From preclinical work to clinical trials : The Nantes experiences

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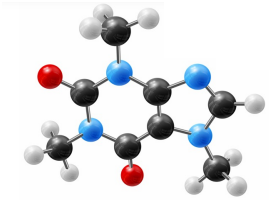
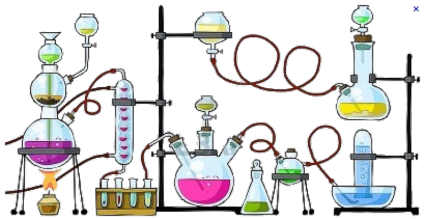
Nuclear Medicine Department – Nantes University hospital
Radiopharmacy Unit – ARRONAX Cycltron

Forewords

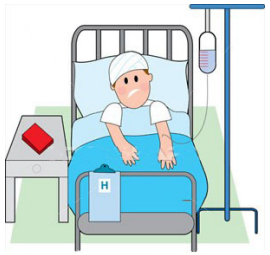


Molecule of interest



1 Radiopharmaceutic Project

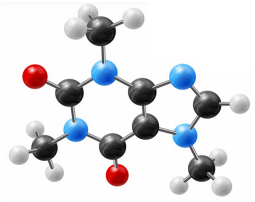
Target identification



Clinical needing

Isotope production

Forewords



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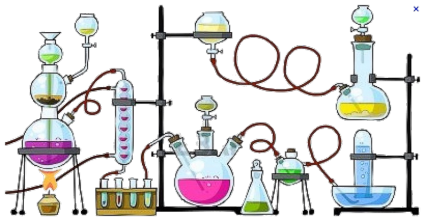

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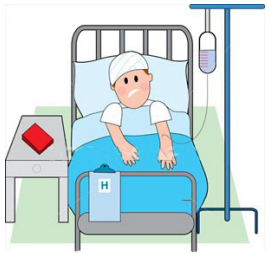

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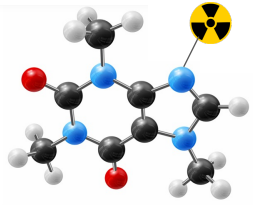


1 radiolabeled compound

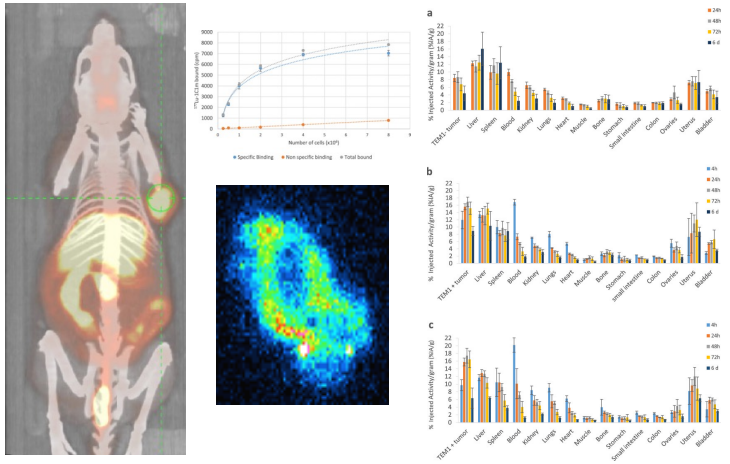
In vitro

In vivo

1 radiopharmaceutical candidate

Forewords

1 radiopharmaceutical candidate



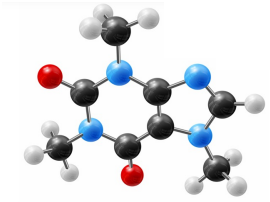
You have a proof of concept

!!! Valorisation !!!

But… you only heal mice !!!

… that you have made deliberately sick

Forewords



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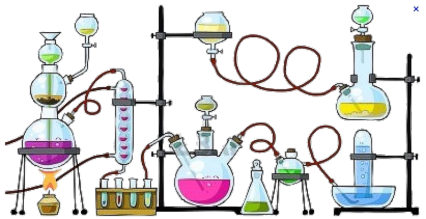

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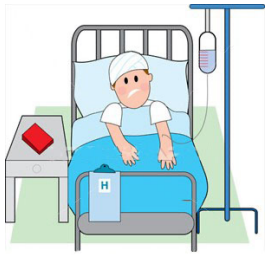

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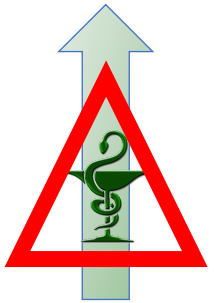
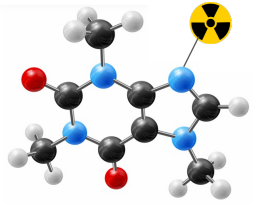




1 radiolabeled compound

In vitro

In vivo

1 radiopharmaceutical candidate

Scale-Up & Regulatory challenge…

Facility for radiopharmaceutical manufacturing

IAEA International Atomic Energy Agency

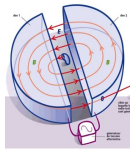
Radiopharmaceuticals: Production and Availability

World Health Organization

Annex 6

WHO good manufacturing practices for sterile pharmaceutical products

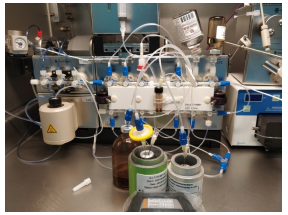
Raw material supply (radioactive and « cold » materials)



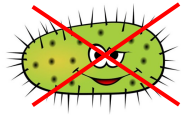
GOOD MANUFACTURING PRACTICE GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS
Q7
19. APIs FOR USE IN CLINICAL TRIALS

European Pharmacopoeia

Repeatability of radiolabeling (Automatisation, 100% batch conformity, Stability)

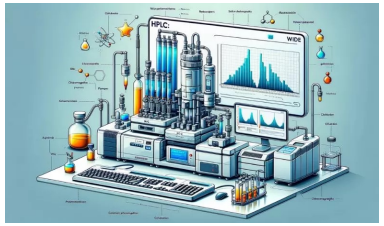


Sterile condition

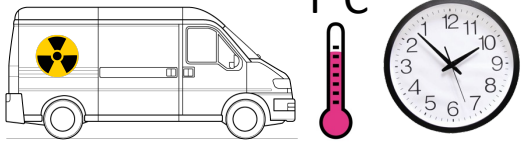


Activity increase (from kBq to MBq or GBq…)

Quality control (Analytical Method Validation, …)



Transport to clinical dept (temperature, time,…)

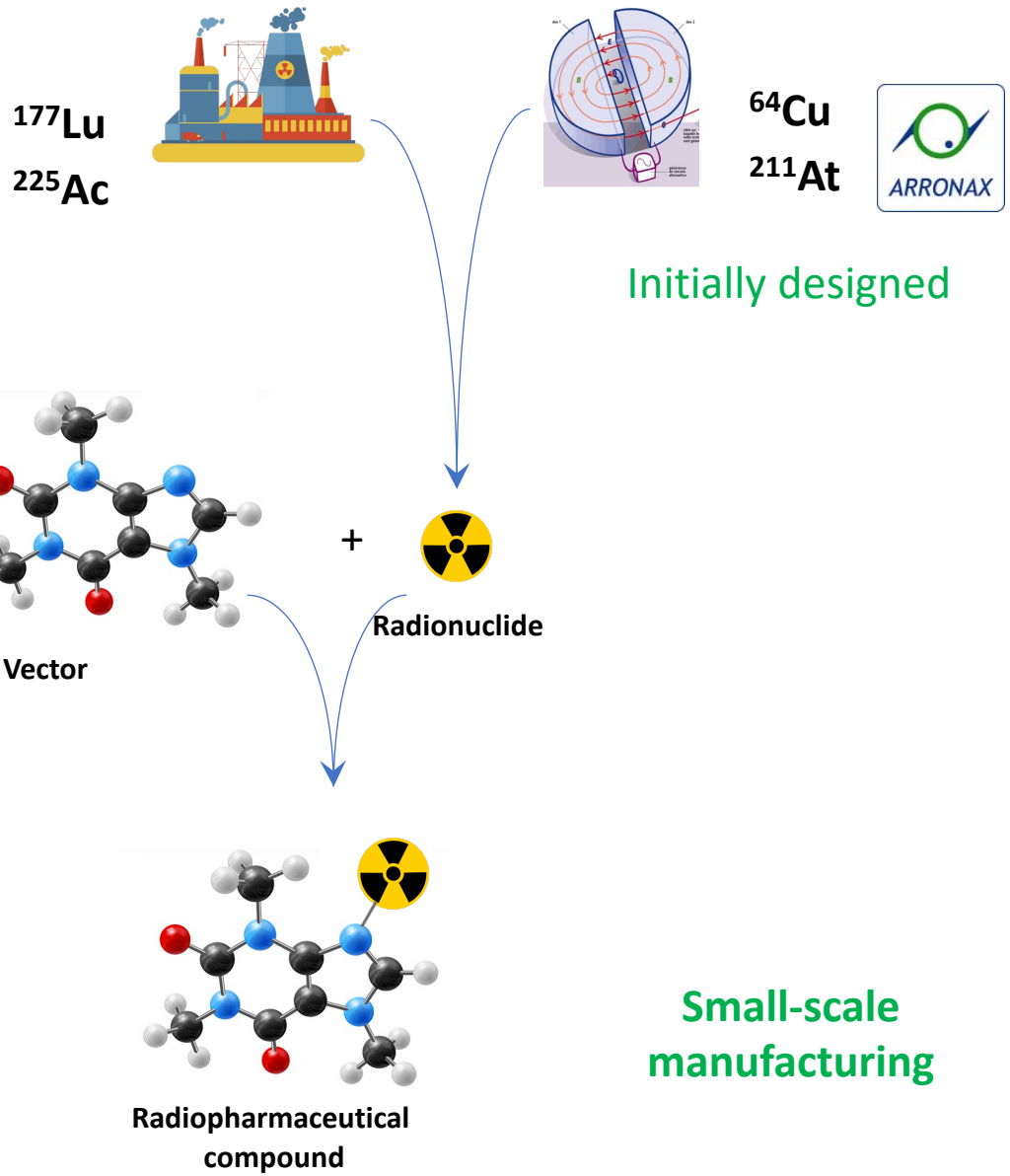


&

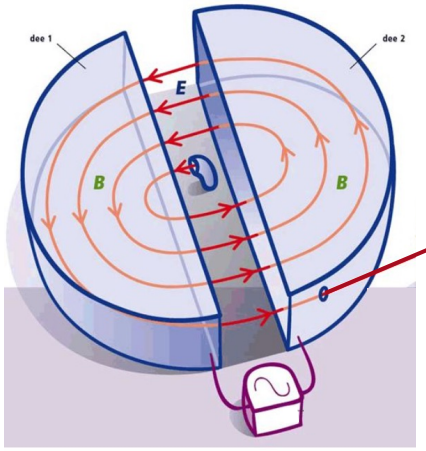
Quality Assurance

ARRONAX Example of process flow

In house radionucleide… or not

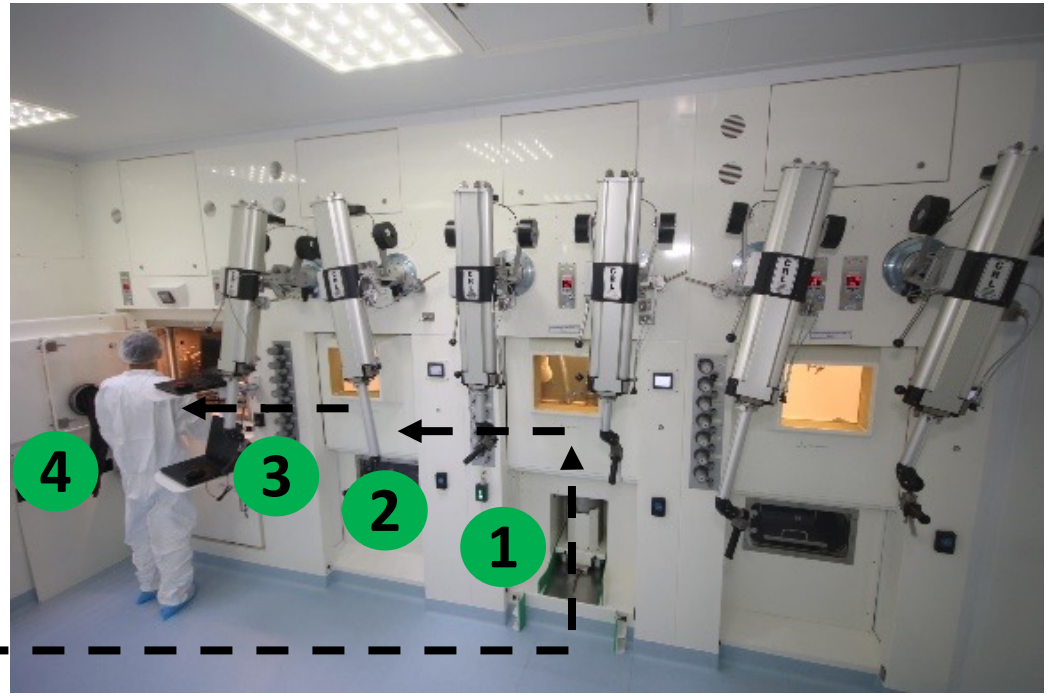


ARRONAX Example of process flow

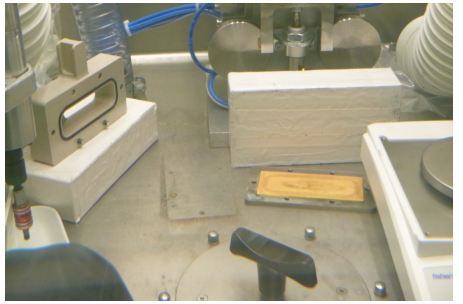


target

$^{64}Ni(d,2n)^{64}Cu$



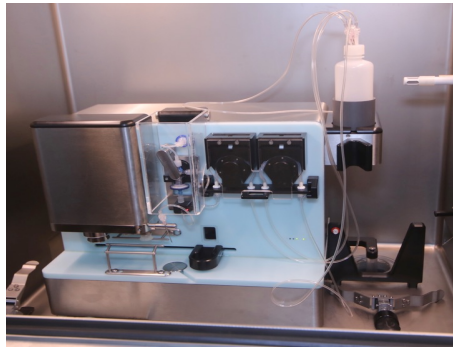
1 Target reception



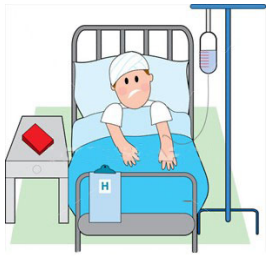
2 Radionuclide purification

3 Radiolabeling

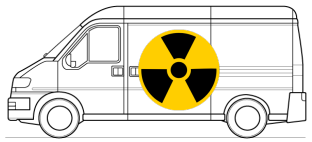
4 Aseptic filling



5 Quality Control



Patient injection



Transport

Nantes network

Nantes Université

Subatech

CEISAM

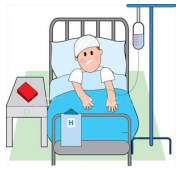
Chimie

Physique

Logistic

ARRONAX

ARRONAX



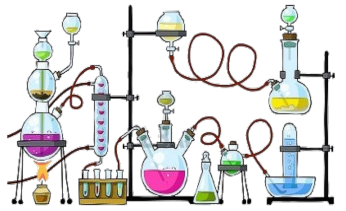
Clinical needing

CHU NANTES

Target identification

CRCI²NA CANCER & IMMUNOLOGY

Production



Radiolabeling

« cold » molecule

ARRONAX

in vitro

in vivo

CRCI²NA CANCER & IMMUNOLOGY

Clinical production

ARRONAX

Clinical trial

CHU NANTES

ARRONAX :

afaq ISO 9001 Qualité AFNOR CERTIFICATION

FDA

CBG MEB COLLEGE TER BEOORDELING VAN GENEESMIDDELEN MEDICINES EVALUATION BOARD

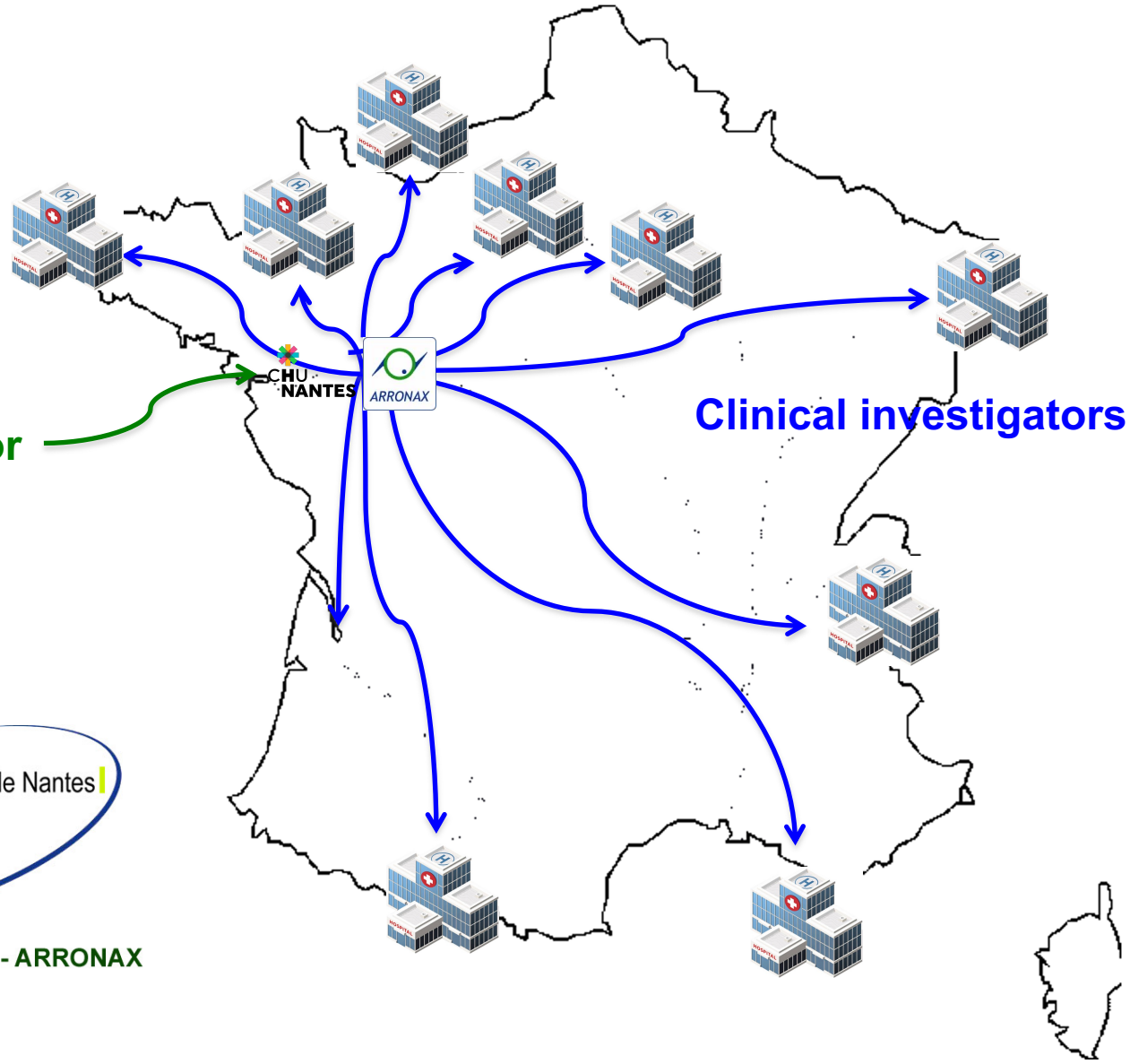
ansm Agence nationale de sécurité du médicament et des produits de santé

asn

Ordre national des pharmaciens

ars Agence Régionale de Santé

Multicentric clinical trial capacity



Clinical trial promotor

institutional / Industrial

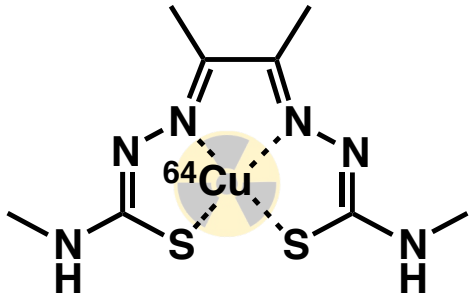
Clinical investigators

Arronax CHU de Nantes

Pharmacie à Usage Intérieur - ARRONAX

National limitation…

Example of [^{64}Cu]-Cu-ATSM Preclinical model

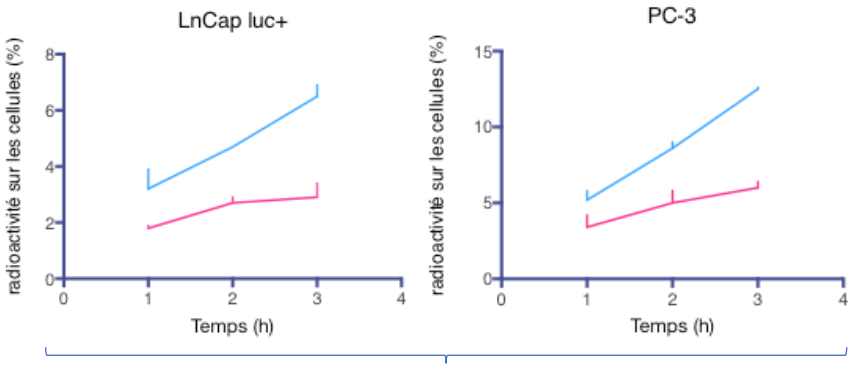


Non imidazoles (thiosemicarbazones)

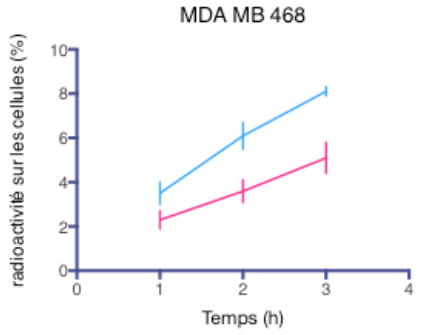
^{64}Cu-diacetyl-bis-(N4-methylthio semicarbazone) = [^{64}Cu]-CuATSM

in vitro validation in various cellular model

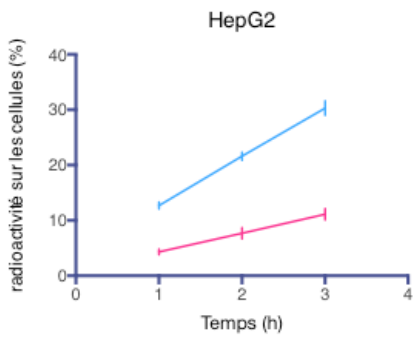
hypoxia / normoxia



Prostate cancer

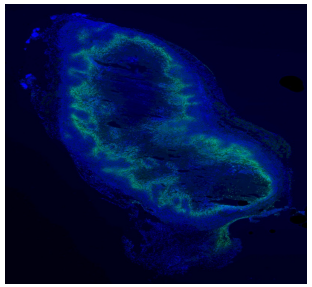


Breast cancer

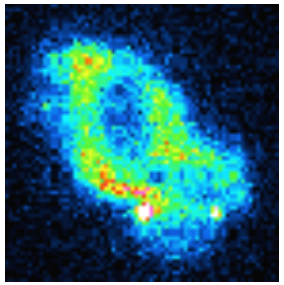


Hepatocellular carcinoma

ex vivo validation in Animal model



pimonidazole



autoradiography

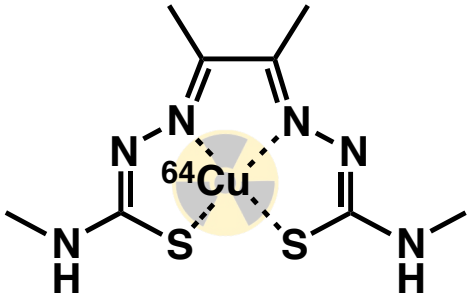
[^{64}Cu]-Cu-ATSM Clinical trial

IMPD

EudraCT 2018-002079-17

U.S. National Library of Medicine ClinicalTrials.gov NCT 03951337

« *Evaluation of 64Cu-ATSM PET/CT in Predicting Neo Adjuvant Treatment Response in Locally Advanced Rectum Cancer* »



Institutional promotion: Institut de Cancérologie de l'Ouest, CHU NANTES, ARRONAX

Principal objective: Relationship between early tumor uptake of ^{64}Cu-ATSM PET/CT images and prediction of histological response to neo-adjuvant chemo-radiotherapy treatment

Secondary objectives

- Relationship between late tumor uptake of ^{64}Cu-ATSM PET/CT images and prediction of histological response to neo-adjuvant chemo-radiotherapy treatment
- Correlation between ^{64}Cu-ATSM uptake and oxidative stress markers
- Progression free survival
- ^{18}FDG-PET/CT and ^{64}Cu-PET/CT uptakes
- Comparison between early and late ^{64}Cu-ATSM uptakes in ^{64}Cu-ATSM PET/CT images
- ^{64}Cu-ATSM toxicity

[^{64}Cu]-Cu-ATSM Clinical trial

2018-002079-17

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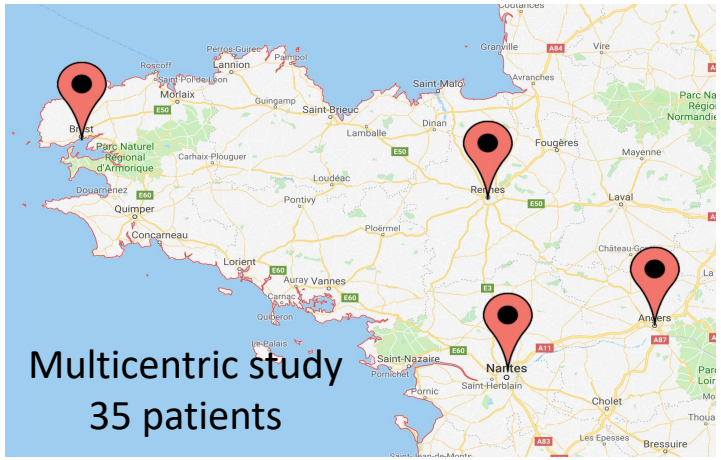
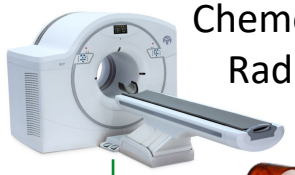


Rectum cancer Diagnostic

MRI
^{18}F-FDG PET

^{64}Cu-ATSM
3 MBq/kg



Chemotherapy (Capecitabine)
Radiotherapy (25 x 2 Gy)

MRI
^{18}F-FDG PET

Surgery

45 D. (max)	5 weeks	4 weeks	2-4 weeks	**2 years following**

[^{64}Cu]-Cu-ATSM Clinical trial

IMPD

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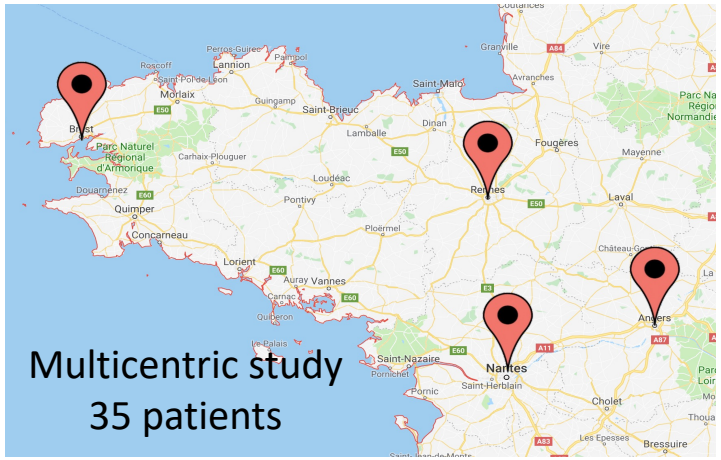

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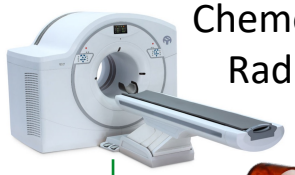

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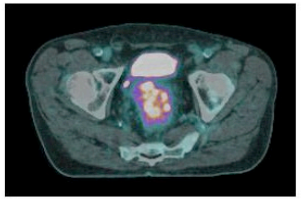
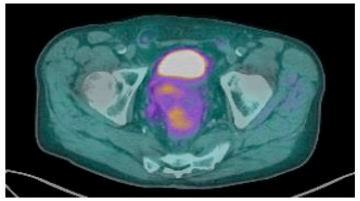
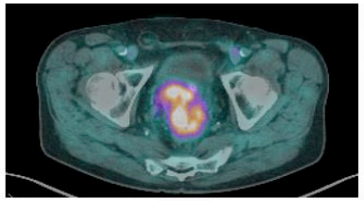


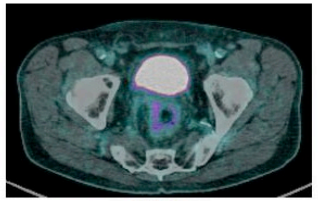
FDG initial



Cu-ATSM 1h



Cu-ATSM 24 h



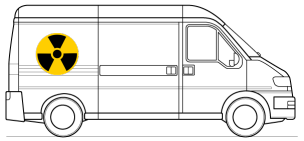
FDG post neoadjuvant treatment

[^{64}Cu]-Cu-ATSM Clinical trial – ARRONAX timeline

Publication of a previsional ^{64}Cu production calendar

Patient inclusion

^{64}Cu-ATSM ordering

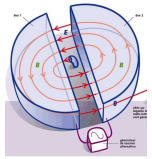


min. 5 days | ^{64}Ni(d,2n)^{64}Cu | Target reception Copper purification | ^{64}CuCl$_2$ QC | [^{64}Cu]-CuATSM Radiolabeling | ^{64}CuATSM QC | Batch release Transport | **Injection**

Monday 08:00 pm

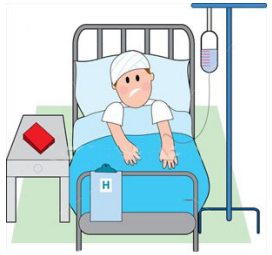
Tuesday 06:00 am 11:00 am 1:00 pm 4:30 pm 6:30 pm 7:30 pm

Wednesday 08:00 am 04:00 pm



Cyclotron production

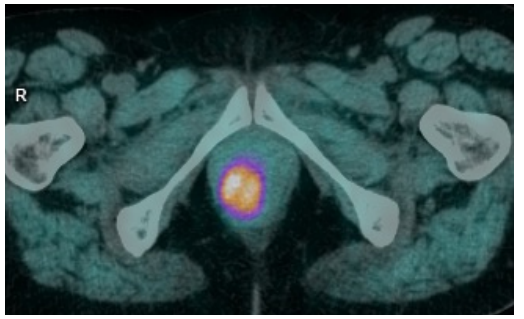
BET
GC
HPLC

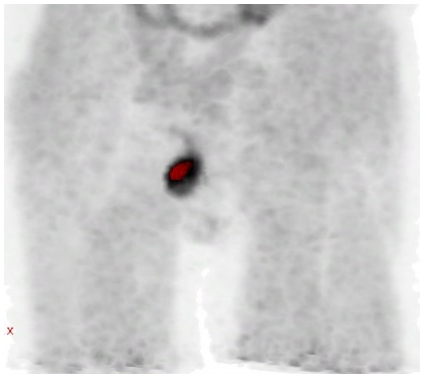


[^{64}Cu]-Cu-ATSM Clinical trial - Methodology

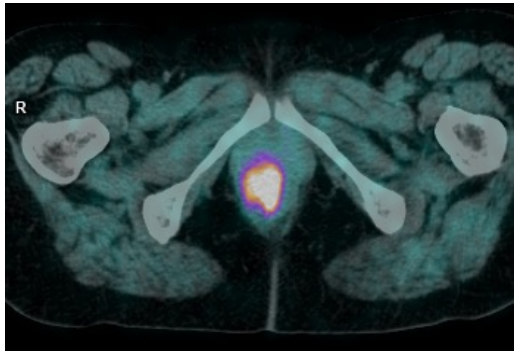
- Acquisitions → pelvic region at 1- and 24-hours
- Segmentation's methods:
  - rectal tumor 70% threshold delineation
  - Gluteal muscle VOIs manual delineation
- Visual and semi-quantitative image analyses:
  - **SUV**max, **SUV**mean,
  - tumor-to-muscle-ratio (**T/M**),
  - Hypoxic-Tumor-Volume (**HTV**),
  - Hypoxic-Burden (**HB**: HTV x SUVmean)
  - Metabolic Tumor Volume (**MTV**)
  - Total Lesion Glycolysis (**TLG**)
- ΔMTV and ΔTLG (FDG1-FDG2/FDG1) were calculated

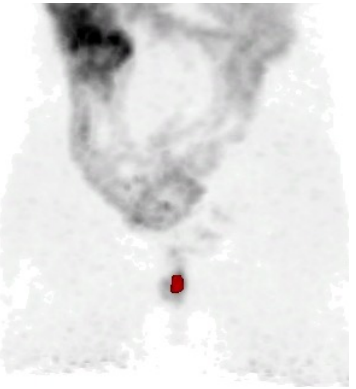
64Cu ATSM-D0



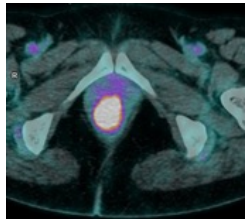


64Cu ATSM-D1

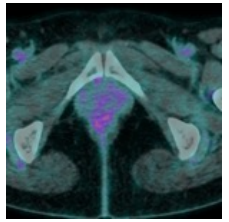




Patient #1

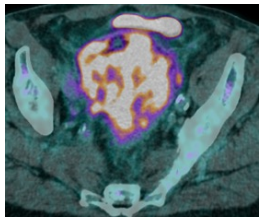


^{18}F-FDG #1

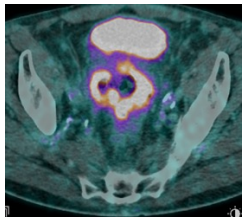


^{18}F-FDG #2

Patient #2



^{18}F-FDG #1

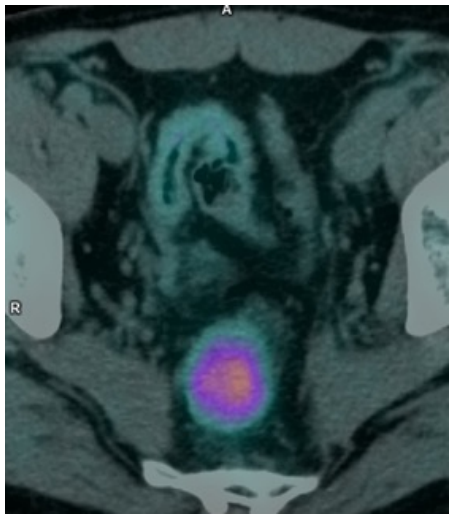


^{18}F-FDG #2

[^{64}Cu]-Cu-ATSM Clinical trial – Preliminary results

RESPONDER PATIENT

64Cu-ATSM D0

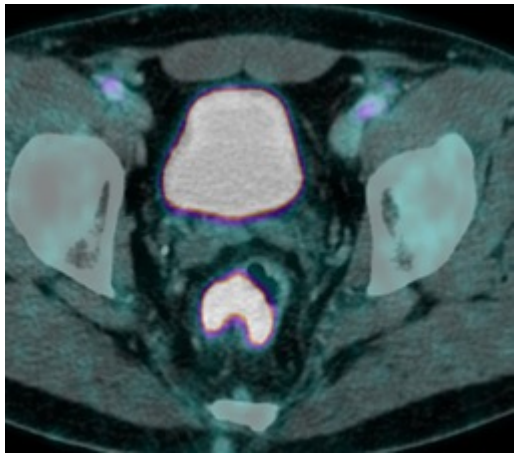


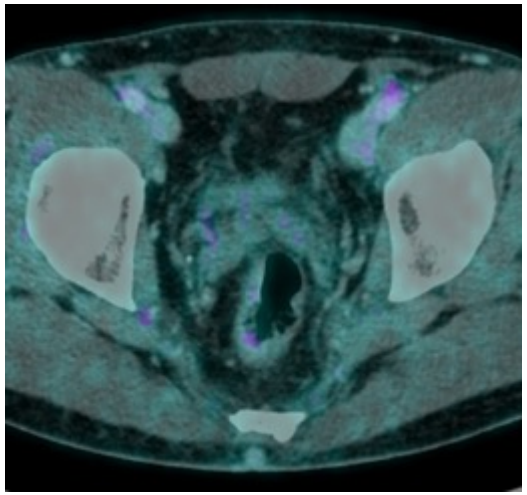
Tumor uptake

FDG 1

ΔTLG -99,7%

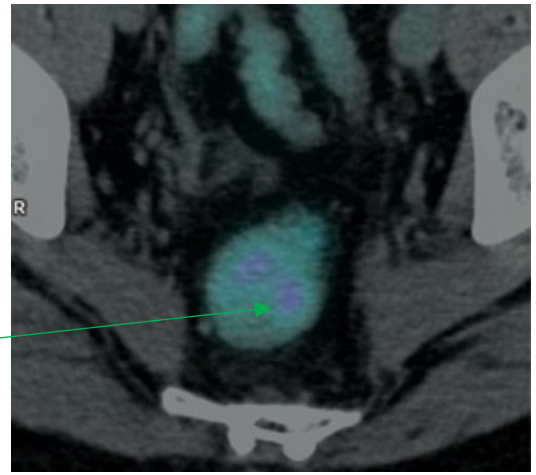
FDG 2





64Cu-ATSM D1

No residual tumor uptake

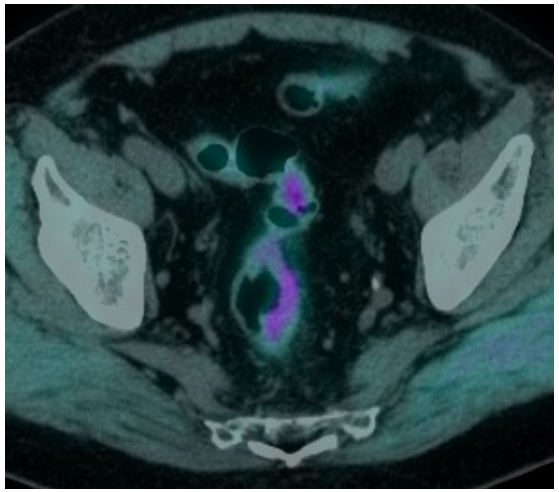


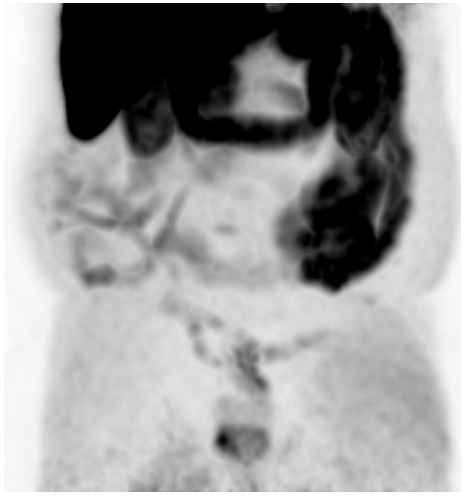
Physiological digestive uptake

[^{64}Cu]-Cu-ATSM Clinical trial – Preliminary results

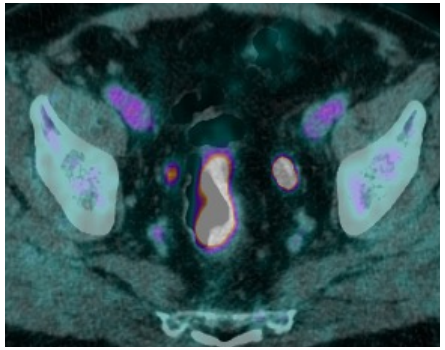
NON RESPONDER PATIENT

64Cu-ATSM D0



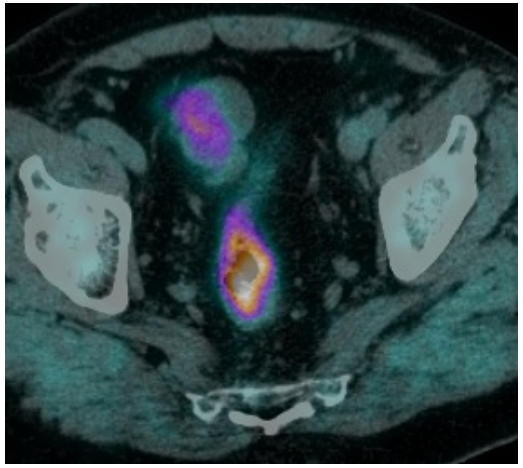


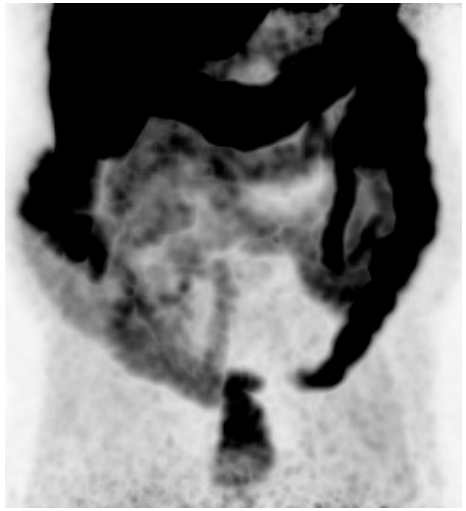
FDG 1



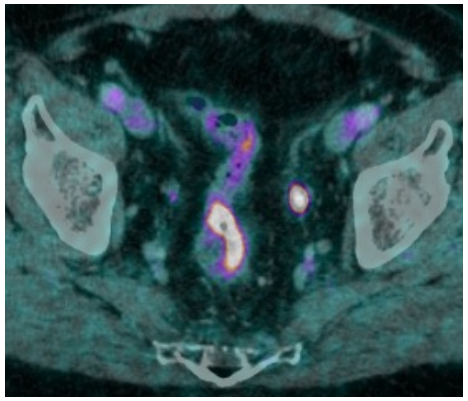
ΔTLG
-79%

64Cu-ATSM D1





FDG 2



Increasing
tumor uptake

Conclusion & Take home message

Multidisciplinary and partnership work

Important scale-up aspect

High repeatibility at each steps

Strong link with clinical team

Legal & Regulatory aspects

ansm
Agence nationale de sécurité du médicament et des produits de santé

Thank you for your attention