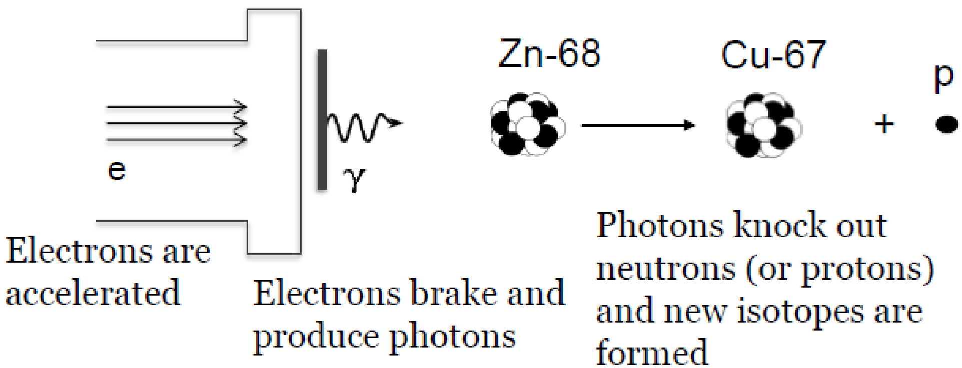
Photoproduction

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

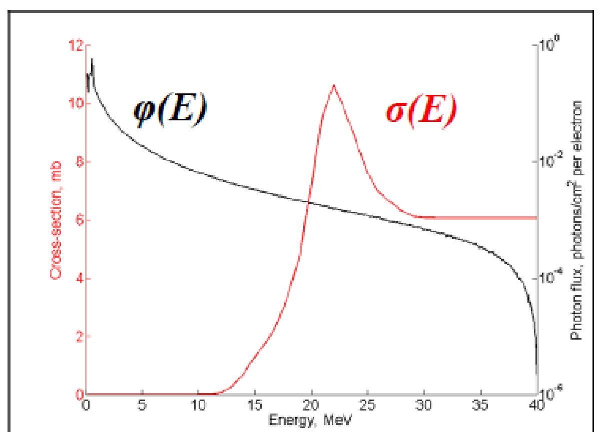
(γ,p) threshold 10 MeV, maximum σ between 20 and 30 MeV around 10 mb

Photo-production of Isotopes

NIOWAVE
www.niowaveinc.com



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



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

16

Conclusions

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"

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