Production and separation of ^{165}Er from natural Ho target on Orléans ' Cyclotron

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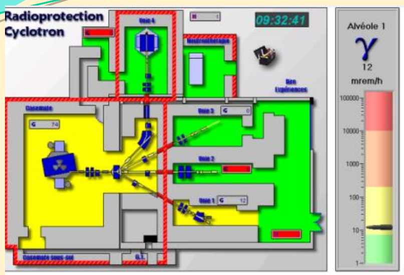
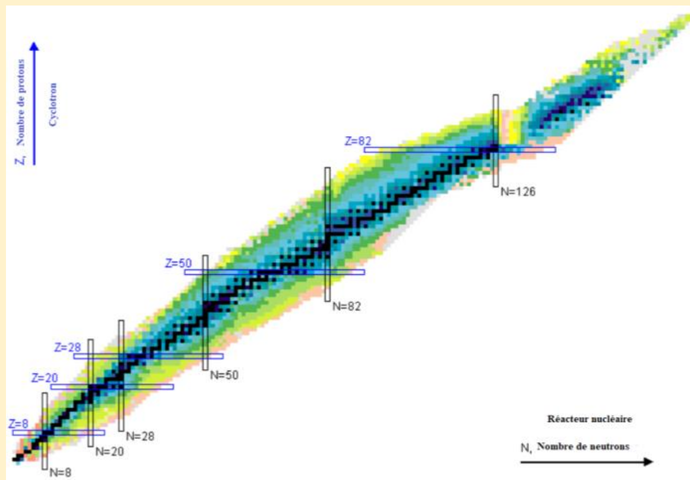
CEMHTI : Conditions Extrêmes et Matériaux : Haute Température et Irradiation
(Extrems conditions and Materials : High Temperature and Irradiation)
UPR 3079, CNRS, Orléans, France

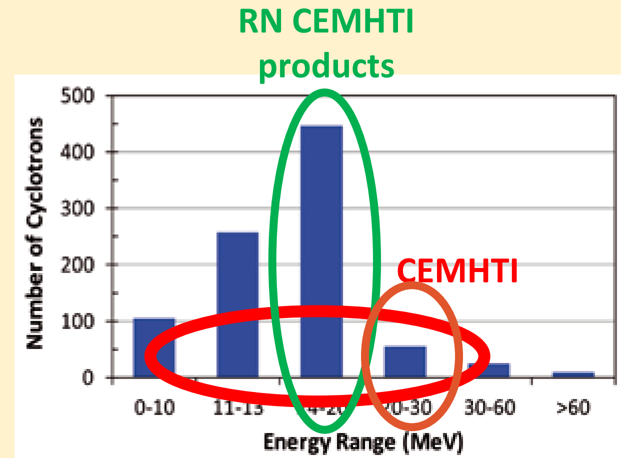
CGR-MeV 680 Cyclotron[1]

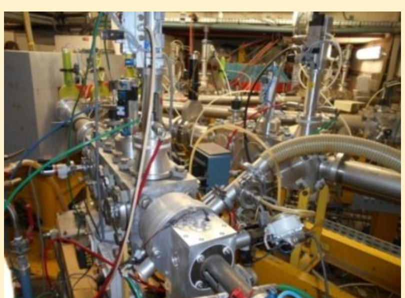


- ❑ Multienergy (10 – 45 MeV)
- ❑ Various particules : proton, deuteron, alpha

RN	Beam Energy (MeV)
^{11}C	12 (p)
^{165}Er	16 (p) → 17,5(d)
^{89}Zr	16 (p)
^{52}Mn	14 (p)
^{64}Cu	12 (p)
^{211}At	29 (a)







→ 10-23MeV : Commercial Cyclotron (I= 100µA) with proton
→ > 23MeV : Research Cyclotron (CEMHTI) exotic Rn

[1] Calandroni D., *Proc. 7th Int. Conf. on Cyclotrons and their Applications, Birkhäuser, Basel, Switzerland*, **1975**, 88-91.

Radiochemistry

Radioactivity + Chemistry

Signal + Form | **Quantification + Speciation**

Scale	"Indicators"		µ-Traces		Traces		"Classic" chemistry	
Atoms number	6	6 x 10^{15}		6 x 10^{18}		6 x 10^{20}		6 x 10^{23}
[Atoms] in mol/l	10^{-23}	10^{-8}		10^{-5}		10^{-3}		1

Example : 50MBq/ml ^{165}Er in 5M HNO3

For physicists
2,7.10^{12} atoms of ^{165}Er
1 atom of interest for 10^9 molecules of solvent

For chemists
4,5.10^{-9} mol/L of ^{165}Er
0,6.10^{-3} mol/l ^{165}Ho cold(0,1mg)

Ratio nat Ho/ ^{165}Er = 10^6

Notion of specific radioactivity: 165 Er 1g ➔ 6,8.10^{16}Bq or 1Bq ➔ 15ag (10^{-18})
Sensibillity ICP-MS : 1ppb (1µg/l) ➔ concentration of 50MBq ^{165}Er/ml

► **A radiochemist develop separation protocol of one or various radionuclides in a mixture, with or not stable elements in macro-concentration and he quantifies these elements by detection techniques for ionizing radiation.**

Radiochemistry : Why ?

- Applications areas :
  - Physico-chemical characteristics **(IRAMAT)**
  - Nuclear characteristics
  - Exotic radionuclides (nuclear physics, astrophysics,…)
  - Dating **(ISTO)**
  - Production of radionuclides for imaging, α-therapy… **(CEMHTI)**

➔ **Concept of radiotracers**

➔Method very sensitive

Applications of Cyclotron

- Material studies under irradiation
  - *In-situ* Raman spectroscopy
  - Interaction defects – rare gases
  - Solid/Water interface radiolysis
  - Mechanical properties under irradiation

- Ultra-Thin Layer Activation (UTLA) and Thin-Layer Activation (TLA)

- Dosimetry

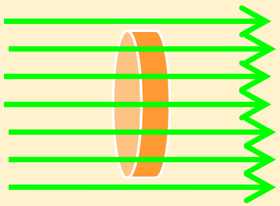
- Archeometry

- Geochronology

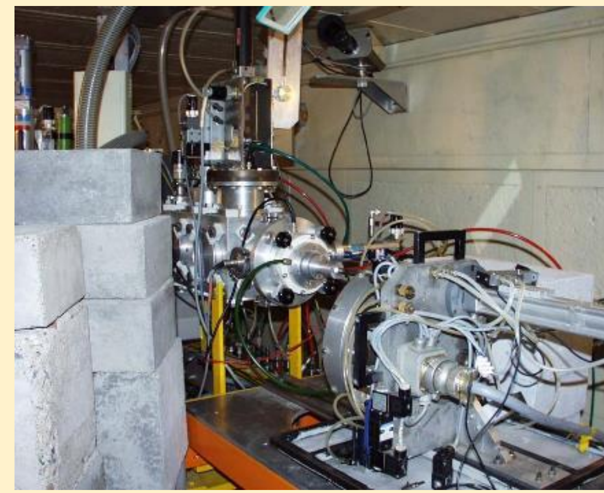
- Radiochemistry

Production of radiotracers

Fast Neutron Activation Analysis using a cyclotron (FNAA)[2,3]

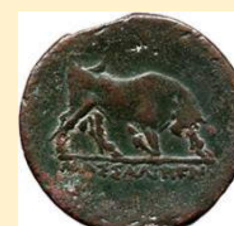


- ❑ Neutron beam : (p,n) nuclear reaction
- ❑ Be target at E= 17,5 MeV (deutons)
- ❑ E(neutrons) = 6-8 MeV
- ❑ Nuclear reactions : (n,p), (n,2n), (n,α)



Developed in 1980’s at Orleans for Cu and Ag based coins (J.-N. Barrandon and his colleagues[1])

- ❑ Radionuclides
- ❑ Homogeneous irradiation : bulk analysis



[2] : Beauchesne, F. & Barrandon, J.-N., 1986, Analyse globale et non destructive des objets archéologiques cuivreux par activation avec des neutrons rapides de cyclotron, *Revue d’Archéométrie*, 10, p. 75-85.
[3] Beauchesne, F. *et al*., 1988, Ion beam analysis of copper and copper alloy coins, *Archaeometry*, 30, 2, p. 187-197.

Elemental analysis of ancient bronze coins

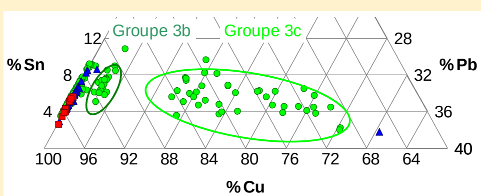
- ❑ Measure ϒ rays emitted coin

Gamma-spectrometry room
(IRAMAT-CEB laboratory)

- ❑ Elemental composition of coins

- ❑ % of pure metals / recycled metals on crucible
- ❑ Composition of ore extracted from a given mine
- ❑ Metallurgical processes applied
- ❑ Behaviour of elements from an allow (melting process)
- ❑ Corrosion phenomena (burial of coin)

Evolution of composition
= fct(Time) → % Pb



Antique bronze coins
Massalia (Marseille)

Unique Method used only at Orleans

- ❑ Non-destructive method
- ❑ Major elements (11) determined :
  - ❑ Ag, Cu, As, Au, Co, Fe, Ni, Pb, Sb, Sn, Zn
- ❑ Sensitive Method :
  - ❑ Cu-based coins: 0.1 ppm < LoDs < 50 ppm
  - ❑ Ag coins : 5 ppm < LoDs < 0.2 %

Dating method in Prehistory : ratio $^{39}Ar/^{40}Ar$

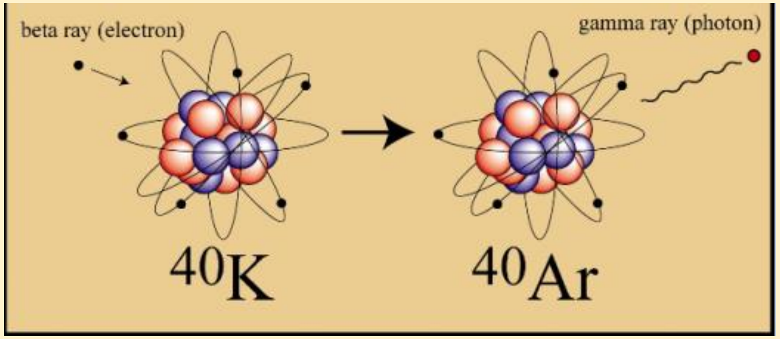
$^{39}K(n\_f,p)^{39}Ar$ (fission neutrons)

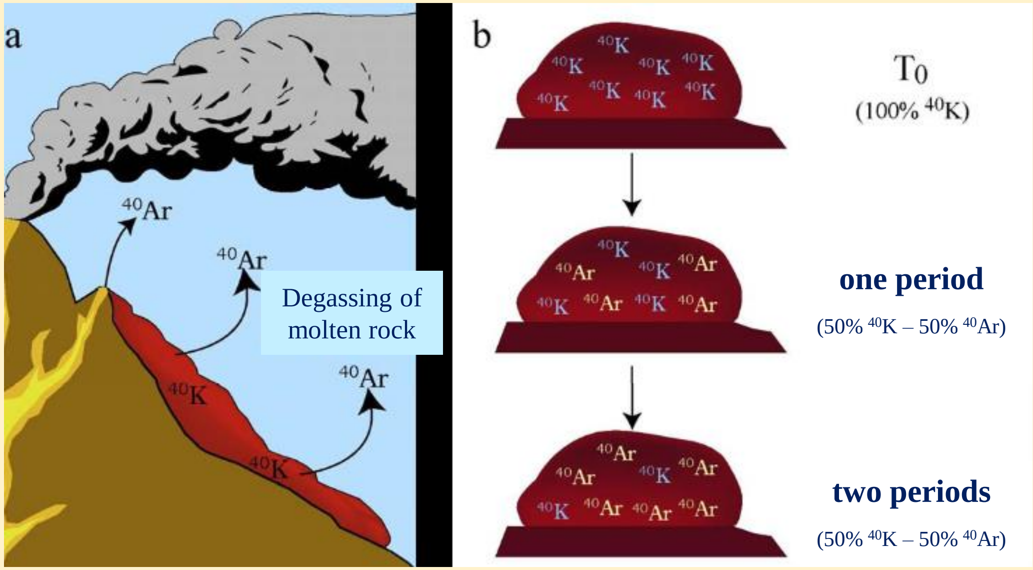
$^{39}K \rightarrow {}^{39}Ar$ / $^{40}K \rightarrow {}^{40}Ar$

$^{39}Ar / {}^{40}Ar \rightarrow {}^{39}K/{}^{40}K$

$^{39}K/{}^{40}K$ nat $\neq {}^{39}K/{}^{40}K$ exp.

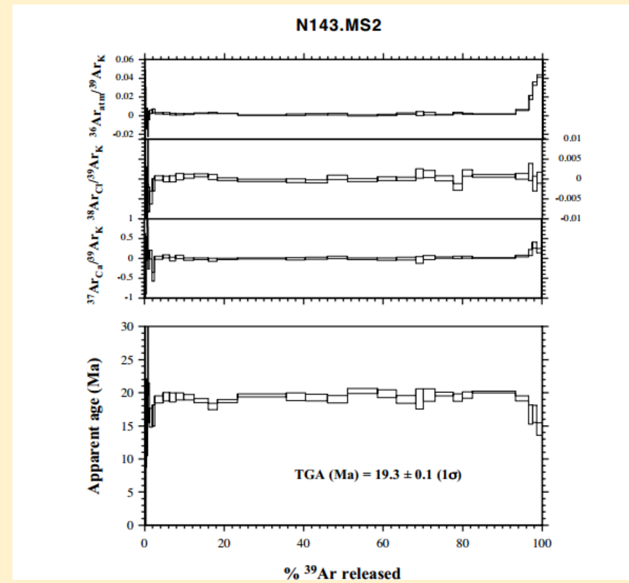
Rock Datation





Courtesy of Pierre Voinchet (MNHN)

Determination of ratio $^{39}Ar/^{40}Ar$



Apparent Age spectrum 20 Million years

- ❑ Analysis by Mass Spectrometer
- ❑ Progressive degassing sample by continuous power laser beam (CO_2 laser)

Age of closure of the mineral
(metamorphic muscovite of a crystalline basement)
during its exhumation (by tectonics and erosion).

Radiotracer and imaging

❑ **Nuclear medicine**

Radionuclide

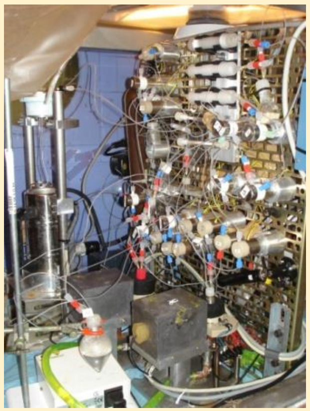
Diagnosis

Therapy

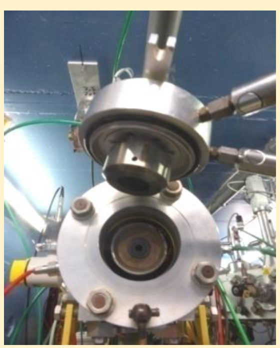
^{81m}Kr, ^{18}F, ^{99m}Tc, ^{11}C

^{131}I, ^{89}Sr, ^{153}Sm, ^{90}Y
(emitter β- pur, é Auger)
^{211}At (emitter alpha)

Radiochemistry : Generalities



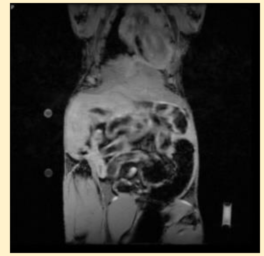
- **<u>Activities</u>** :
  - Engeneering for production « exotics » Rn :
    ^{52}Mn, ^{89}Zr, ^{165}Er, ^{211}At, ^{64}Cu
  - Development of Rn for analytical use :
    ^{88}Y (^{89}Zr) , ^{51}Cr (^{52}Mn), ^{166}Ho (^{165}Er)
  - Automation of separation process



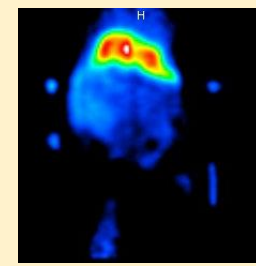
- **<u>Means</u>** :
  - 4 shielded cells
  - Targetry for solid target (< 3µA/h)
  - Detection : gamma spectrometry

What kind of imaging for the living ?

- **<u>3 kinds of imaging :</u>**

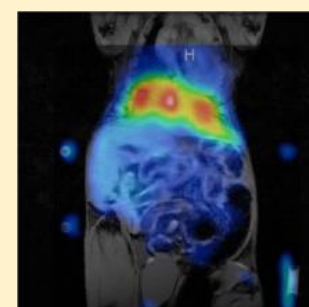


- <u>Morphological</u> : anatomy study
  - MRI scanner…



- <u>Functional</u>: studies of biochemical and physiological process
  - Imaging scintigraphic imaging, SPECT/PET (Single Photon Emission Computed Tomography/ Positon Emission Tomography)

- <u>Molecular</u> : visualisation specific proteins or signals from these compounds
  - Scintigraphic imaging, optical, MRI, SPECT-PET

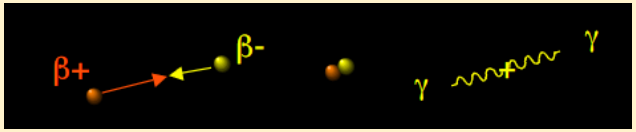


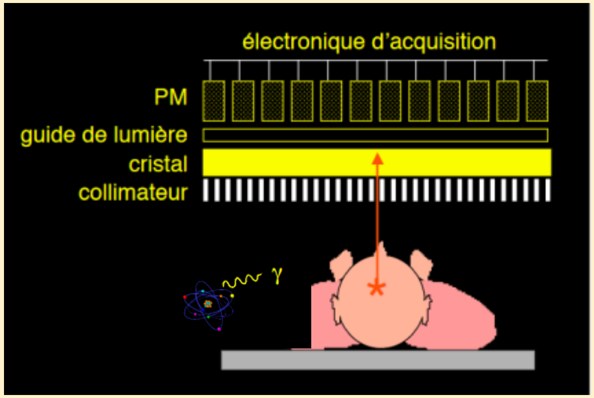
  - Development of bimodality imaging :
    - morphology+ molecular for example ➔ MRI/PET

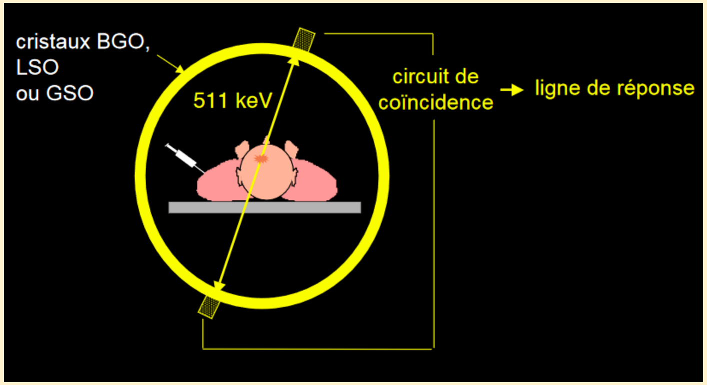
Bimodality MRI/ SPECT-PET

- ❑ MRI : Magnetic Resonance Nuclear
  - ➢ Resolutive but not quantitative imaging
- ❑ SPECT-PET :
  - ➢ Quantitative but no resolutive imaging

ɣ emission (SPECT) Positon emission (PET)



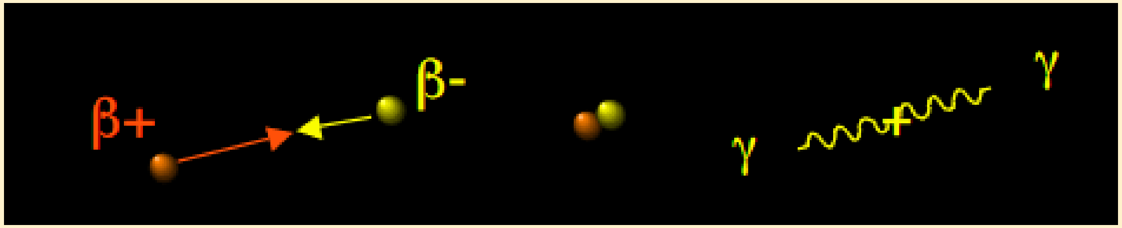




Why these limits ?

- **MRI**
  - contrast agent→ paramagnetic element
    - 2 bons candidates : Gd et Mn
    - Toxicity → [Gd^{3+}] ou [Mn^{2+}] mmoles

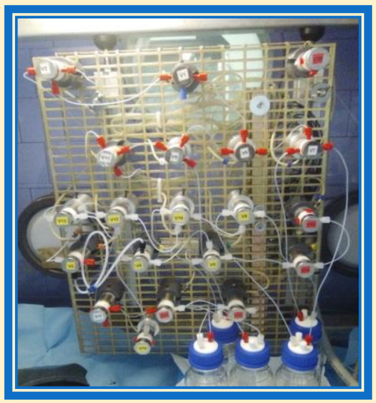
- **SPECT/PET :**



  - Origin of emission and annihilation not same, average distance depend from E(β+)max

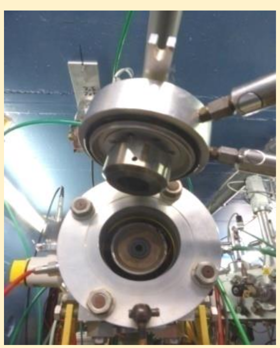
➔ **Limiting factor for intrinsic spatial resolution of skill.**

Bimodality at Orleans' Cyclotron : ^{165}Er and ^{52}Mn



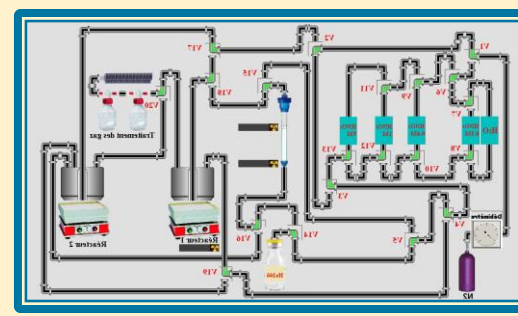
❑ ^{165}Er :

- Determination of Dw (Ho/Er)
- Separation on column



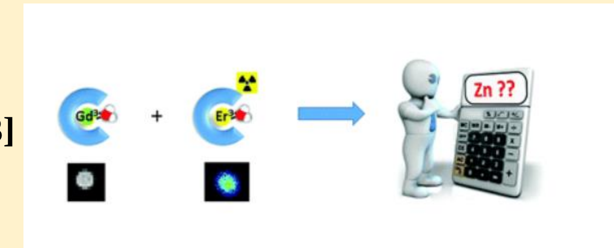
❑ ^{52}Mn :

- Design of target Cr
- Dw (Cr/Mn)



➢ **First tests of automated separation with ACCRA**

Bimodality, first step : ^{165}Er ($T_{1/2}$=10,36h) [4]



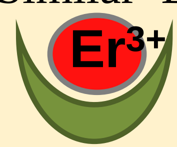
- **Goal : Development of bimodal probes for MRI**
- **- PET/SPECT imaging to detect Zn (II) (in vitro) [3]**

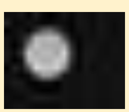
- **For MRI → Gd $^{3+}$ and for SPECT imaging Er $^{3+}$**

La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu

- Ln^{3+} : Different physical properties but similar chemistry → Similar Biodistribution

Bimodality imaging



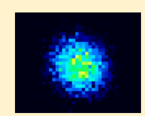


T1

MIR 1,5T

→ **Resolution**

→ **Sensitivity**



Activity (MBq)

ϒ caméra

[4] P. K. Malikidogo, I. Da Silva, J-F. Morfin, S. Lacerda, L. Barentin, T. Sauvage, J. Sobilo, S. Lerondel, E. Toth and **C. Bonnet**, *"A cocktail of $^{165}Er^{3+}$ and Gd^{3+} complexes for quantitative detection of zinc by SPECT/MRI"* , ***Chem. Commun.***, 2018,**54**, 7597-7600

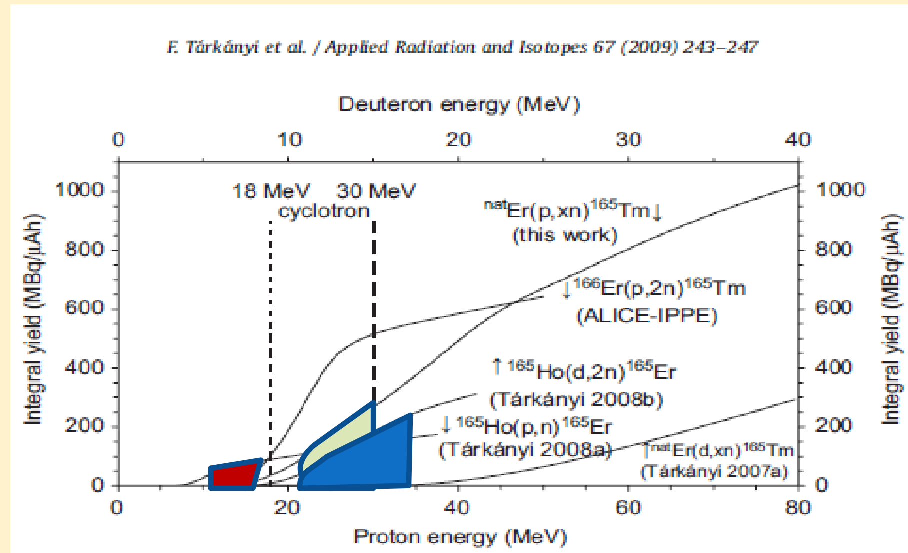
Production of ^{165}Er

Nuclear reactions to ^{165}Er :

- ❑ Target natural Er [25]
  - ^{nat}Er (p, xn) ^{165}Tm → (by decay) ^{165}Er
  - ^{nat}Er (d, xn) ^{165}Tm → ^{165}Er

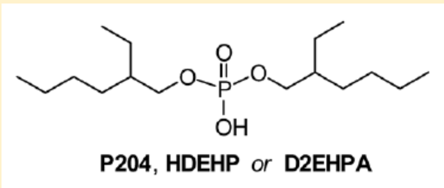
➔ But ^{nat}Er multiisotopes

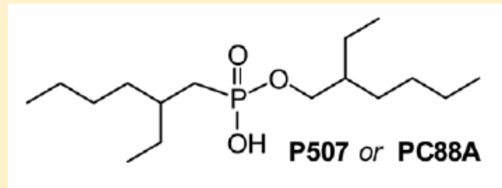
- ❑ **Target natural Ho (monoisotope 165)**
  - **^{165}Ho (p, n) ^{165}Er at 16MeV**
  - **^{165}Ho (d, 2n) ^{165}Er at 17.5MeV**

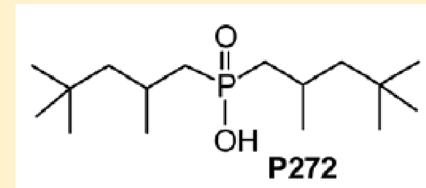


➢ **Yield by deuteron as higher than proton way**
  - Production of ^{166}Ho (27.2h)
  - Ratio $^{165}Er/^{166}Ho$: 8/1 in deuteron and 400/1 in proton

Separation of Ln adjacents : Ho/Er [5]





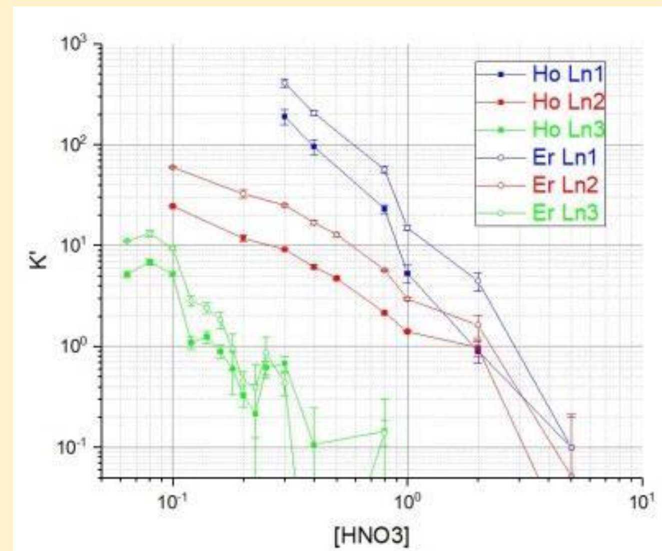


LN **LN2** **LN3**

➢ **Resin LN (Triskem)**

❑ Batch Method : Parameters

- ❑ [HNO3] : 0,02 → 5M
- ❑ Time contact (min) : 30minutes



➔ Phosphonic and phosphinic acids are more hydrolytic stable and effective extractants /HDEHP [6].

➔ High selectivity for the "heavy"REE (hREE) compare to "light"REE (lREE) .

[5] Justine Vaudon , Louis Frealle, Geoffrey Audiger, Elodie Dutillly, Mathieu Gervais, Emmanuel Sursin, Charlotte Ruggeri, Florian Duval, Marie-Laure Bouchetou , Aude Bombard , Isidro Da Silva ,*First steps at the cyclotron of Orléans in radiochemistry of radiometals: ^{52}Mn and ^{165}Er, mdpi 2018 (on press)

[6] Nifant'ev, I.E.; Minyaev, M.E.; Tavtorkin, A.N.; Vinogradov, A.A.; Ivchenko, P.V. Branched alkylphosphinic and disubstituted phosphinic and phosphonic acids: Effective synthesis based on α-olefin dimers and applications in lanthanide extraction and separation. RSC Adv. **2017**, 7, 24122–24128.

Factor Separation of resin LN2

- ❑ Determination of Dw at 50% of capacity of resin

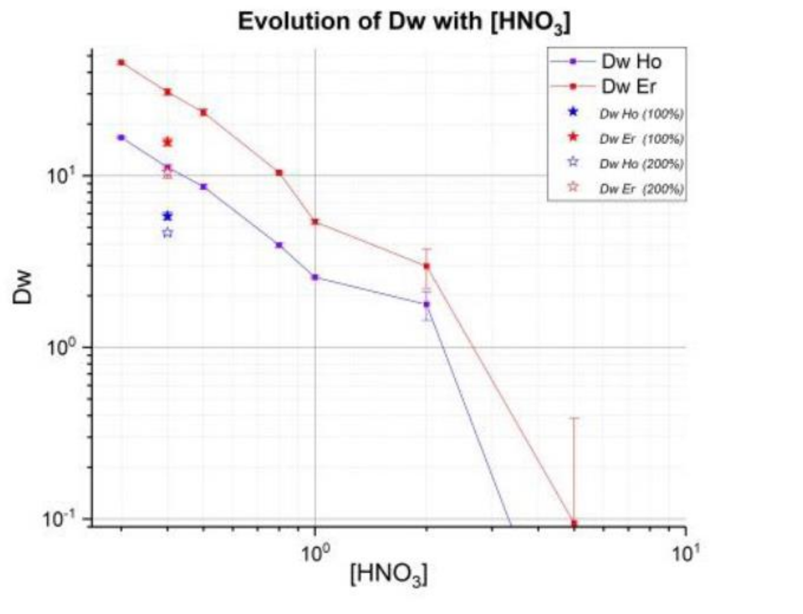


Figure 6. D_W de Er/Ho with LN2.

Table 1. D_W and SF of Er and Ho in HNO_3.

HNO_3	D_W (Er)	D_W (Ho)	SF $_{Er/Ho}$
0.3 M	45.7 ± 1.3	16.7 ± 0.4	2.74
0.4 M	30.8 ± 2.0	11.2 ± 0.5	2.75
0.4 M 100	15.4 ± 1.2	5.8 ± 0.4	2.70
0.4 M 200	10.5 ± 1.1	4.7 ± 0.2	2.25
0.5 M	23.4 ± 1.5	8.6 ± 0.4	2.71
0.8 M	10.4 ± 0.2	3.9 ± 0.1	2.65
1 M	5.4 ± 0.2	2.6 ± 0.1	2.11
2 M	3.0 ± 1.0	1.8 ± 0.4	1.67
5 M	0.1 ± 0.4	-0.4 ± 0.3	-0.21

Separation with column of resin LN2

- Target irradiated with deuterons 17,5MeV
- Resin Ln2 (TRISKEM)
- Gradient elution in nitric acid :
  - 1/ 0.4M ….110mL (90% of Ho extracted)
  - 2/ 1M……..40mL (98% of Er extracted) (need to be fractionned)
  - Yield of extraction (%) : Ho= 91 ± 5 (n=3) / Er = 94 ± 7 (n=3)
  - Reduction ratio Ho/Er : 1294 ± 1183 (n=3)

Sample	HNO_3 Vol. (mL)	HNO_3 [conc.] (M)	Batch of ^{165}Er — % of all activity of Rn: ^{166}Ho	Batch of ^{165}Er — % of all activity of Rn: ^{165}Er
1	11	1	0.07	72.7
2	10	1	0.00	63.9
3	15	2	0.08	75.7
4	4	1	0.37	76.8
mean			0.13	72.3

Test	Ext. Yield (%) ^{166}Ho	Ext. Yield (%) ^{165}Er	Cutted target Mass (mg) ^{165}Ho	Batch of ^{165}Er Activity (Bq) ^{166}Ho	Batch of ^{165}Er Activity (Bq) ^{165}Er	Batch of ^{165}Er Ratio $^{165}Er/^{166}Ho$	$F_{Ho\ (cont.)}$
1	92	98	88.4	5.7E+03	5.4E+07	9397	1123
2	95	98	57.4	1.4E+03	3.0E+07	21070	2553
3	ND	ND	53.8	3.1E+03	2.6E+07	8356	ND
4	86	86	74.7	1.7E+04	3.0E+07	1773	206
Mean	91	94				10149	1294

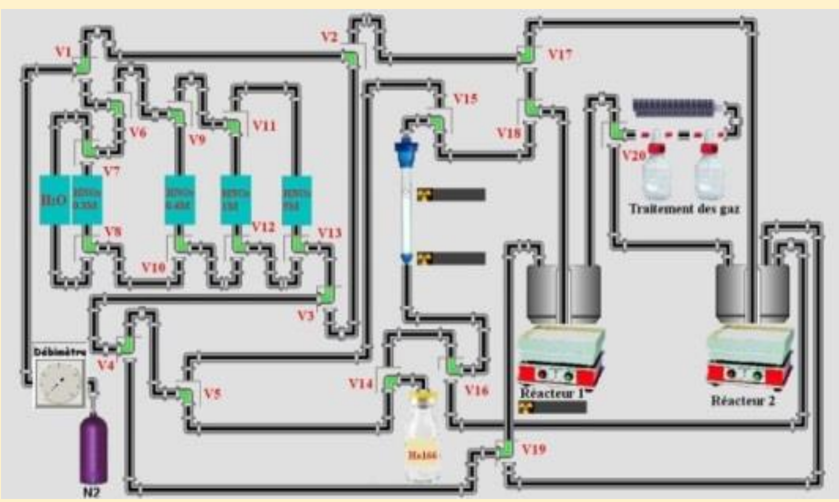
^{165}Er : Automation system

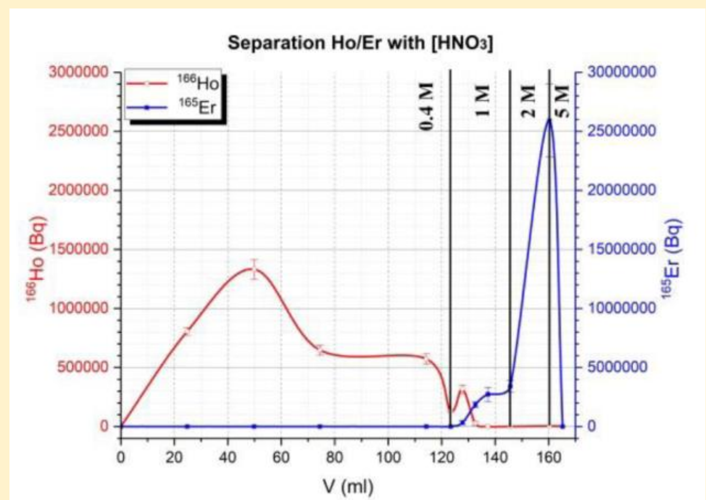
Use of ACCRA (Automatisme & Contrôle Commande Radiochimie)

22 INPUT-OUTPUT controlled by siemens automate (competence in electronics) state 0 or 1

Now that it's easy for a radiochemist not have big competences in electronics !!!

- Create a sketch of your set up in paint file
- Create a word file to coordinate real command of switch with position in sketch
- Create a second word file to define for all step state of switch,



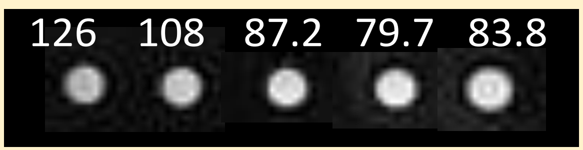


Proof of concept validated (*in vitro*)

❑ Applications of ^{165}Er

- ❖ Radiolabelling molecules
- ❖ Proof of concept for imaging and biodistribution
  - (a) T_1-weighted images (T_1 values in ms are given)
  - (b) images from the γ-camera (activities in kBq are given) of the 5 samples.

a)



b)

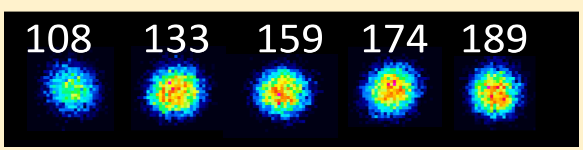


Table 1. Zn^{2+} concentration determined by the use of the bimodal cocktail of LnL (exp), and by ICP (th).

	$[Zn^{2+}]_{exp}$ (mM)	$[Zn^{2+}]_{th}$ (mM)	Error (%)
Sample 1	0.33	0.32	2.6
Sample 2	0.29	0.29	1.7
Sample 3	0.54	0.49	11.0
Sample 4	0.62	0.55	13.1
Sample 5	0.10	0.12	16.1

Conclusions

- **First goods results in the separation Er/Ho with LN2 resin,**
- **Proof of concept of bimodality demonstrated for in case of ^{165}Er**

➔ 2 articles in published in 2018

An oral presentation at 17th Workshop on Targetry and Target Chemistry in Coimbra 27 - 31 August 2018.

instruments MDPI

Article

First Steps at the Cyclotron of Orléans in the Radiochemistry of Radiometals: ^{52}Mn and ^{165}Er

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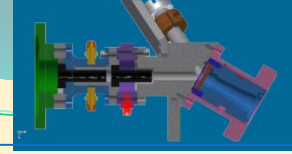

Perspectives

❑ Separation Ho / Er :

- Modification process :
- ➢ Use of 2 – 3 resins operating in series (DOWEX 50, LN, DGA)
- ➢ New resin for increase capacity of adsorption ?

❑ ^{52}Mn bimodality PET/MRI :

- ➢ Separation Cr/Mn by resin AC (Triskem)

Thank you

- **Student :**
  - Charlotte Ruggeri (Dw and resin tests)

- **CEMHTI :**
  - Louis Frealle for radiochemistry and spectrometry gamma, radiation protection service and all technical staff of cyclotron (particularly Patrice Rifard and William Hate for automation,

- **CBM** :
  - Eva Toth (project and collaboration)
  - Célia Bonnet (Manager of ANR Zicores)
  - Sara Lacerda (radiochemist in charge of all radiolabeling molecules)

- **TRISKEM** :
  - Aude Bombard and Steffen Happel

Obrigado pela atenção !!!