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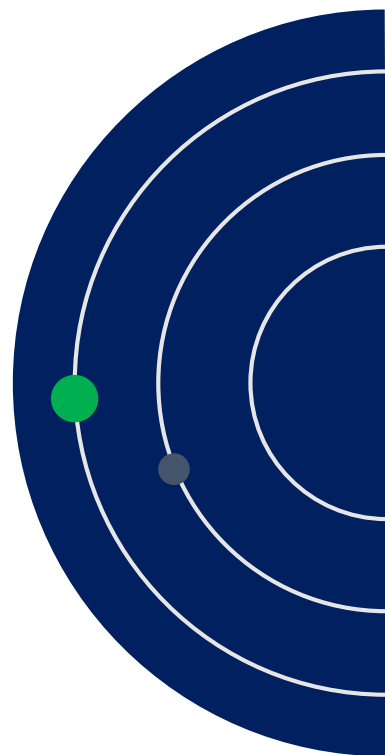
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Optimization of the Separating Resin for establishing a $^{103}\text{Ru}/^{103\text{m}}\text{Rh}$ Generator

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on the Physical, Molecular, Cellular and Medical Aspects of Auger Electron Processes

September 6-8, 2023

Institut de Recherche en Cancérologie de Montpellier - France

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Optimization of the Separating Resin for establishing a $^{103}\text{Ru}/^{103\text{m}}\text{Rh}$ Generator

I – Context

- A- Auger electron for Targeted Radionuclide Therapy
- B- $^{103\text{m}}\text{Rh}$: potential candidate for Auger therapy
- C- $^{103\text{m}}\text{Rh}$: production via generator

II – Evaluation of Ru/Rh separation with chelating resin

- A- Litterature review
- B- Retention Evaluation : Batch experiments
- C- Column tests : generator simulation
- D- Column tests : Ru^{III} retention evaluation

III – Conclusion and outlooks

I – Context

Auger electron for Targeted Radionuclide Therapy

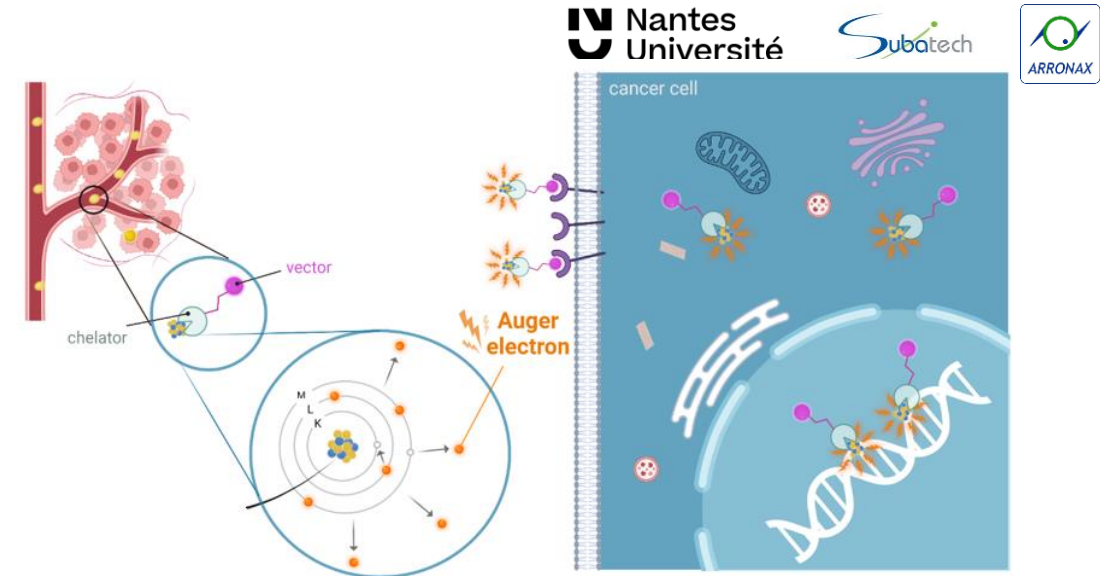
Auger and conversion emission can be applied for Targeted Radionuclide Therapy

→ Very selective treatment on the level of individual cell

1																	2	
1	H																	He
3	Li	Be															Ne	
11	Na	Mg															Ar	
19	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
37	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
55	Cs	Ba	57-71	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
87	Fr	Ra	89-103	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn	Nh	Fl	Mc	Lv	Ts	Og

● PET	● Beta Therapy
● SPECT	● Alpha Therapy
	● Auger e ⁻ Therapy

[2] T. I. Kostelnik and C. Orvig, *Chem. Rev.*, 2019, **119**, 902–956.



[1] J. Bolcaen and al., *JNudMed.*, 2023

Criteria for potent candidates

Dosimetry consideration : high level of electrons with energy less than 50 keV

Half-life

Availability of the radionuclide/Production

Chemical procedure for the radiopharmaceutical preparation

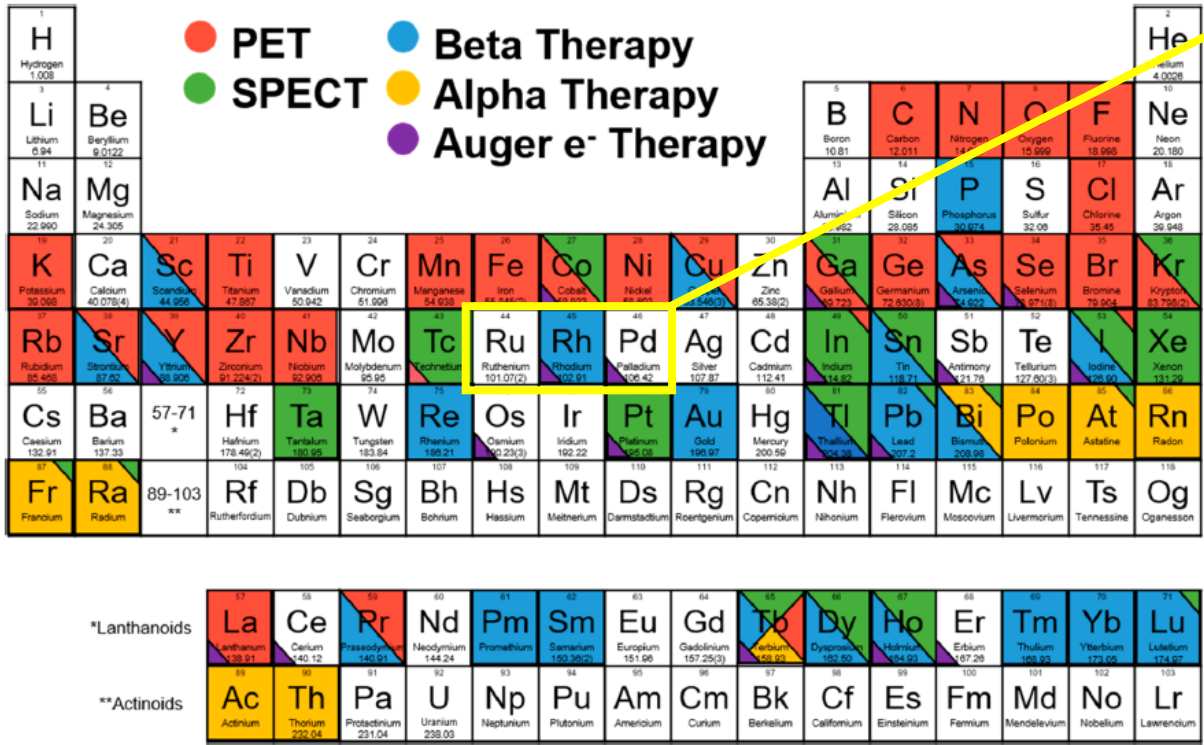
→ ¹¹⁹Sb, ⁷¹Ge, ^{58m}Co, ^{189m}Os, ^{103m}Rh, ¹⁰³Pd, ^{191g}Os, ¹⁶¹Ho, ¹⁹⁷Hg, ²³⁹Am, ¹⁷⁷Ta, ¹⁸⁹Ir, ¹⁵⁵Tb, ²⁰¹Tl, ¹²⁵I and few other. [1]

I – Context

^{103m}Rh : potential candidate for Auger therapy

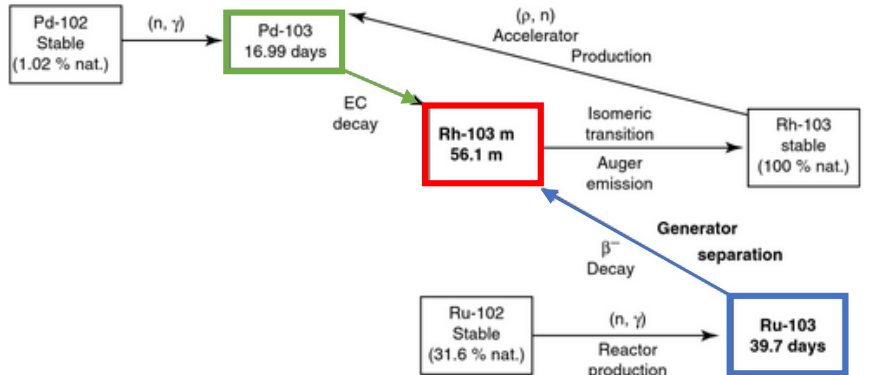
^{103m}Rh (56,1 min) : identified as a very promising therapeutic Auger electron emitter

- High electron-to-photon yield
- Associated gamma emissions are negligible (avoids non-specific irradiation)
- Decay on a **stable nucleus** (^{103}Rh)
- Short half-life = **higher dose rate**



[2] T. I. Kostelnik and C. Orvig, *Chem. Rev.*, 2019, **119**, 902–956.

Can be obtained from ^{103}Ru or ^{103}Pd

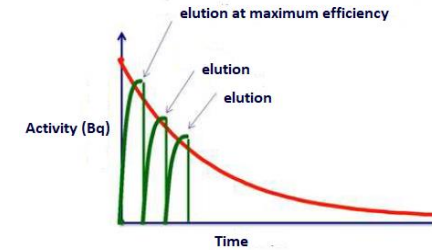
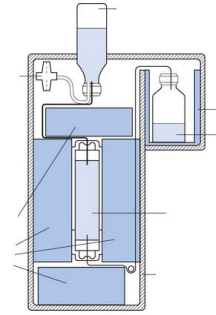


[4] Vértes, A. and al. ; *Handbook of Nuclear Chemistry* : Vol. 1.

I – Context

^{103m}Rh : production via generator

^{103m}Rh : a short half-life (56,1 min)



Radionuclide Generator

$^{103}\text{Pd}/^{103m}\text{Rh}$ Generator

More famous

- **Abundance of ^{102}Pd in $^{\text{nat}}\text{Pd}$ is very low (1,02%) : reactor production is difficult**
- **More suitable separation characteristics (and more studies)**
- $t_{1/2} = 17,0$ days for ^{103}Pd
- No gamma ray emission for ^{103}Pd = no indication of its presence
- ***in vivo* generator possible**



$^{103}\text{Ru}/^{103m}\text{Rh}$ Generator

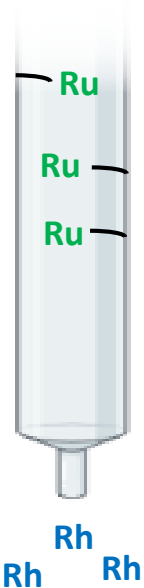
Our work

- **Several ways to produce ^{103}Ru** (neutron irradiation of $^{\text{nat}}\text{Ru}$ or $^{\text{nat}}\text{U}$, from ^{99}Mo production,...)
- ^{103}Ru easily produced in large quantities (neutron activation of Ru)
- **Complex chemical behavior**
- $t_{1/2} = 39,7$ days for ^{103}Ru
- Gamma ray ^{103}Ru : 610 keV

II – Evaluation of Ru/Rh separation with chelating resin

Main goal : Find an effective way of separating Ru and Rh (using a chromatographic system, in chlorinated media)

Not an easy task



Very similar chemistries
neighbour in the periodic table

44 101.1 Ru Ruthenium Transition Metal	45 102.9055 Rh Rhodium Transition Metal	46 106.42 Pd Palladium Transition Metal
76 190.2 Os Osmium Transition Metal	77 192.22 Ir Iridium Transition Metal	78 195.08 Pt Platinum Transition Metal

Complex chemistries

Mixture of species with different charges, polynuclear species, colloids...

Lack of data on Ruthenium chemistry in HCl and aqueous medium



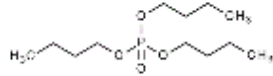
Ruthenium speciation (my first thesis work ;
Poster S.Huclier)

II – Evaluation of Ru/Rh separation with chelating resin

A- Litterature review

Liquid-liquid separation

- CCl_4 as organic phase + oxidising agent (*Epperson and al / Chiv and al*)
- Tri-n-butyl phosphate (*Haasbroek and al*)



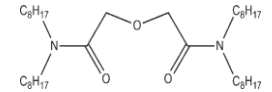
Combinaison of solvent extraction and evaporation via RuO_4

$^{103}\text{Ru}/^{103\text{m}}\text{Rh}$ generator proposed by Bartos and al.



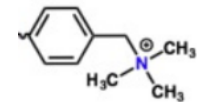
Resins tested: poor retention of Ru/ no real separation

- DGA resin Triskem[®] in HCl or HNO_3 : retention Ru < 50%



- Amberlite IRA400 Cl^- , HCl 2M + oxidising condition (*Berman al al.*)

$$\alpha_{\text{Ru/Rh}} \approx 10$$

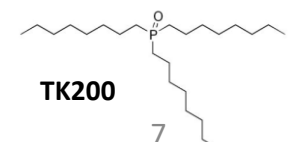
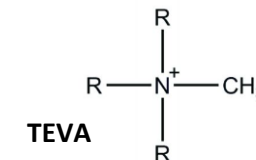


Optimal conditions :

Use of chelating resin (more specific)
Separation based on the difference in the degree of oxidation ; via Ru(IV) and Rh(III)

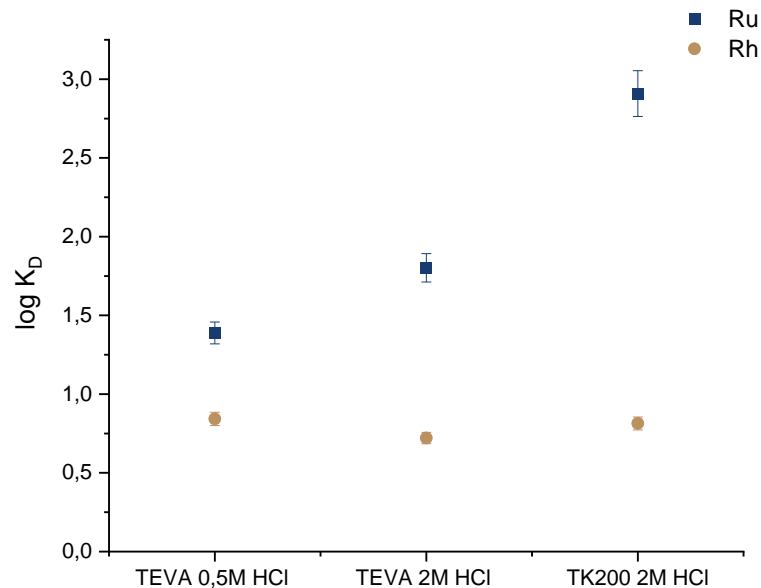


Triskem[®] TEVA and TK200



II – Evaluation of Ru/Rh separation with Triskem[®] chelating resin

B- Retention Evaluation : Batch experiments



$$\alpha_{Ru/Rh} = \frac{K_{D,Ru}}{K_{D,Rh}}$$

	%Ru on resin	%Rh on resin	$\alpha(Ru/Rh)$
TEVA 0,5M HCl	32±1%	17±1%	~3
TEVA 2M HCl	49±2%	12±1%	~7
TK200 2M HCl	97±7%	0,5 ±0,3%	~1600

Comparison of Ru and Rh retention on different Triskem resins ; $m_{résine} = 250mg$; contact time =24h ; element concentration determined by ICP-MS measurment.

TK200 Triskem resin in 2M HCl = best candidate
But slight retention of Rh on resin possible

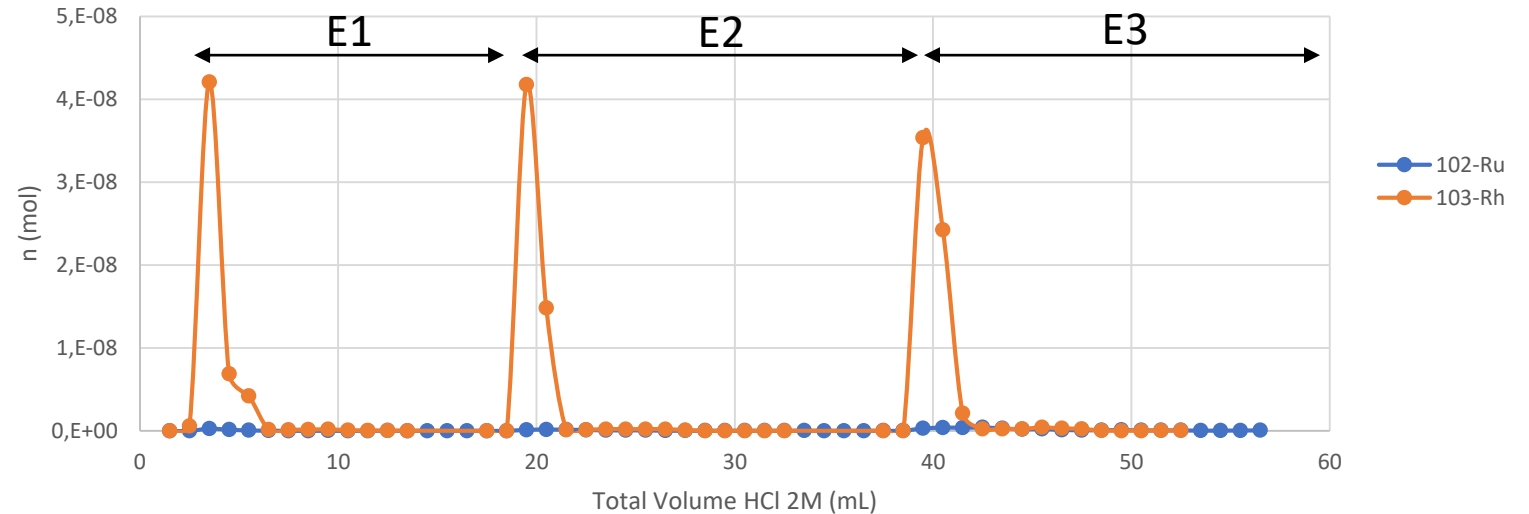


**First tests in column
Ru/Rh generator simulation**

II – Evaluation of Ru/Rh separation with Triskem[®] chelating resin

C- Column tests : generator simulation

Conditions
 $n_{Ru} = n_{Rh} \sim 5.10^{-8}$ mol (generator simulation with
 A= 100-200 MBq)
 1 load of Ru / 3 load of Rh
 V=1mL
 2M HCl
 $m_{resin} = 1,51g$
 81,5 μ L/min
 Quantification by ICP-MS



	E1	E2	E3
Age (day)	0	1	7
Ru breakthrough (%)	1,74±0,07%	2,6±0,2%	7,4±0,3%
Rh eluted (%)	80,5±0,6%	86±3%	94±3%



Slight retention of Rh on resin

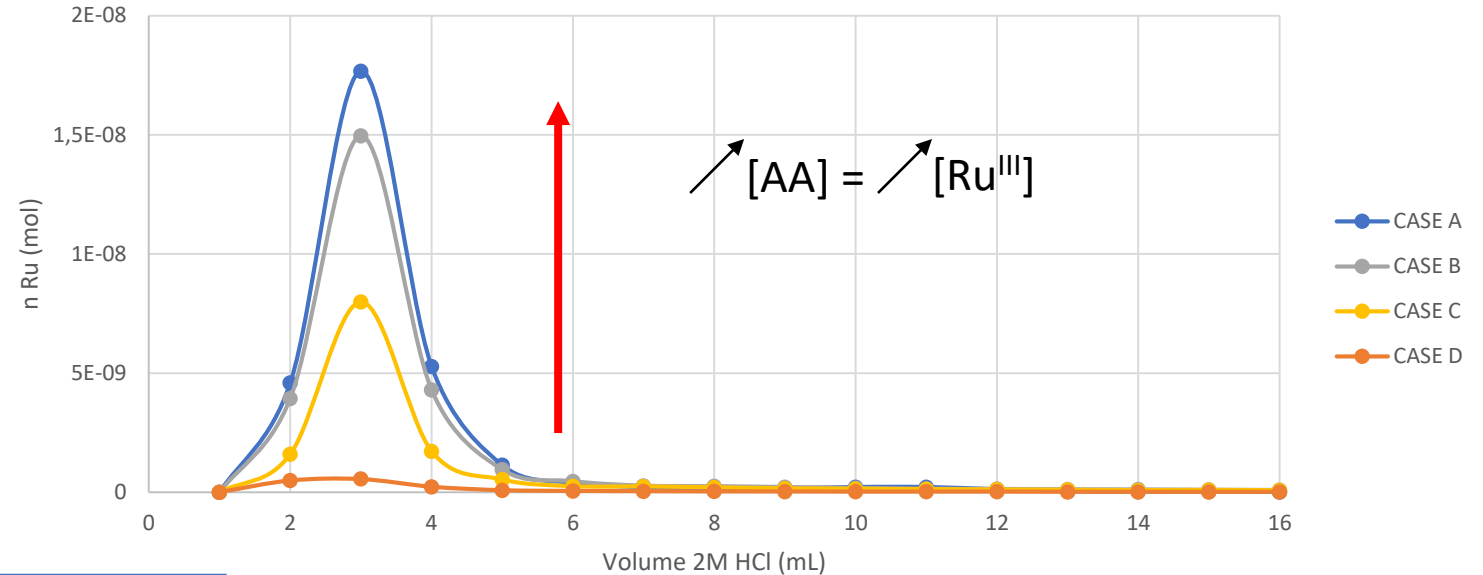
Ruthenium breakthrough increase with time

Hypothesis : partial reduction of Ru(IV) to Ru(III), not retained ??

II – Evaluation of Ru/Rh separation with Triskem[®] chelating resin

D- Column tests : Ru^{III} retention evaluation

Conditions
 $n_{Ru} \sim 5.10^{-8}$ mol (generator simulation with
 A= 100-200 MBq)
 V= 500 μ L
 2M HCl
 $m_{resin} = 1,01$ g
 1mL/min
 Variable ascorbic acid concentration :
 Quantification by ICP-MS

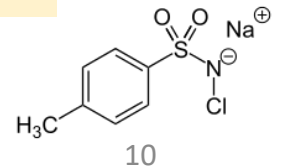


CASE	[AA] (mol/L)	Supposed %Ru(III)	% Eluted Ru
A	$1,2.10^{-2}$	100%	80 \pm 5
B	$3,75.10^{-5}$	50%	55 \pm 5
C	$1,87.10^{-5}$	25%	28 \pm 5
D	0	?	5 \pm 5

Ru^{III} not retained on TK200
 Partial reduction of Ru^{IV} in 2M HCl

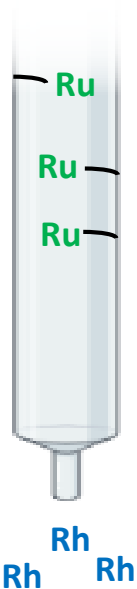
Use an oxydant to ensure that all Ru is in Ru^{IV} form ($1,0 \text{ V} < E^\circ < 1,3 \text{ V}$)

Experiments are in progress with Chloramine-T as oxydant



III – Conclusion and outlooks

Main goal : Find an effective way of separating Ru and Rh (using a chromatographic system, in chlorinated media)



- TK200 seems to be the best candidate $\longrightarrow \alpha_{\text{Ru/Rh}} \sim 1600$
- **Tests in column (Ru/Rh generator simulation)** : Slight retention of Rh + Ru breakthrough (increase with time)
- **Test retention Ru(III) on TK200** : Ru(III) not retained + partial reduction of Ru(IV) in HCl 2M

Outlooks

- Tests with an oxydant (e.g Chloramine-T) to ensure Ru^{IV} form
- First tests with ¹⁰³Ru

Thank you for your attention !