Radionuclide production for medical Application at the ARRONAX facility

Prof. F. Haddad

SUBATECH and GIP ARRONAX

Innovative radionuclide production

To be of interest, it must :

- Have an interest for end-users
- Be produced in enough quantity
- Be of good quality
- Have a high reliability

Motivations

There is a demand for **radionuclides**

- with different **Half-lives:**

  to match with vector distribution time in targeted therapy or imaging

- with different **decay radiations**:

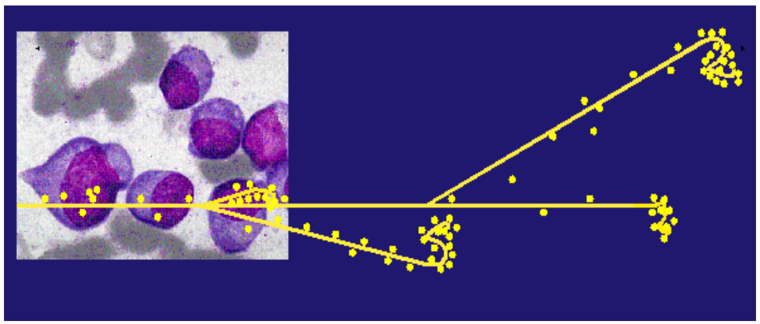
  imaging / therapy

  short range High LET vs long range Low LET

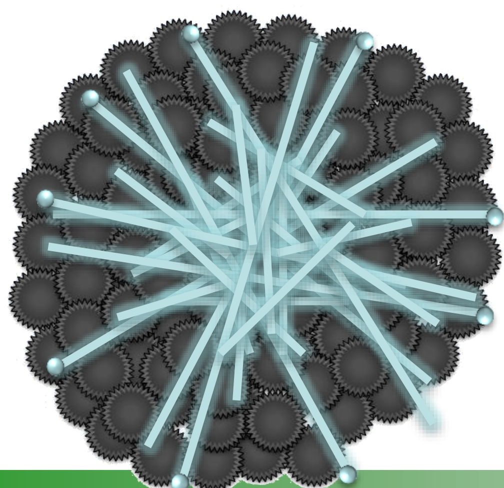
α and β radiations are complementary

β emitter

- <1 MeV dissipated over 1 to 10 mm
- Energy deposited outside the target cell

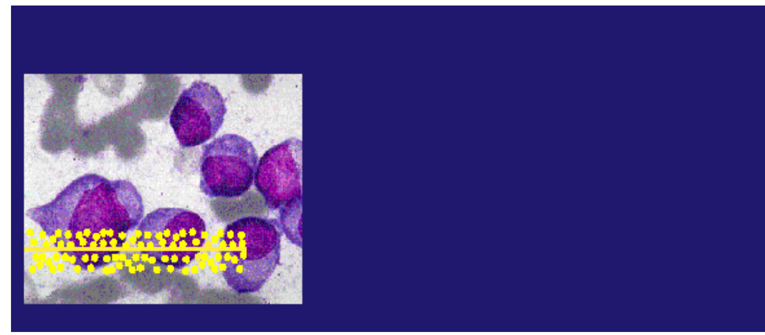


- TARGET: macro-clusters

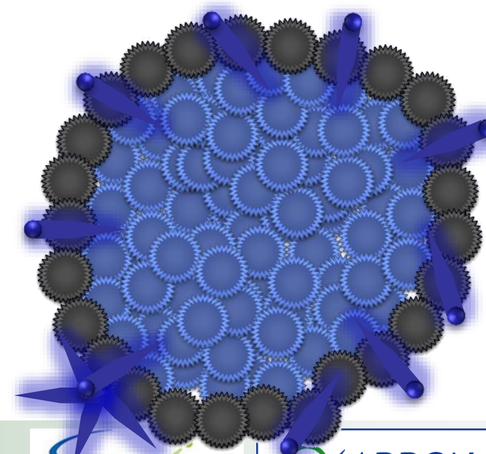


α emitter

- 5-6 MeV dissipated over 0.1 mm
- Energy deposited within the target cells



- TARGET: isolated cells / micro-clusters



Motivations

There is a demand for **radionuclides**

- with different **Half-lives:**

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  imaging / therapy

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- with different **Chemical properties**
- produced via **generator** (ease the availability)
- To be used for the Theragnostic approach

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

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

  R**adionuclides** with comparable properties (**^{99m}Tc / ^{188}Re**)

Innovative radionuclide production

To be of interest, it must :

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- Be produced in enough quantity

  → **High intensity accelerator**

- Be of good quality

  → **Radiochemistry & select the right nuclear reaction**

- Have a high reliability

ARRONAX

an Accelerator for Research in Radiochemistry and Oncology at Nantes Atlantique

3 Fields of investigations:

Radionuclides production
for nuclear medicine

Associated research fields
Radiolysis, Radiobiology and Nuclear Physics

Training

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

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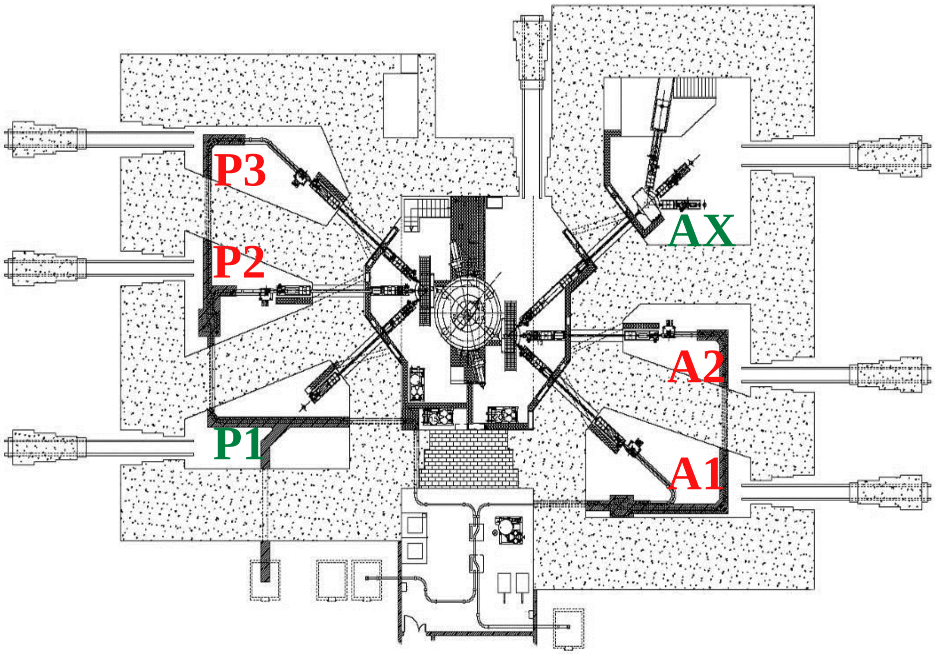
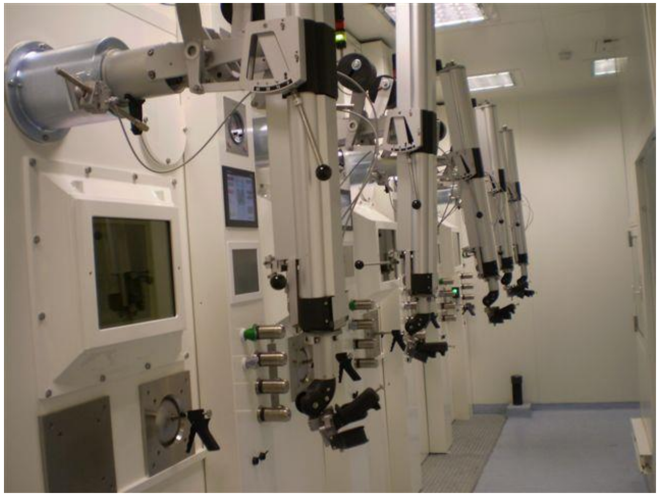
ARRONAX: the facility



4 Vaults devoted to isotope production and connected to ***hot cells*** through a **pneumatic system**

Vault **P1** devoted to a neutron activator system (*collaboration with AAA company*)

Vault **AX** devoted to physics, radiolysis and radiobiology experiments



Radionuclides production : our priority list

– **Radionuclide targeted therapy**:

^{211}At (α emitter)

^{67}Cu, ^{47}Sc (β^- emitters)

– **Dosimetry prior therapy** :

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

- **Imaging** :

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

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

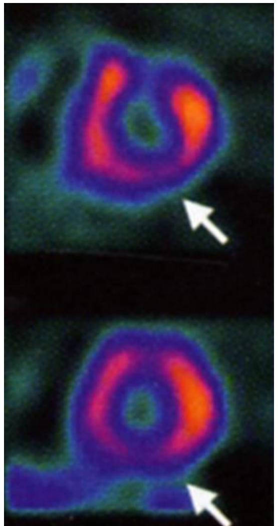
Hypoxia : **^{64}Cu + ATSM**

Immuno–PET (**^{64}Cu, ^{44}Sc**, …)

-**Neutron production for particle activation: ^{166}Ho**

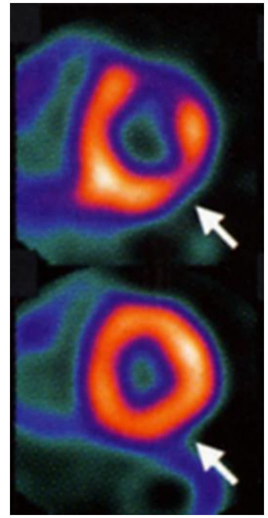
Rubidium-82 (82Rb): PET imaging in cardiology

^{99m}Tc-MIBI SPECT



Bad corrections

^{82}Rb-TEP

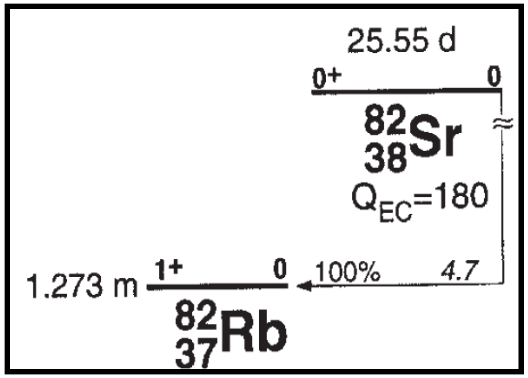


D. Le Guludec et al, Eur J Nucl Med Mol Imaging 2008; 35: 1709-24

In use in North America

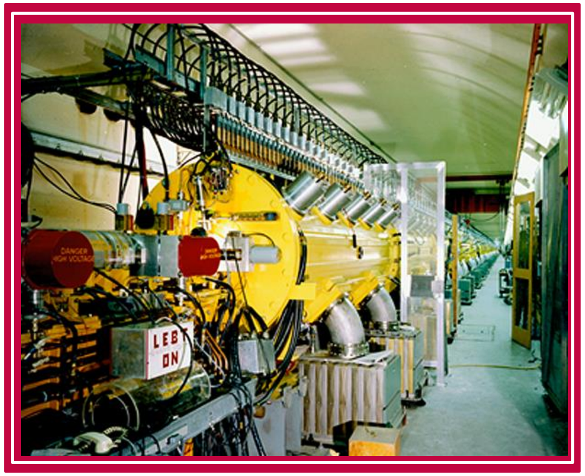
Several advantages:

- Better corrections
- Quantification
- Shorter duration of the exam
- Lower dose to patient
- Available through a generator



Sr-82 production facility in the World

- LANL, USA – 100 MeV, 200µA
- BNL, USA – 200 MeV, 100µA
- INR, Russia – 160 MeV, 120µA



BLIP

- iThemba, South Africa – 66 MeV, 250µA
- TRIUMF, Canada – 110 MeV, 70 µA
- ARRONAX, France – 70 MeV, 2*100µA

Copper-64

Why Copper-64?

PET isotope with low energy positron ($T_{1/2}$=12.7 h).

Theragnostic pair with ^{67}Cu

Easily produced on biomedical cyclotron @ affordable price

Potential Applications:

Hypoxia, imuno-PET , …

Projects for funding clinical studies (submitted)

Routine irradiation conditions:

Deuteron beam with 16 MeV and I=90 µAe on target around 3h

One run every month

*In 2015/2016, **collaborations** with 10 labs in France (none in 2013)*

Astatine-211

Why Astatine?

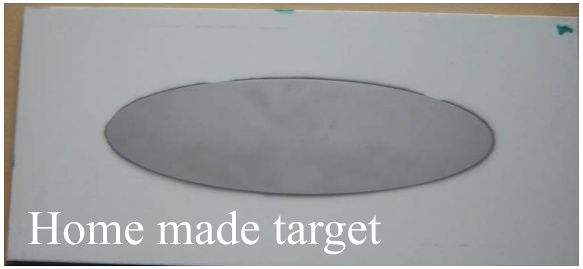
Alpha targeted therapy

Only alpha emitter easily produced using on-shell accelerator.

→ ***Capacity can be increased easily by adding an accelerator***

Potential Applications:

Prostate cancer, Multiple myeloma, …


Home made target

Routine irradiation conditions:

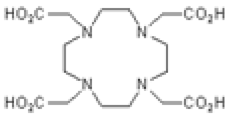
Alpha beam with 67.4 MeV and I=15 μAe on target around 3h

One run every two weeks

Scandium-44(^{44}Sc)

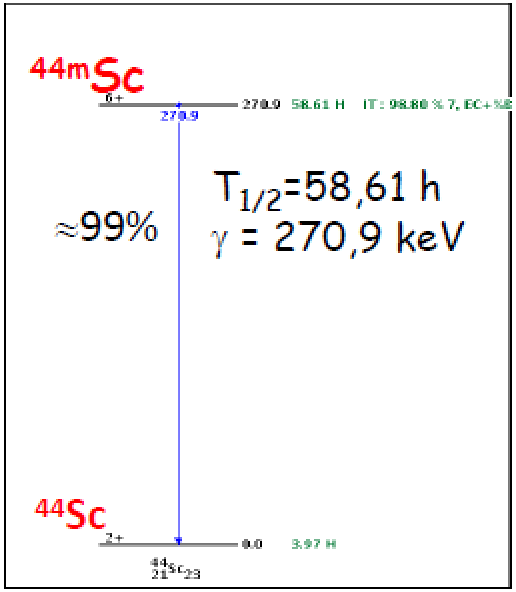
Why Scandium-44?

- TEP isotope with $T_{1/2}$=4h
- Theragnostic pair with ^{47}Sc
- DOTA can be used as chelator
- Co-production of ^{44m}Sc → in-vivo generator
- Decay through positron + gamma emission (1157 keV – 99%)



DOTA

Potential Applications: *imuno-PET* , 3γ imaging ...



Routine irradiation conditions:

- Max intensity on target: <1 µAe deuteron beam
- Run on demand

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- Be produced in enough quantity **- OK**
  - → **High intensity accelerator**

- Be of good quality **- OK**
  - → **Radiochemistry & select the right nuclear reaction**

- Have a high reliability – **underway**

Set-up network : GDR MI2B in France
collaborations in Europe

Conclusions

ARRONAX is fully **operational since** February 2011.

ARRONAX priority list covers both **isotopes for therapy** (^{211}At, ^{67}Cu, ^{47}Sc) and **imaging** (^{82}Sr, ^{68}Ge, ^{64}Cu, ^{44}Sc)

- **^{82}Sr** is produced routinely as a radiochemical to be used in generator for clinical use.

- **^{64}Cu** is produced as radiochemical product. Clinical trials will start soon.

- **^{211}At** is produced as radiochemical product. Preclinical trials have started

- **^{44}Sc** is produced as radiochemical. Radiolabeling studies is done.
  Next step is preclinical studies

- **^{166}Ho:** The neutron activator is validated at **350 µA** proton on target.
  Preclinical studies will start soon.

Remaining Challenges

- Alternative production route for well established radionuclides: **^{99m}Tc**

- Use of high LET particles: **alpha emitters** or Augers emitters

- New isotopes for new concepts – 3 γ imaging in close connexion to ^{44}Sc production

- High purity radioisotopes : Mass separation
  On-line : ISOLDE @ CERN
  Off-line: MEDICIS@CERN,

- Neutron production without reactor for some applications:
  secondary neutrons from accelerator

- New developments in accelerator:
  Linac : **boost intensity**
  Compact cyclotrons to **ease dissemination**

Subatech ARRONAX afaq ISO 9001 Qualité AFNOR CERTIFICATION

Credit

C. Alliot[2,3], N. Audouin[2], J. Barbet[2,3], O. Batrak[1], A.C. Bonraisin[2], Y. Bortoli[1], C. Bourdeau[2], M. Bourgeois[2,3], G. Bouvet[1], J.M. Buhour[1], A. Cadiou[1], C.Coban, J.B. Etienne, S. Fresneau[1], S. Girault[2], M. Guillamet[1], F. Gomez[2], X. Goiziou[2], F. Haddad[1,2], A. Herbert, S. Huclier-Markai[1], C. Huet[2], J. Laizé[2], L. Lamouric[2], E. Macé[2,3], G. Mechin[2], N. Michel[1,2], T. Milleto[1], M. Mokili[1,2], M. Pageau[2], S. Pauper, L. Perrigaud[2], F. Poirier[1,2] , D. Poyac[2], C. Roustan[2],H. Trichet[2], A. Vidal, N. Varmenot[2].

[1] ***SUBATECH (CNRS/IN2P3 - Ecole des mines - Université de Nantes)***
[2] ***GIP ARRONAX***
[3] ***Inserm U892,Nantes, France***

Thank you for your attention

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