Production of innovative radionuclides at ARRONAX

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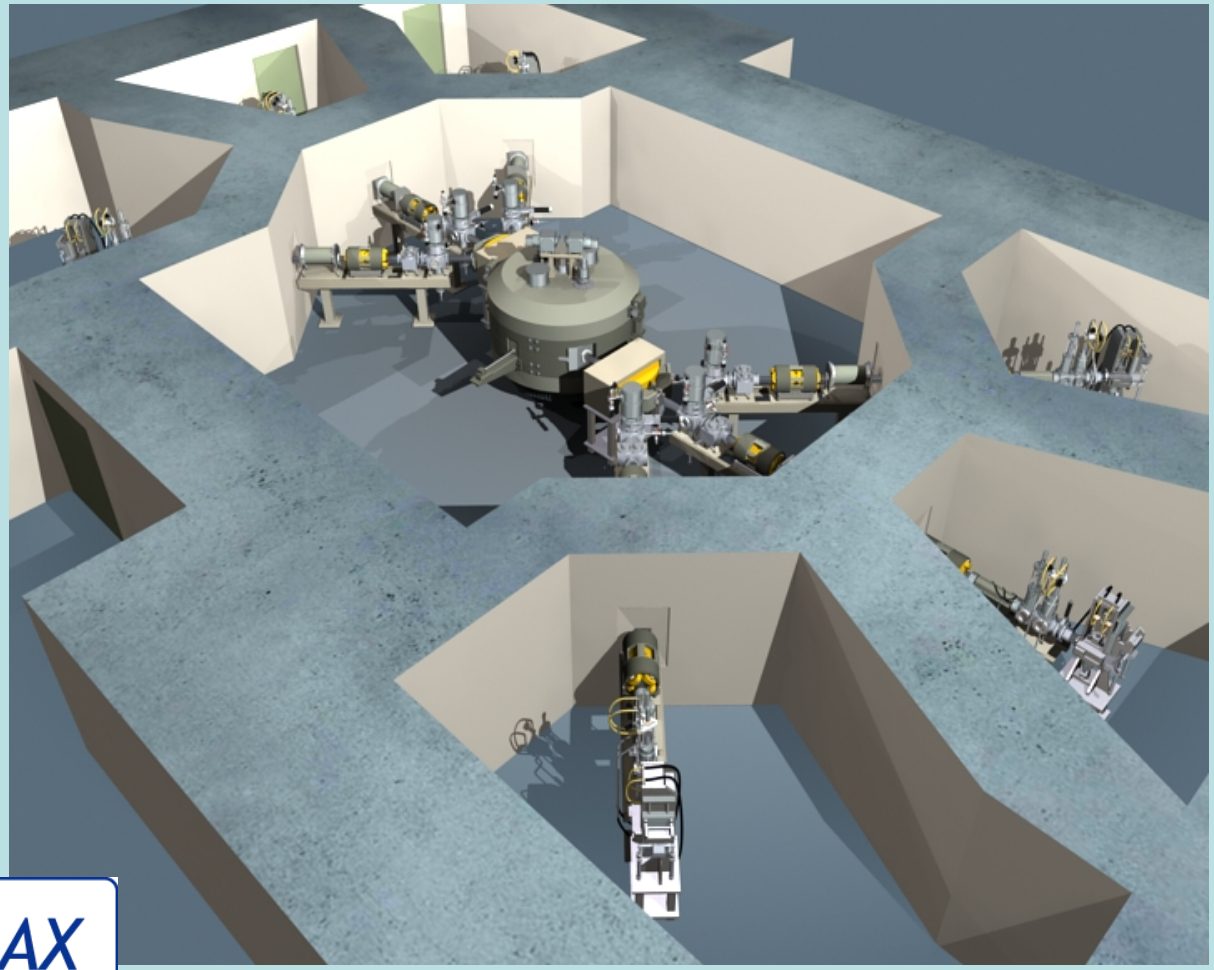


Subatech

Inserm
Institut national
de la santé et de la recherche médicale

ARRONAX

ARRONAX

an Accelerator for Research in Radiochemistry and Oncology at Nantes Atlantique

Located in **Nantes** (France)

High energy (**up to 70 MeV**)

High intensity (**up to 750 µA for protons**)

3 main fields of investigations

- Radionuclides for nuclear medicine
- Radiolysis and Nuclear Physics
- Teaching & Training

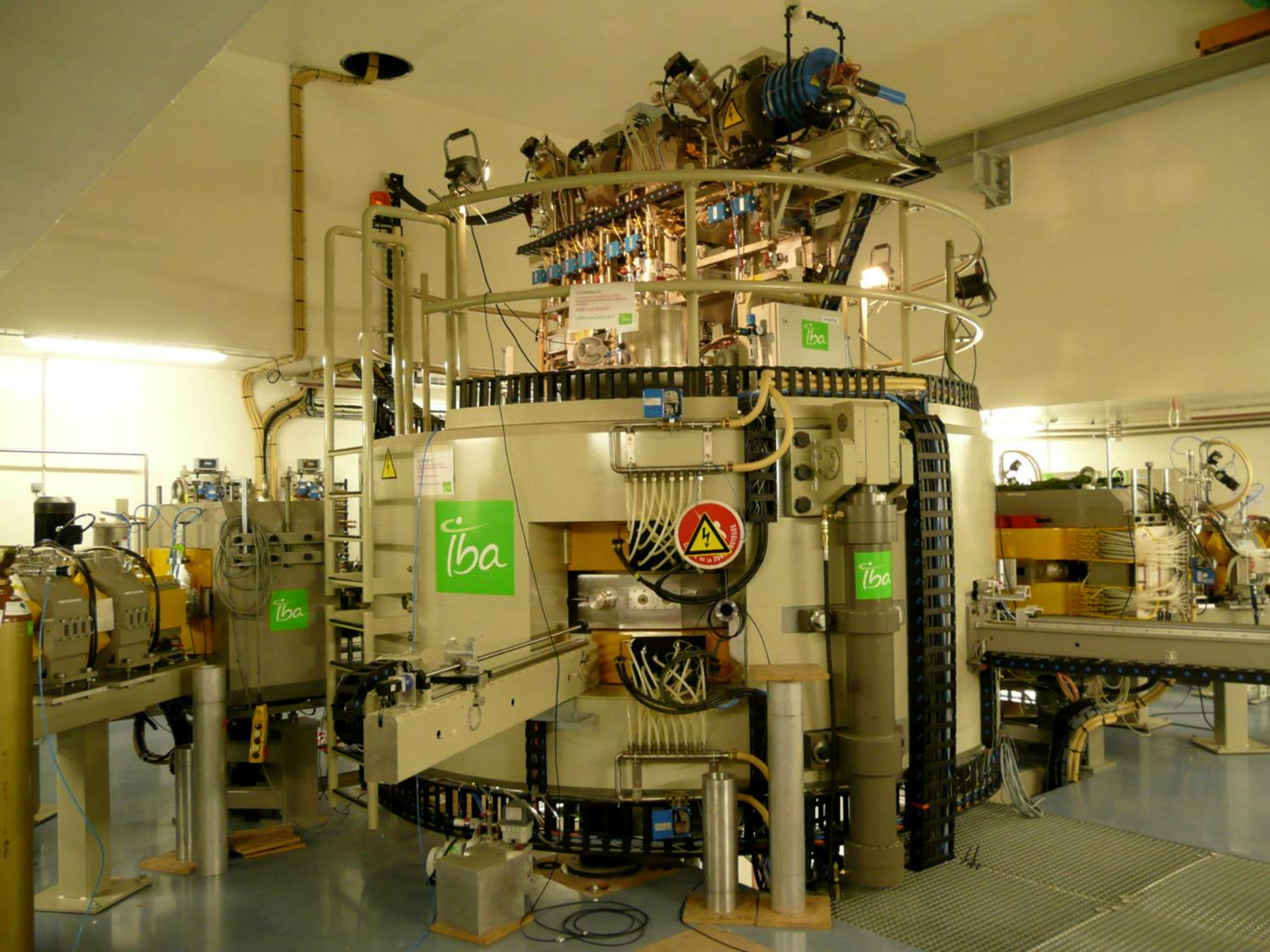
Beam Characteristics

Beam	Accelerated particles	Energy range (MeV)	Intensity (µA)	Number of beams	Number of vaults
Proton	H-	30-70	<375	2	6
	HH+	17.5	<50	1	3
Deuteron	D-	15-35	<50	2	6
Alpha	He++	68	<70	1	3

6 experimental **vaults** connected to **hot cells** through a **pneumatic system**

Surrounding labs :

radiochemistry , biochemistry, cell biology, chemical analysis, nuclear metrology, quality control,…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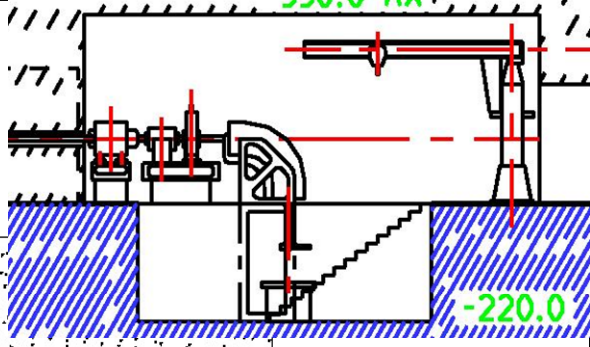
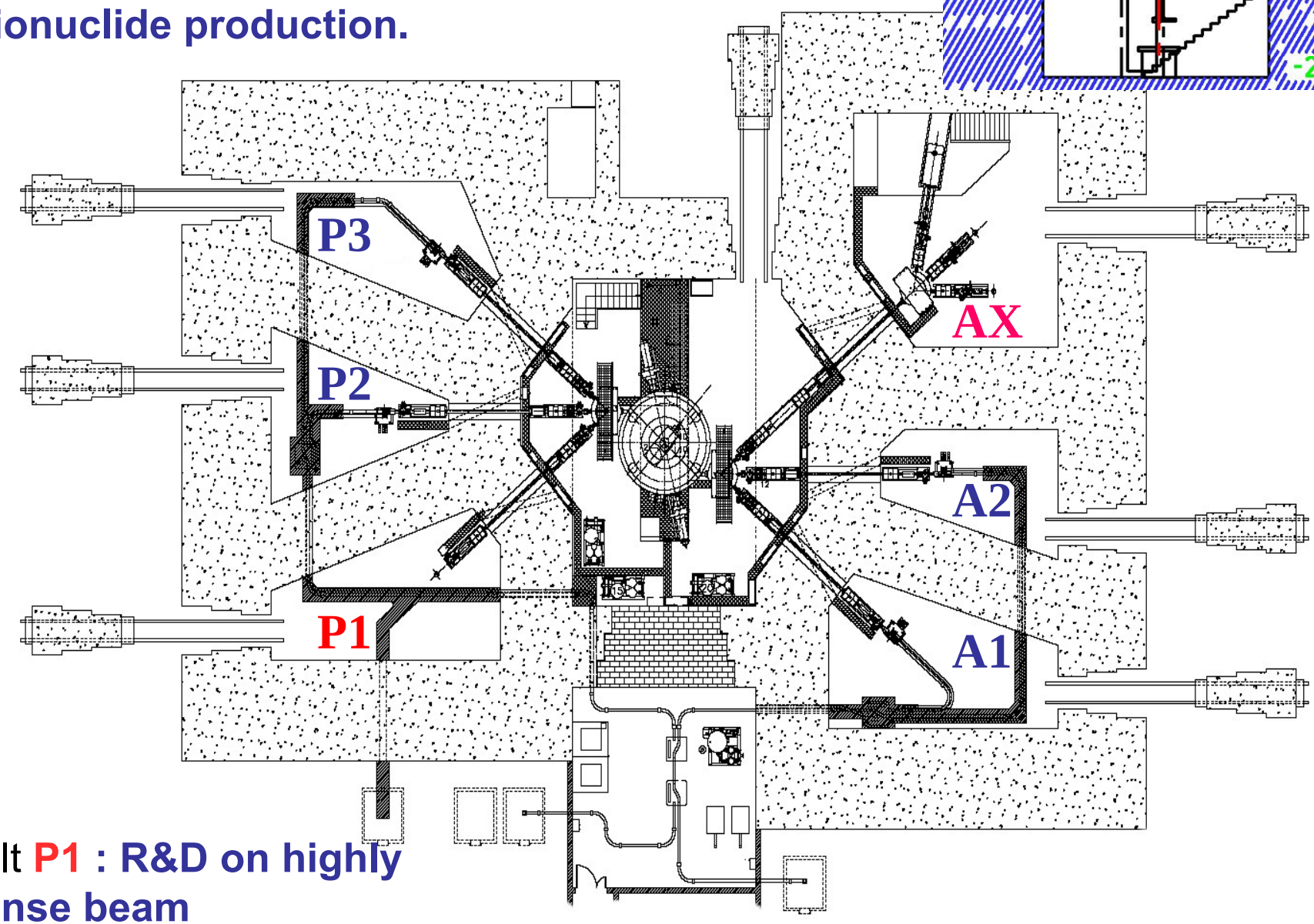
Vault **AX**:
Alpha pulsing
Vertical beam



vaults **A1, A2, P2 and P3:**
radionuclide production.

Proton beam

Proton and alpha beam



Vault **P1** : **R&D on highly intense beam**

Beam lines devoted to production

We need to irradiate solid **target under different forms** (powder, foils,…).

Two target designs will be available **(**medium beam current)

- A 15° rabbit (cooling through backing)
- A multi target rabbit with 4 Pi cooling

Hot Cells

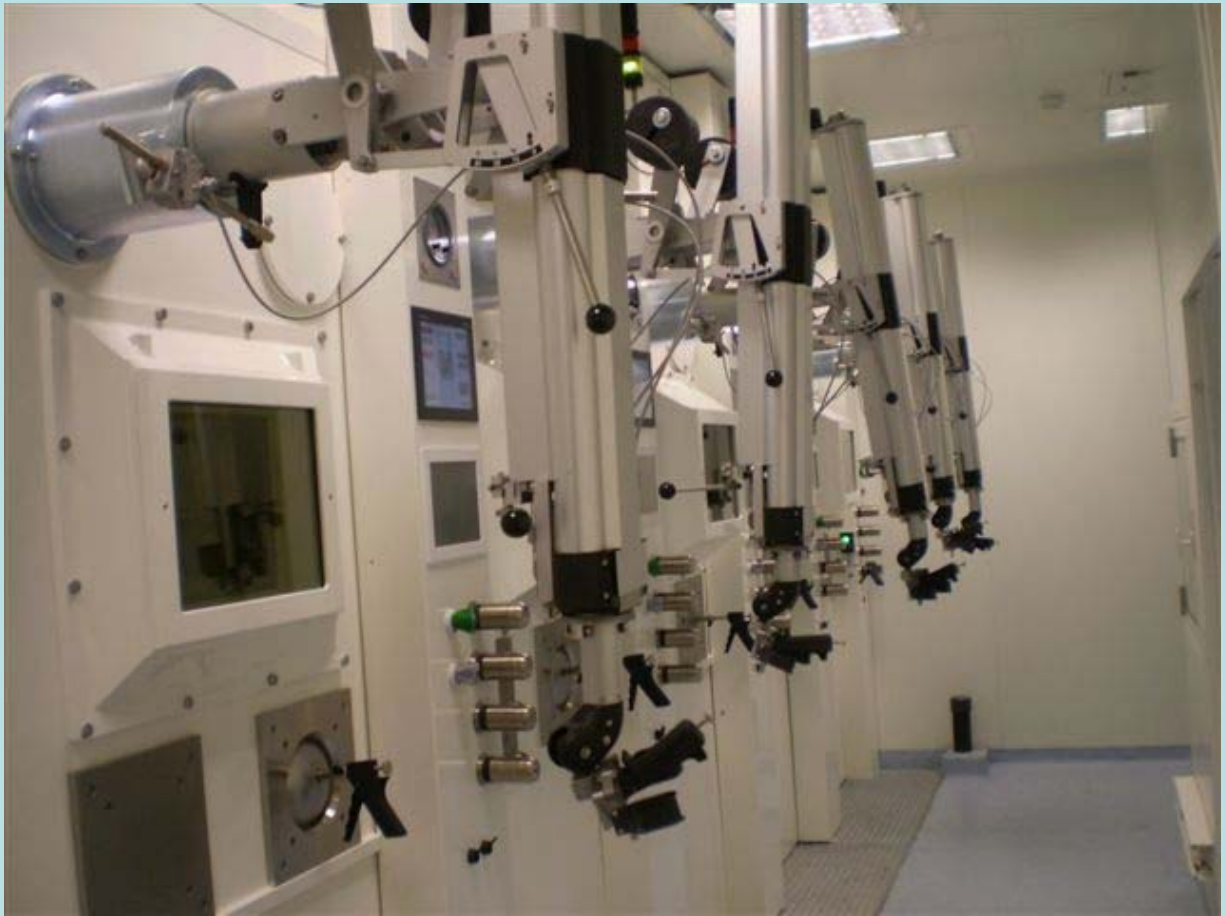
3 Rooms:

- 1 sterile equipped with 5 Hot cells (another one exist but not yet equipped)

- 1 GMP equipped with 3 hot cells

From Von Gahlen

Installed last September



Final Acceptance Test are underway.

85% of the acceptance tests passed with success

Protons:

Beam transport validated at 375µA- 70MeV

Dual beam 2x200µA -70MeV extracted

1x500 µA - 30 MeV extracted

Alpha particles:

25 µAe – 68 MeV extracted

Still to be done:

Protons:
Dual beam 2x375 µA -70MeV

Alpha particles:
70 µAe – 68 MeV

Alpha pulsing integration

Radionuclides of interest

Based on ARRONAX capabilities and the analysis of the needs of the community (2006)

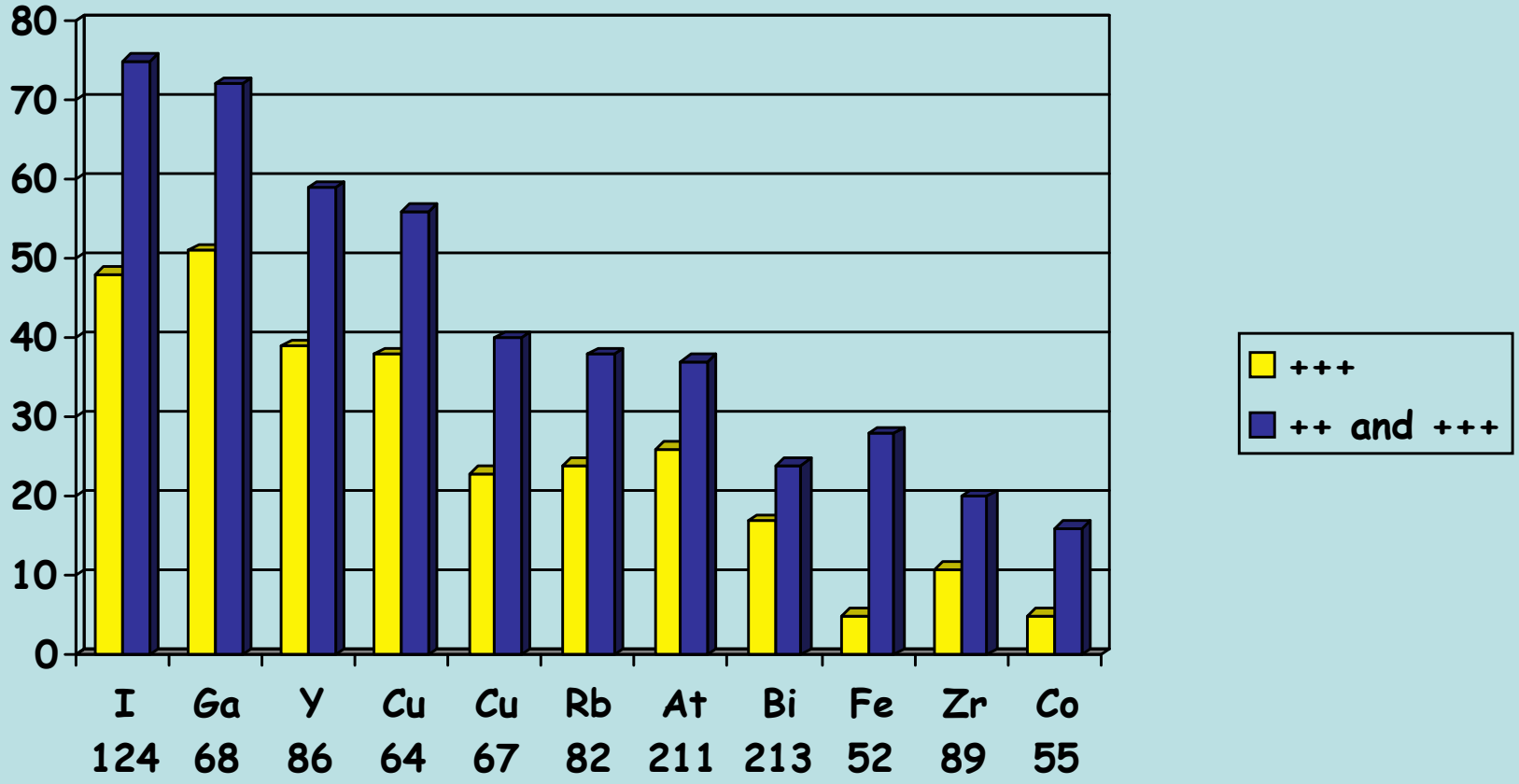
A questionnaire was sent to **107 EANM** members and, through the **french nuclear medicine society**, to 119 members.

« **European group** » 27 responses (25%) from 10 countries

Italy (7), Germany (5), Great Britain (4),
The Netherlands (3), Belgium (2), Switzerland (2)
Spain (1), Austria (1), Poland (1), Romania (1)

« **French group** » 40 responses (34%) from 27 centers

Merged results (67 responses, 11 countries)



Our priority list

Targeted radionuclide therapy:

^{211}At : appropriate for **α-therapy** due to its half-life (7.2 hours).

^{67}Cu and **^{47}Sc** : **β-therapy** (same β energy)

require high proton energy and high current intensity
(small production cross sections (p,2p))

PET imaging:

^{64}Cu and **^{44}Sc**: pre-therapeutic PET dosimetry before injection of their beta-emitting counterparts ^{67}Cu and ^{47}Sc

^{82}Sr/^{82}Rb and ^{68}Ge/^{68}Ga generators

^{44}Sc: β^+ γ emitter (3 γ imaging)

Therapeutic isotopes on ARRONAX

Two projects are being launched on **therapeutic issues** in collaboration with radiopharmaceutical companies:

Alpha-RIT: Radio Imuno-Therapy using ^{211}At

major indication: prostate cancer

Partners

UNIVERSITE DE NANTES

ARRONAX

U601 INSERM Département de Recherche en Cancérologie (DReC)

Subatech

CHELATEC

ATLAB PHARMA RADIO•ANTIBODIES AGAINST CANCER

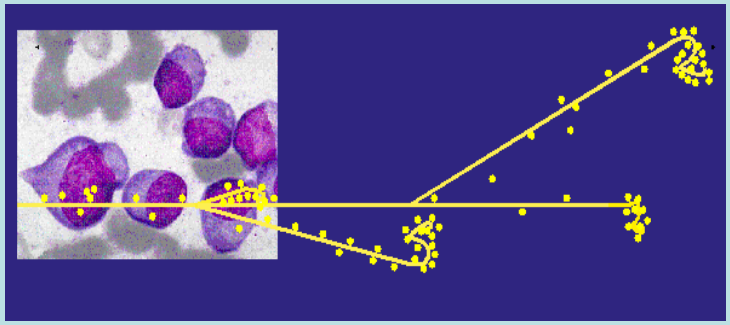
iba Molecular

Coordination

Active agent: β or α radio-isotope

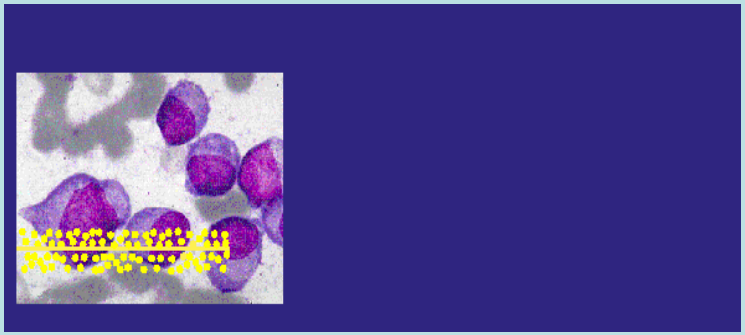
β emitter

- <1 MeV dissipated over 1 to 10 mm
- energy deposited outside the target cell
- TARGET: **cell macro-clusters, metastases**

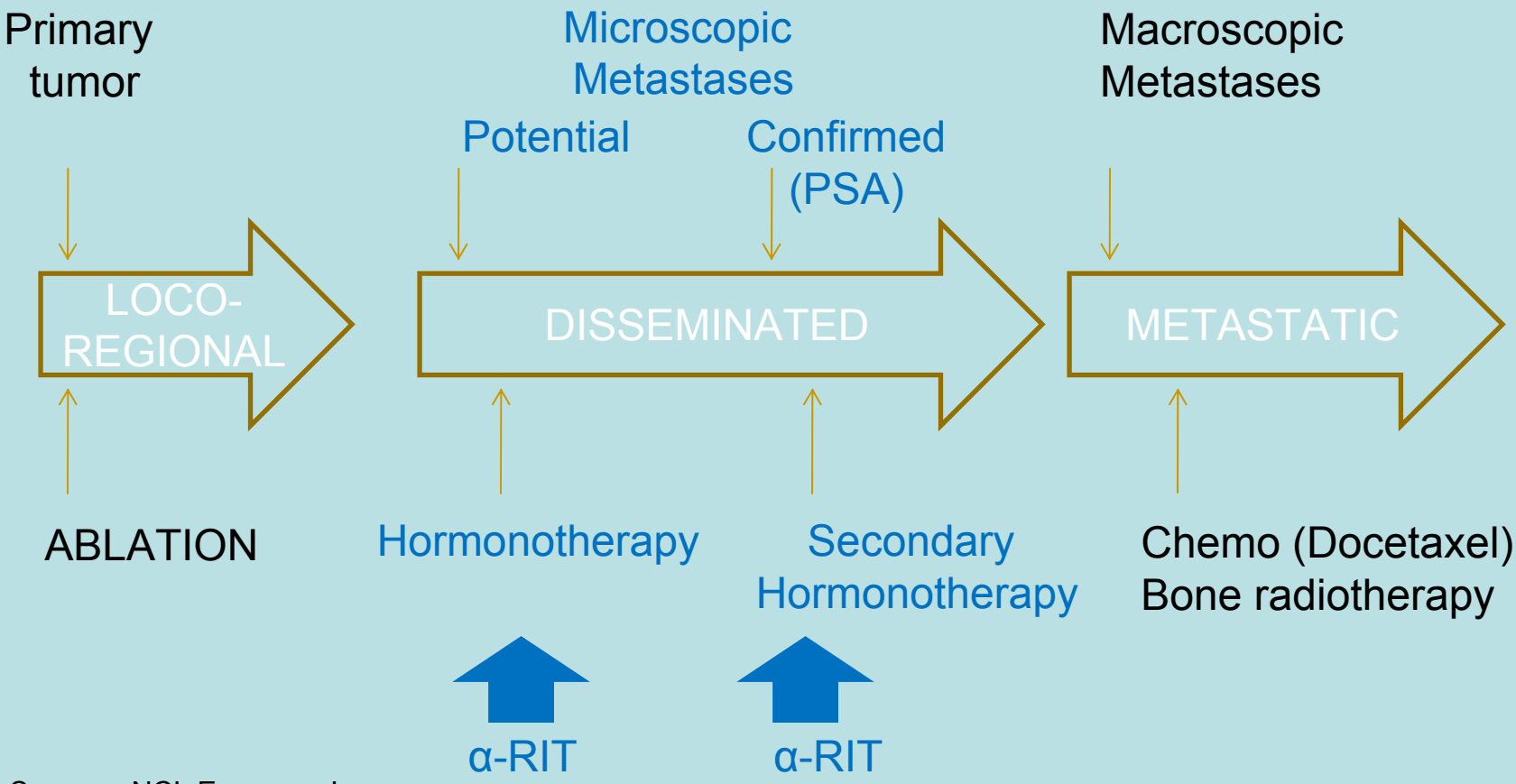


α emitter

- 5-6 MeV dissipated over 0.1 mm
- energy deposited within the target cells
- TARGET: **isolated cells, micro-clusters**



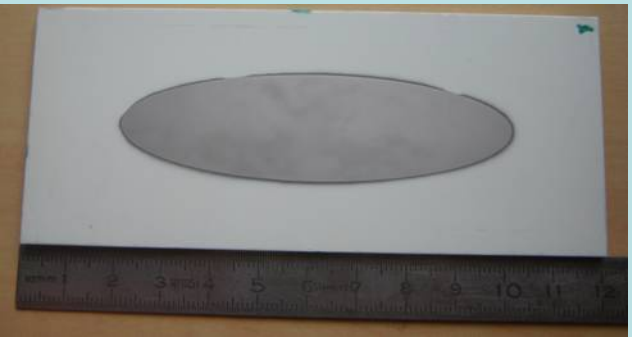
Alpha-RIT in prostate cancer



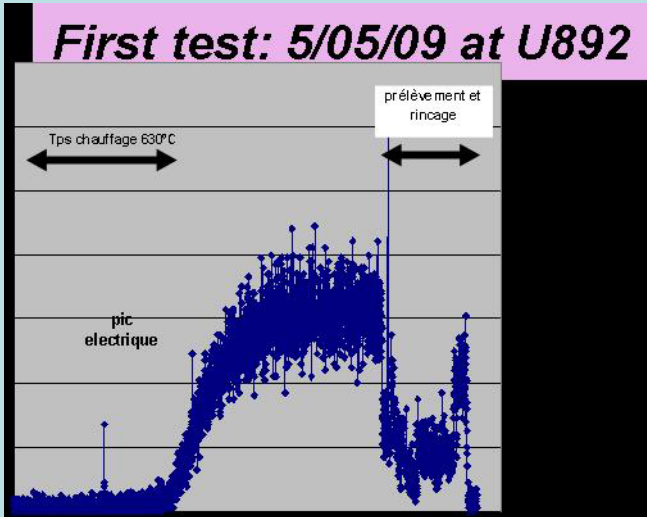
Sources: NCI, Eurocare. Inca

Alpha-RIT: Why Astatine-211 ?

- Few potential candidates
  - ^{211}At, ^{213}Bi, ^{223}Ra, ^{224}Ra, ^{227}Th, ^{225}Ac
- Medical use
  - Half-life of 7.2 h vs. 46 min (Bi) or >10 jours (Ra, Th)
  - No alpha-emitting decay products
- Easier manufacturing
  - Cyclotron (α–beam) rather than reactor
  - Stable target (Bi) rather than radioactive target
- Appropriate chemistry
  - Coupling to antibodies vs. encapsulation



Bi target on AlN



Monitoring of the dry extraction of At

Alpha-RIT: The issues

- Combine the specificity of an **antibody** targeting prostate cancer cells with an alpha-emitter
- **Produce the alpha-emitter** in larger (industrial) amounts
- Chemistry, biology, toxicology and clinical **tests** have to be carefully taken in account
- Alpha-emitters for medical use are new and **new rules** for handling these radionuclides have to be invented, approved and adopted

THERANEAN project:
Therapy through Neutron Activation using Nanoparticles

L. Maciocco
Project Leader AAA
M. F. Mariani
Head Research and Development AAA

Advanced Accelerator Applications
BRIDGING SCIENCE WITH LIFE

cerma

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INSA LYON

Subatech

nanoH
Value-Added Nanotechnology

UFB

ARRONAX

ATLANPOLE
Land of innovation

l'esprit grand ouvert
Région PAYS DE LA LOIRE

LYONBIOPOLE

Theranean:

A method for production by neutron activation of isotopes for cancer therapy using medium-sized cyclotrons

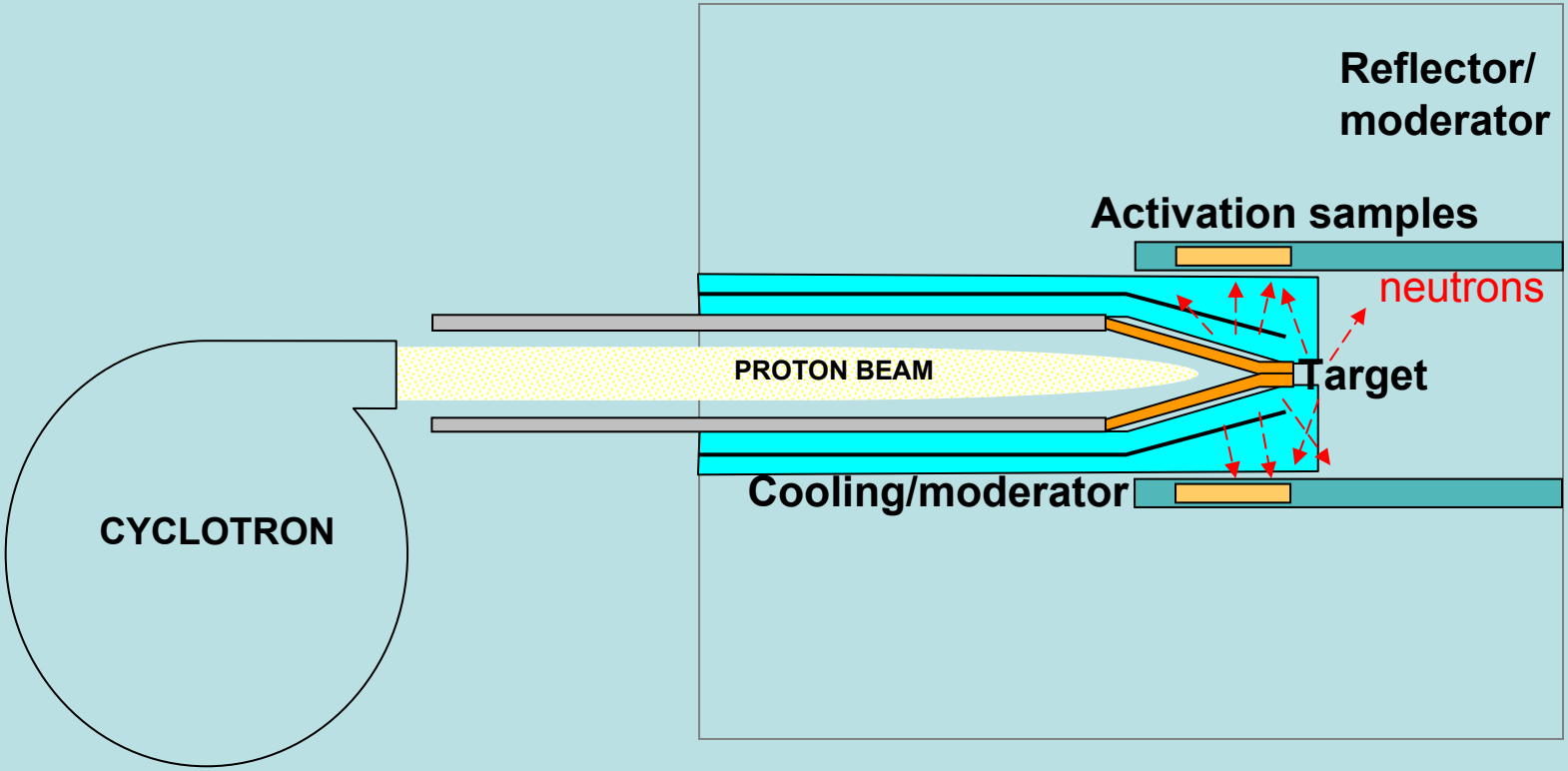
Based on a principle of **Adiabatic Resonance Crossing** (ARC) patented by C. Rubbia (CERN). **Experimentally proven** at CERN between 1995 and 1997 with the TARC experiment

2005-2009: **INBARCA** project at JRC ISPRA

The neutron activator: principle of operation

- A proton beam is generated by a cyclotron
- Protons interact with a solid target (Be,Ta)
- Fast (high energy) neutrons are generated

- Neutrons are moderated (water)
- Neutrons are reflected and further moderated (graphite)
- Nanoparticles are activated by moderated neutrons



The INBARCA projects officially ends in March 2009 with the following results

- ✓ A prototype of the neutron activator has been built and validated at JRC, coupled with a 40 MeV-50 μA cyclotron, demonstrating the possibility to produce radioisotopes for cancer therapy using medium sized cyclotrons for medical applications.

- ✓ Animal tests carried out carried out at HEH using LAGEP and Nano-H nanoparticles gave clear evidences of the anti-tumoural effect of the proposed brachytherapy technique

- ✓ The general methodology, including animal model, nanoparticles activation, injection, follow-up and analysis was successfully demonstrated

- ✓ It is however clear that **a more powerful cyclotron is necessary for an efficient industrial production of activated nanoparticles**

Objectives of the THERANEAN project

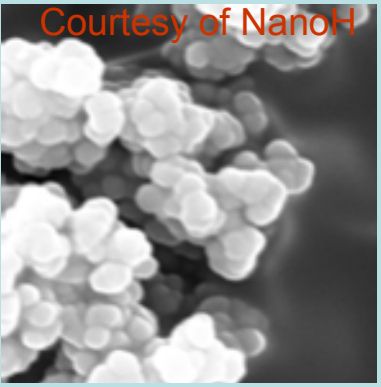
Global aim:

Development of an innovative brachytherapy technique using micro/nanoparticles activated in an accelerator-driven neutron activator

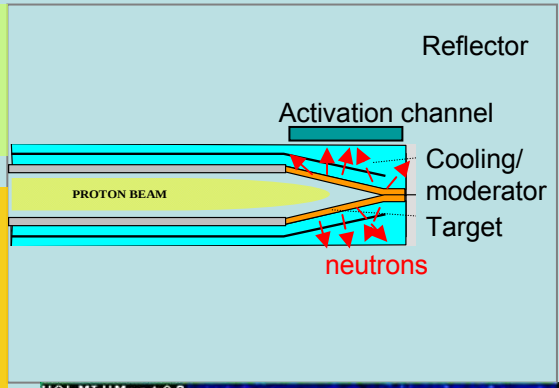
Project objectives:

- Design and construction of a high-power neutron activator using 70 MeV – 350 μA proton beam.
- Characterisation of Ho/Lu-oxide, non coated/coated nanoparticles of different sizes (100-300 nm).
- Development of a medical device for the safe and effective intra-tumoral/intra arterial injection of activated nanoparticles
- Development of a personalised dosimetric method based on the Monte Carlo-simulation of the dose released in the tissues, starting from SPECT/CT data
- **Potential clinical indications**: Liver cancer, Prostate cancer, Glioblastoma

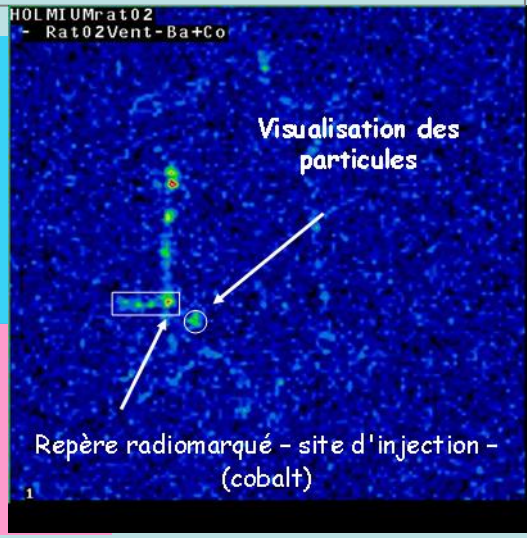
The THERANEAN method



- Synthesis of various types and sizes of nanoparticles with lanthanide-oxide core, containing the stable (non radioactive) isotope to be activated
- Pharmaceutical preparation of sterile injectable nanoparticles suspension



- Insertion of injectable doses in the cyclotron-driven activator for neutron activation (no alteration of pharmaceutical characteristics)



- Intra-tumoral/intra-arterial injection using the TMT injector
- SPECT detection of nanoparticles distribution, CT for morphological data

- Transfer of imaging data to Monte-Carlo dosimetry model for dose distribution calculation

Conclusions

ARRONAX is under completion

85% of the acceptance tests have been passed with success

Several isotopes for therapy are in its priority lists (**^{211}At, ^{67}Cu, ^{47}Sc**)

2 projects are being launched for therapeutic purposes:

- **Theranean**: activation of nanoparticle for brachytherapy
- **Alpha-RIT**: alpha immunotherapy using ^{211}At

Thank you for your attention

The **ARRONAX** project is supported by:
the **Regional Council of Pays de la Loire**
the **Université de Nantes**
the **French government** (CNRS, INSERM)
the **European Union**.