Overview and new Developments RadPharm

RRMC Workshop

Steffen Happel

03/11/2025

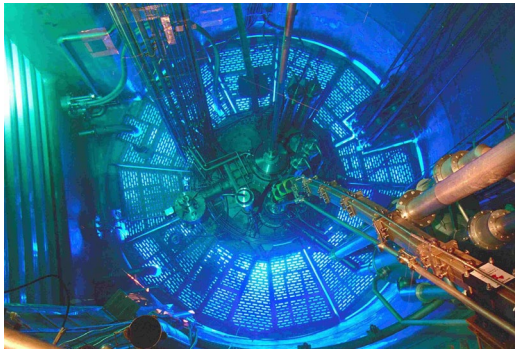
TRISKEM
Expertise in Separation Chemistry

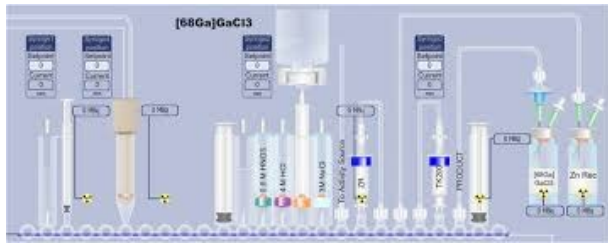
Overview

- Research interests ‘RadPharm’
- ZR Resin
  - Zr-89 from Y targets
  - Zr-89 via TBP/TK400
  - Ga-68 from Zn targets
- Cu-61/4/7
  - TK201 Resin
  - CU Resin
  - TK250
- Radiolanthanides
  - Tb-161 from Gd targets
- Ac-225
- Ra-226
- Tc-99m from Mo
- Quality Control – Sheets
- Other on-going R&D

Radionuclide production

- ‘Legacy materials’
  - “Th”/Pb-212, Th-229/Ac-225
- Cyclotron
- Reactors (or other neutron sources)
  - Fission (e.g. Mo-99)
  - ‘Carrier added’ Lu-177 => Lu-176 (n, γ) Lu-177
  - ‘Non-carrier added’ Lu-177 => Yb-176 (n, γ) Yb-177 → Lu-177 + β^-
- Common challenges:
  - Large excess of matrix (target material) => Very high decontamination factors required
  - Cyclotron, often short-lived => rapid separations
  - Very high radioactivity levels => increased radiation stability
- Requirements for resins:
  - Choice of right resin particularly important
    - No selectivity for target material, high selectivity for product
    - Elution under ‘soft‘ conditions in small volume => labelling/injection
    - Fast kinetics
  - Combining several resins can facilitate the separation
    - Conversion (high acid to dilute acid)
    - Removal of impurities upfront





ZR Resin

Original scope: Hydroxamate based resin

- Different form Holland et al.
- Standard for Zr separation from Y targets
- Ready to use / no activation
- Facile Zr elution (avoid 1M oxalic acid)

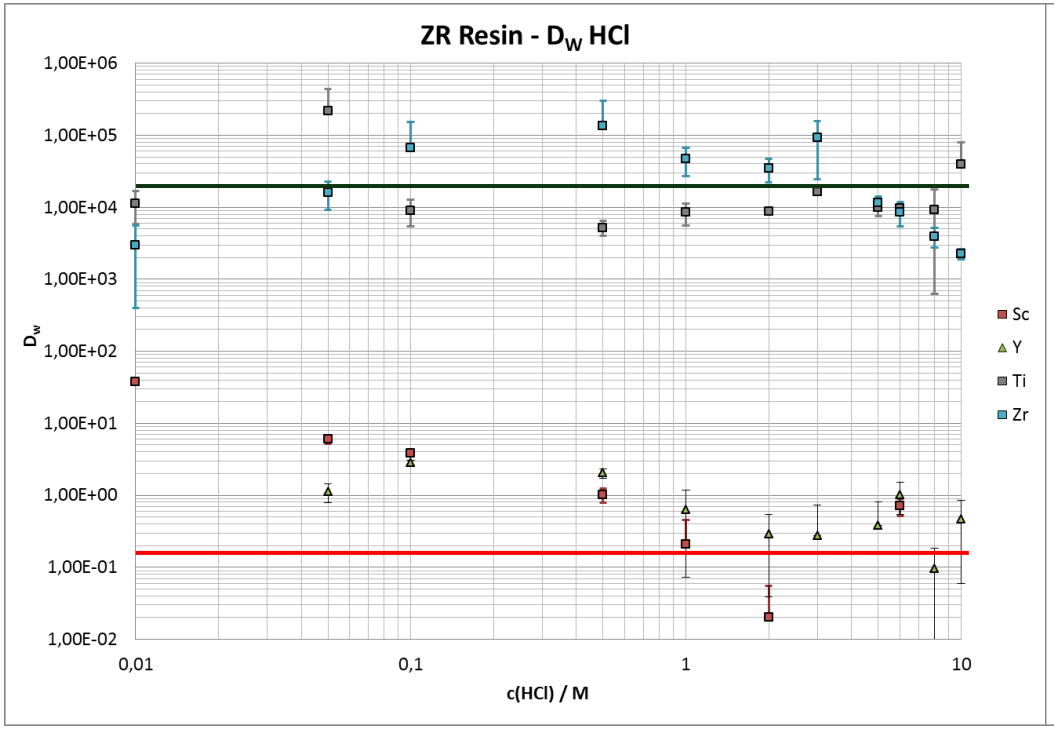
Zr-89 production via (p,n) reaction from ^{nat}Y targets

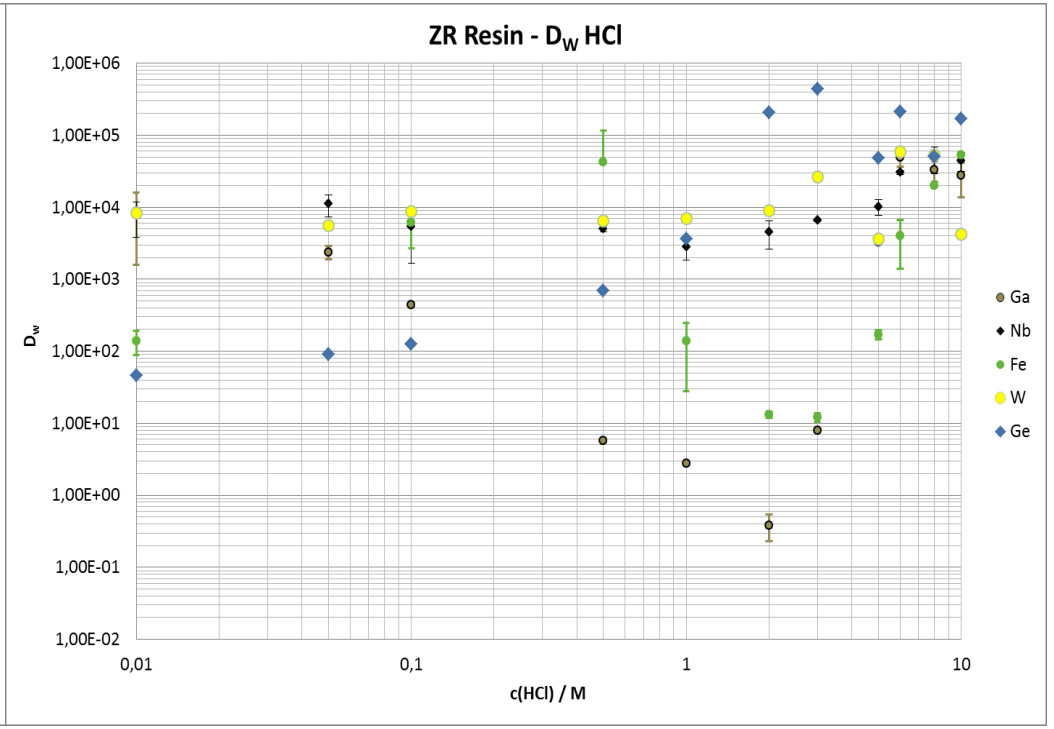
- High Zr/Y selectivity necessary
- Alternative e.g. TBP Resin (=> Graves et al.)

Application for other separations: **Ti/Sc**, **Ga/Zn, Ge/Ga**

On-going work => improvement of radiolysis stability

ZR Resin – HCl

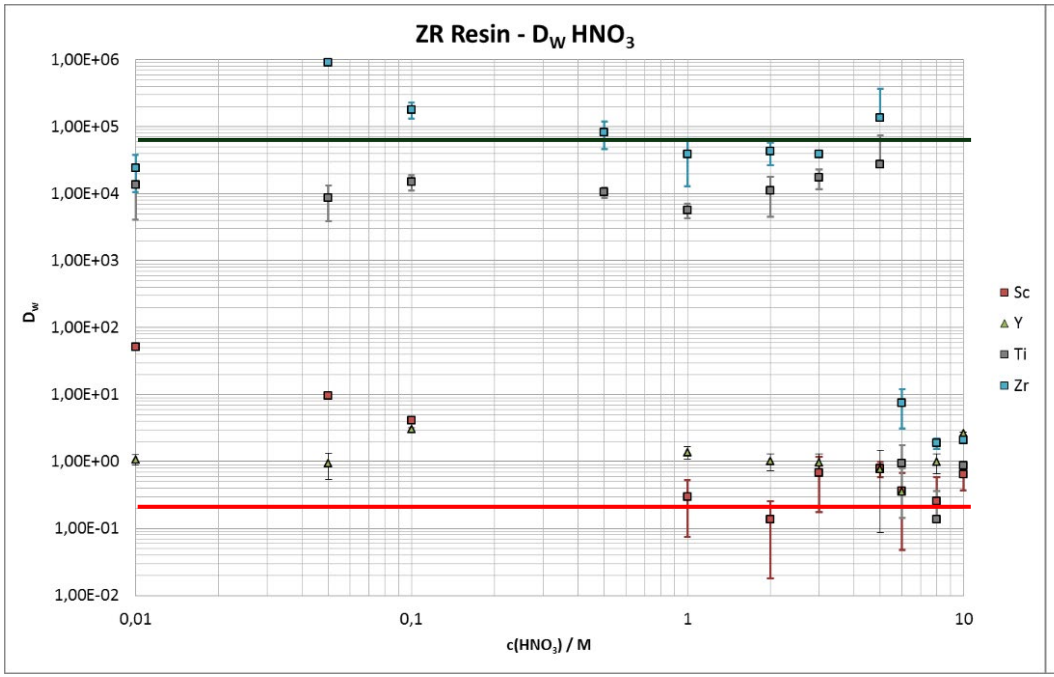


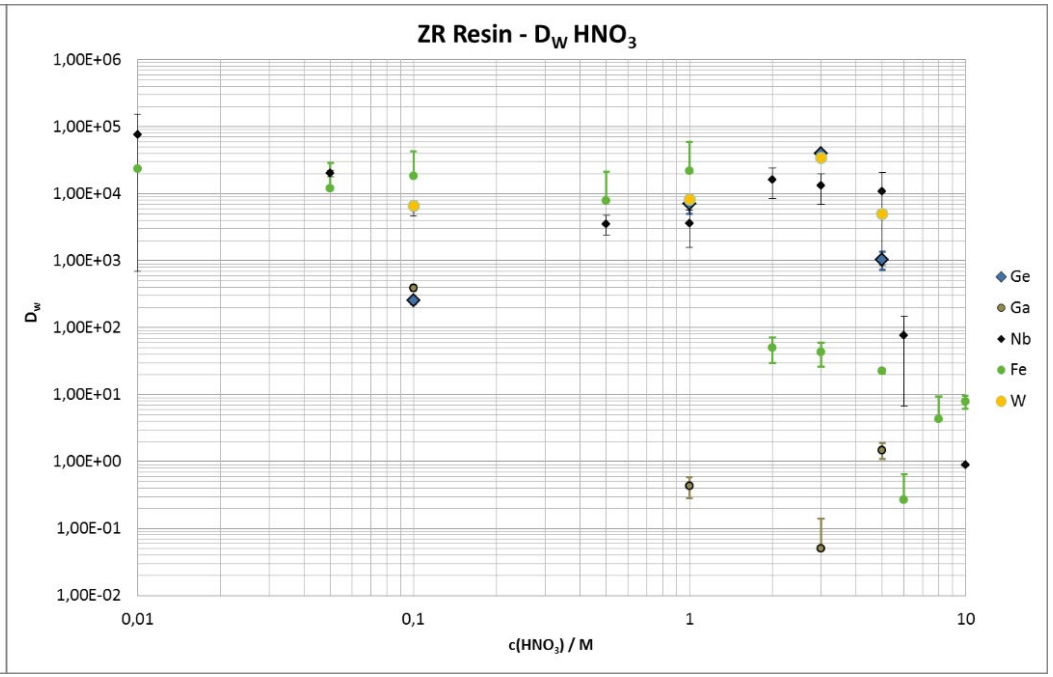


- No selectivity for Y, Sc
- High selectivity for Zr, Ti, Nb, W over wide HCl conc. range
- High Ge/Ga selectivity at elevated HCl

- No selectivity for alcalines and earth alcalines
- Lanthanides not retained
- Fe retention (dip at 2 – 3M HCl)

Zr Resin – HNO_3



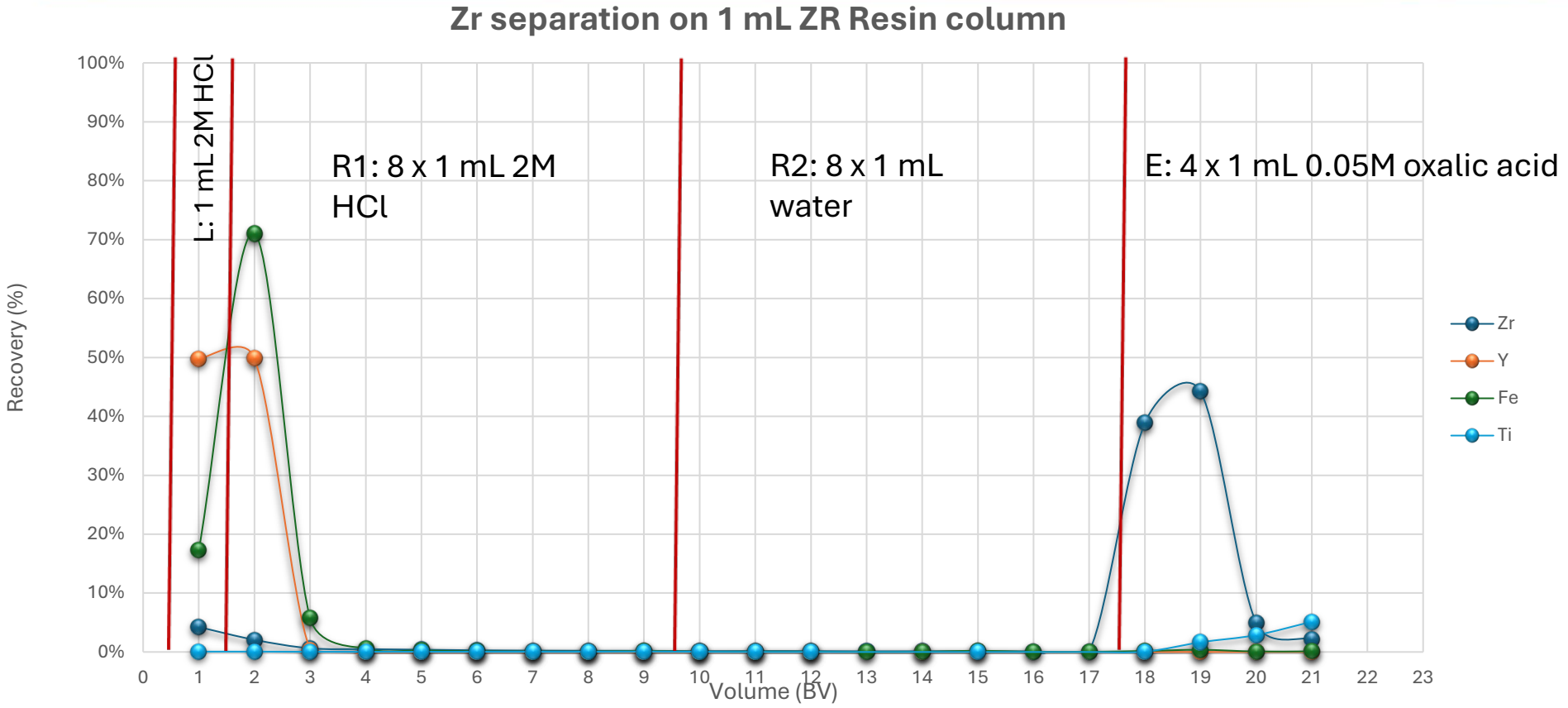


- High selectivity for Zr, Ti, Nb, W over wide HNO_3 concentration range
  - Loss of selectivity at 6M HNO_3

  => Resin shows colour change

- No selectivity for Y, Sc, lanthanides, earth alcalines, most transition metals,…
- High Ge/Ga selectivity at 3M HNO_3

Zr-89 separation from Y targets



- Load from 2 – 6M HCl
- Rinsing described by Holland may be used
- No activation with acetonitrile

- Quantitative Zr elution in 1.5 - 2 mL ≥ 0.05M oxalic acid
- Clean Fe removal
- Requires oxalate to e.g. chloride conversion

Zr-89 chloride via TBP and TK400

Nuclear Medicine and Biology 136–137 (2024) 108943

Contents lists available at ScienceDirect

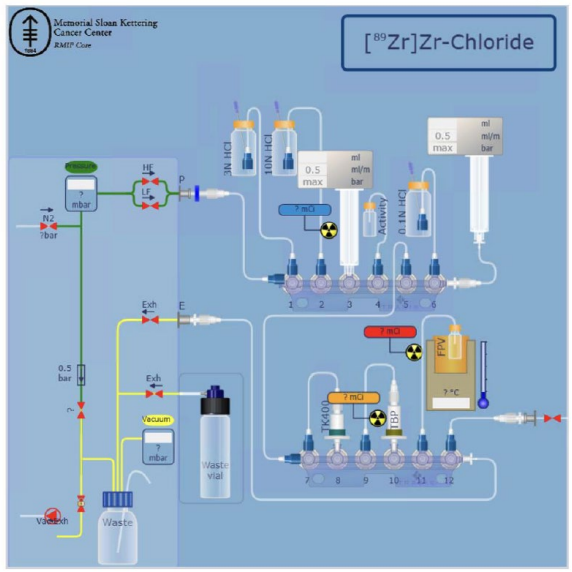
Nuclear Medicine and Biology

journal homepage: www.elsevier.com/locate/nucmedbio

[^{89}Zr]$ZrCl_4$ for direct radiolabeling of DOTA-based precursors☆

Serge K. Lyashchenko [a,b,*], Tuan Tran [a], Steffen Happel [c], Hijin Park [a], David Bauer [b], Kali Jones [b], Tullio V. Esposito [b], NagaVaraKishore Pillarsetty [b], Jason S. Lewis [a,b,d]

[a] Radiochemistry and Molecular Imaging Probe Core Facility, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[b] Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[c] Triskem International, Inc., USA
[d] Program in Molecular Pharmacology, Memorial Sloan Kettering Cancer Center, New York, NY, USA



- Improvement of method published by Graves et al. (TBP only) => insufficient Fe removal
- Load and rinse on TBP Resin at ~10M HCl, elution in dilute HCl
- Use of 2xTK400 before TBP Resin for Fe removal
- Production of 11.1 – 14.4 GBq of [^{89}Zr]Zr-PSMA-617 and [^{89}Zr]Zr-PSMA-I&T
- Apparent specific activities of 11.1 - 14.4 MBq/µg
  - 2–3x more than before at industrial quantities.
- On-going:
  - Use of TK201 instead of TK400 for impurities removal (catch additional impurities? E.g. Cu)
  - Alternative methods for Zr oxalate conversion to Zr chloride (avoiding QMA)

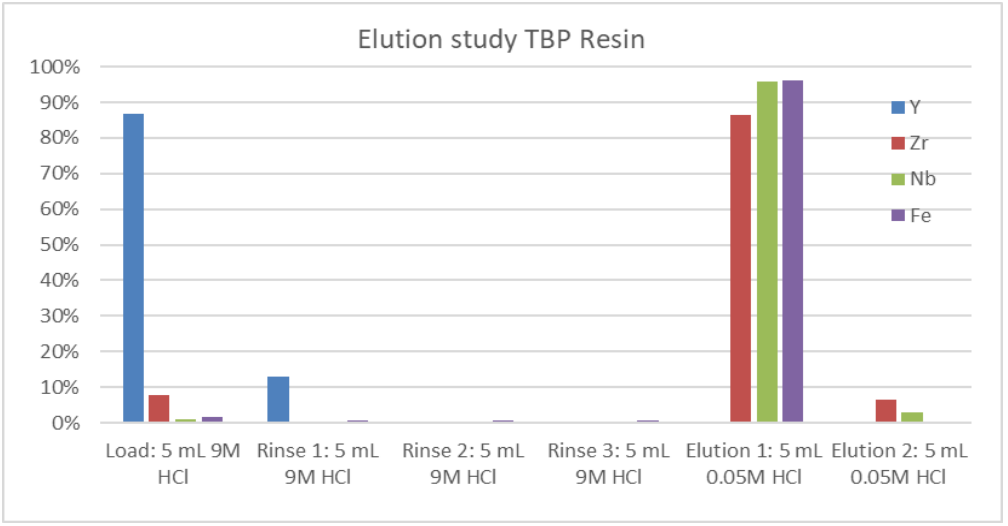
Table 1. Summary of Measured Iron Content in TBP-purified solutions.

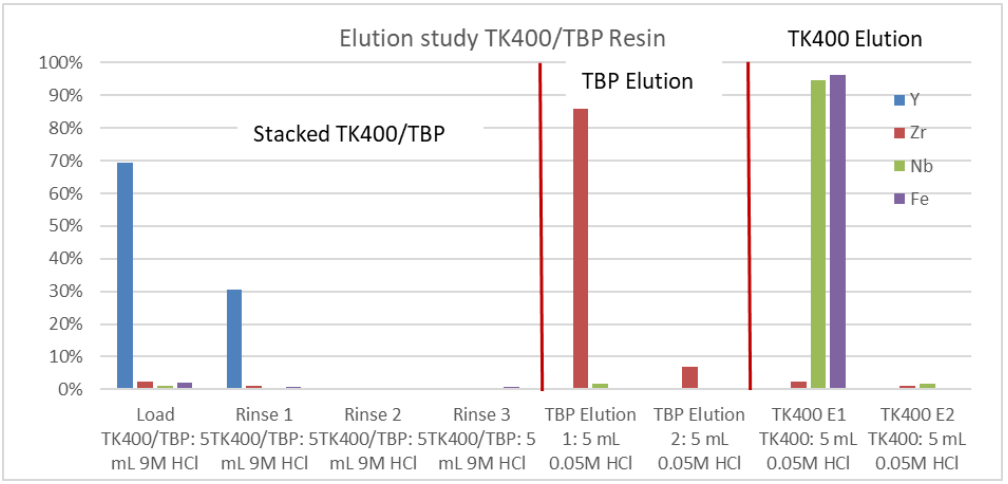
Purification Intervention	Measured Iron Content (ppm)	Source
No TK400, TBP only	32.7–38.8 (n = 6)	Graves et al.
Single TK400, followed by TBP	8 (n = 3)	This Study
Double TK400, followed TBP	< 1 (n = 3)	This study

Table 2. Summary of Radionuclide Purity Measurements in [^{89}Zr]$ZrCl_4$ Solution.

Batch	[^{89}Zr]$ZrCl_4$ - Batch 1	[^{89}Zr]$ZrCl_4$ - Batch 2	[^{89}Zr]$ZrCl_4$ - Batch 3	[^{89}Zr]$ZrCl_4$ - Batch 4
Radionuclidic Purity	≥99.9%	≥99.9%	≥99.9%	≥99.9%
% of ^{88}Zr	6.9×10^{-10}%	2.9×10^{-10}%	4.7×10^{-9}%	1.2×10^{-8}%
% of ^{88}Y	3.6×10^{-10}%	2.0×10^{-10}%	2.2×10^{-9}%	5.1×10^{-9}%

Use of TK400 for Fe/Nb removal

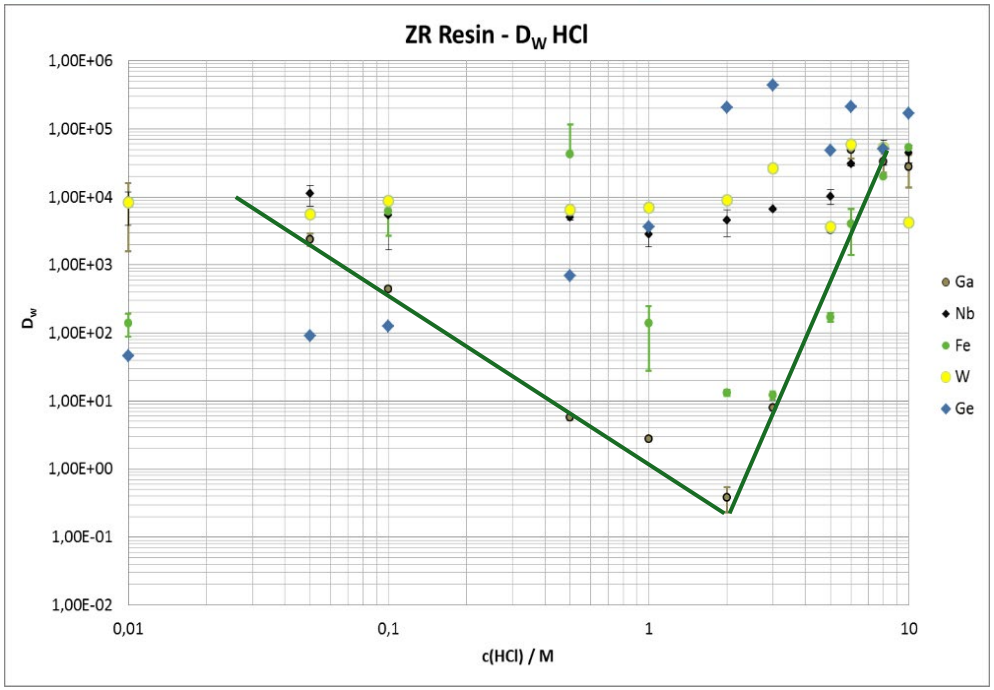


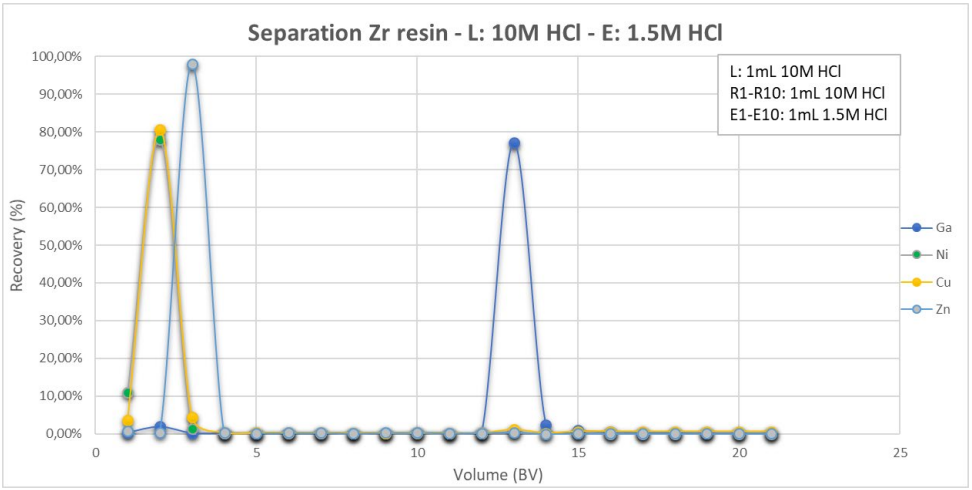


- On TBP only: Fe and Nb follow Zr
- Removal of Fe & Nb upfront possible using TK400 Resin
- Test with stacked 2 mL TK400/TBP cartridges
  - Load and Rinse at 10M HCl with TK400 stacked above TBP
  - Splitting of cartridges and separate elution with dilute Hcl
    - TBP => ZR only
    - TK400 = > Fe & Nb
    - For Nb/Fe separation => Fe(II)
    - Y passes through both
- Potential for Nb separation from Zr targets

Ga-68 separation from Zn targets

- Irradiation of Zn-68 targets in cyclotron
- Ga-68 separation on ZR Resin
  - No selectivity for Zn (target material)
  - Loading possible from:
    - dilute acid (**liquid targets => typically HNO_3**)
    - >6M HCl (**solid targets**)
  - Rinse under loading condition
  - Elution with ~1 - 2M HCl
- Too acidic for injection or labelling



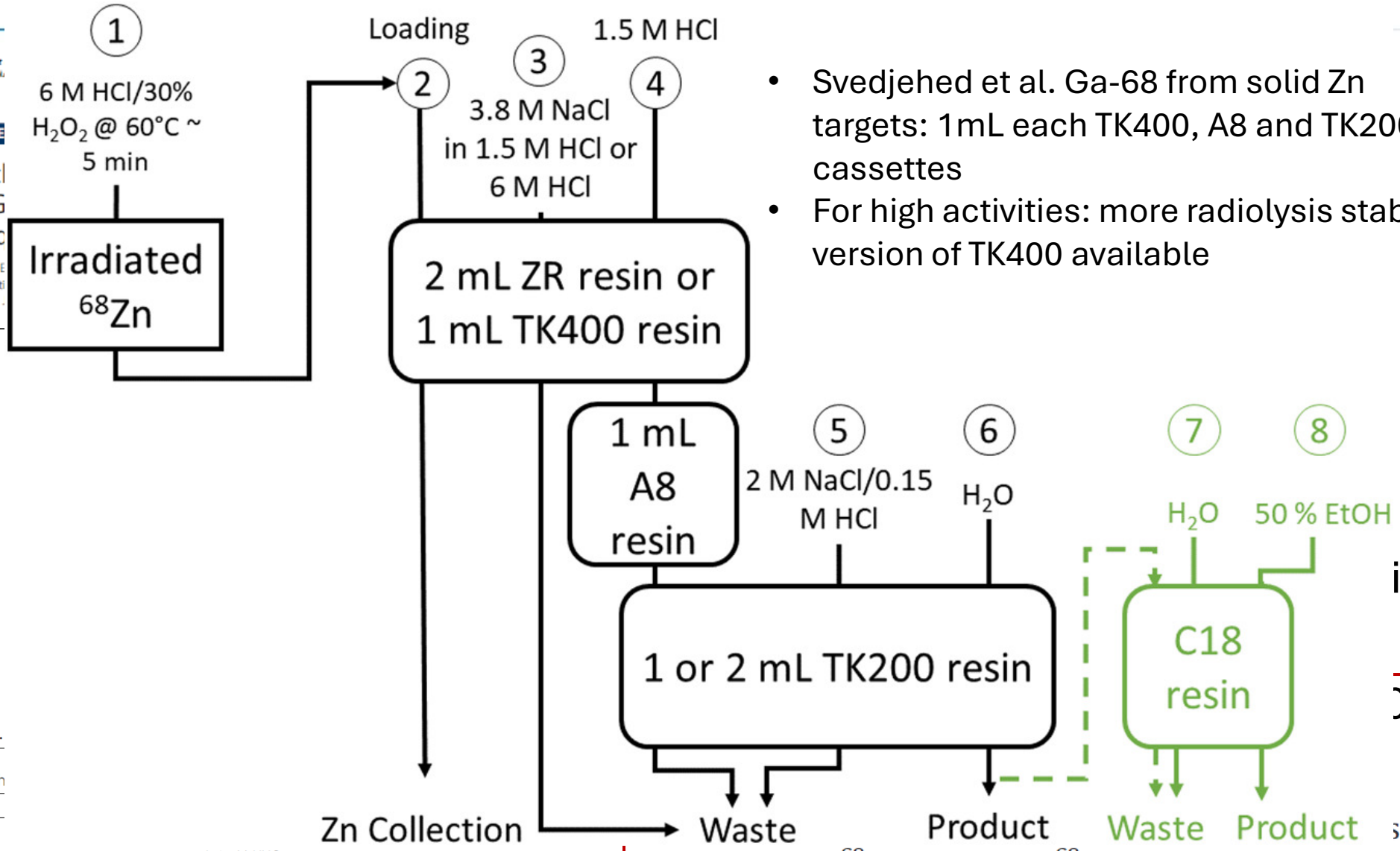


- Ga-68 'conversion' necessary
  - Evaporation & dissolution difficult to automize
- Easier => use of another resin
- TK200 Resin (TOPO) load from 1 - 2M HCl
- Rinse with e.g. 1 - 2M HCl
- Elution in 2 – 3 BV water, dilute acid,..

⇒ **New IAEA TechDoc:**

https://www-pub.iaea.org/books/IAEABooks/13484/Gallium-68-Cyclotron-Production

Cyclotron production of Ga-68



- Svedjehed et al. Ga-68 from solid Zn targets: 1mL each TK400, A8 and TK200 cassettes
- For high activities: more radiolysis stable version of TK400 available

Table 1 High

(1) ZR Load		
(2) ZR Wash	15 mL 0.1 M HNO_3	
(3) ZR Elution / Trapping on TK200	5–6 mL ~ 1.75 M HCl	
(4) TK Wash	–	3.5 mL 2.0 M NaCl in 0.13 M HCl
(5) TK Elution	H_2O	1–2 mL H_2O followed by dilute HCl to formulate

*Process as reported previously (Nair et al. 2017)

production of [^{68}Ga]$GaCl_3$ and [^{68}Ga]Ga-PSMA-11

Johan Svedjehed, Martin Pärnaste, Katherine Gagnon *

Cyclotrons and TRACERcenter, GEMS PET Systems AB, GE Healthcare, Uppsala, Sweden

Ag/Pd separation

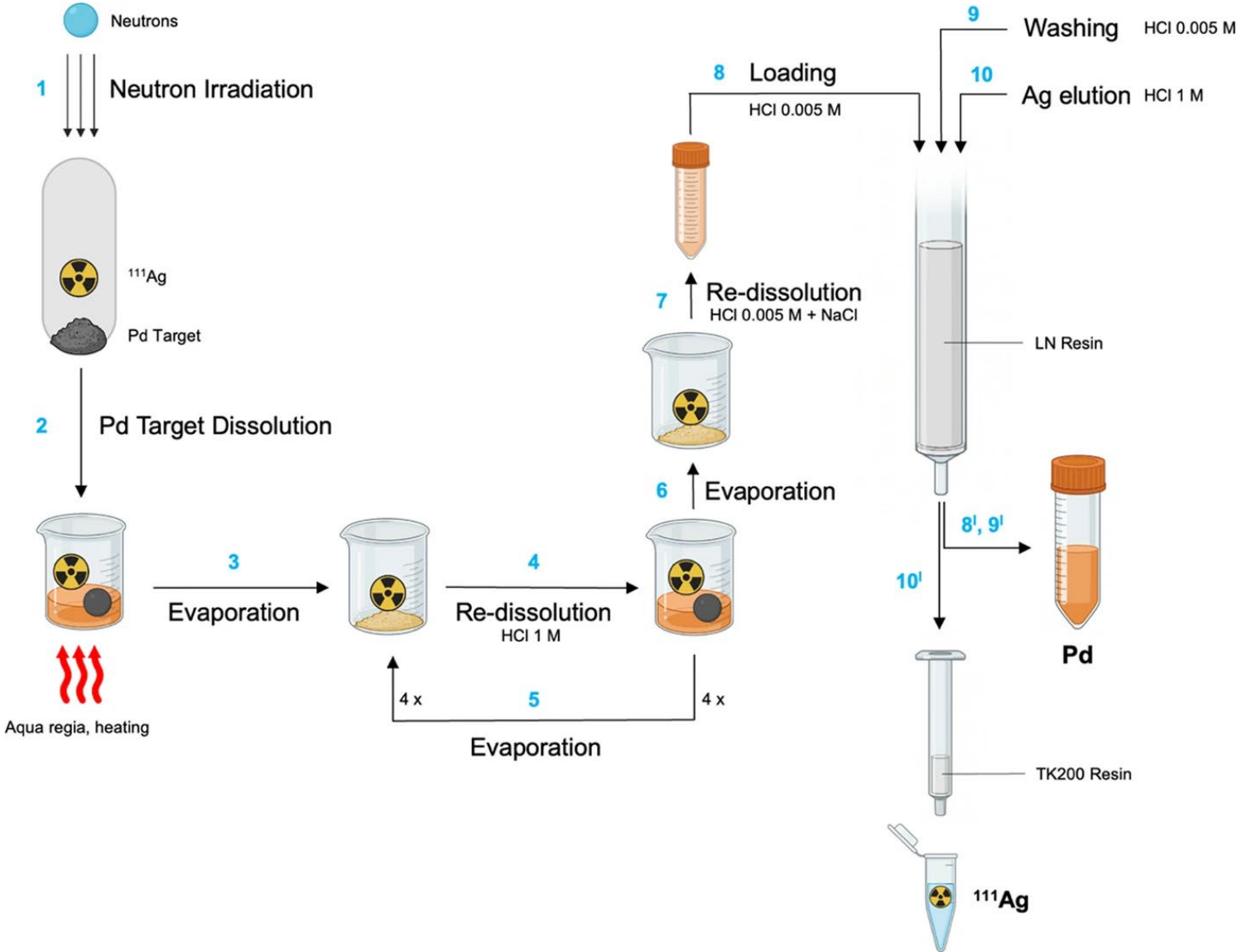
Tosato *et al.*
EJNMMI Radiopharmacy and Chemistry (2023) 8:43
https://doi.org/10.1186/s41181-023-00232-0

EJNMMI Radiopharmacy and Chemistry

RESEARCH ARTICLE Open Access

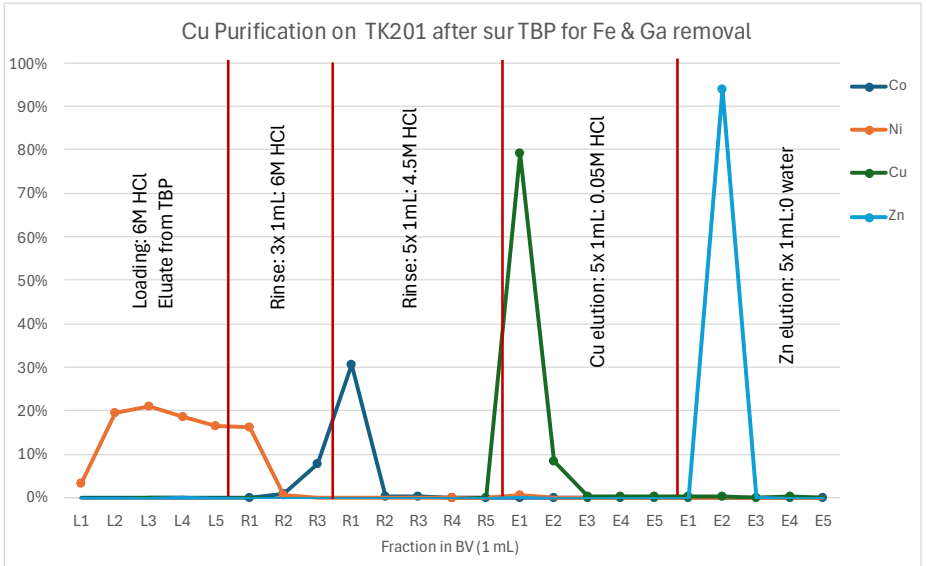
Chromatographic separation of silver-111 from neutron-irradiated palladium target: toward direct labeling of radiotracers

Marianna Tosato[1,2], Andrea Gandini[3], Steffen Happel[4], Marine Bas[4], Antonietta Donzella[5,6], Aldo Zenoni[5,6], Andrea Salvini[3], Alberto Andrighetto[7], Valerio Di Marco[2] and Mattia Asti[1*]



Cu-61/4 separation on TK201

- Cu-61/4 separation from solid Ni targets
  - Target dissolution in high HCl => 6M HCl
  - TK201 retains Cu, Zn, Co, Fe, Ga at 6M HCl
  - Run through TBP (or TK400) for Fe/Ga removal
  - Load eluate on TK201 and rinse at 6M HCl
    - Ni removal and recovery/recycling
  - Co elution with 4 – 5M HCl => Co separation
  - Cu elution in 0.05M HCl
    - HCl concentration of Cu eluate >0.05M HCl
  - Preferably avoid water (risk of Zn co-elution)



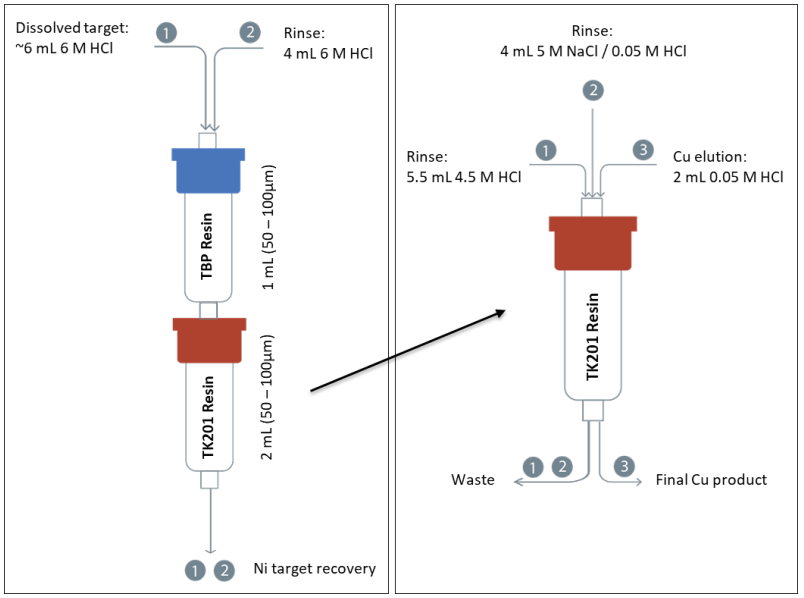
Svedjehed et al. EJNMMI Radiopharmacy and Chemistry (2020) 5:21
https://doi.org/10.1186/s41181-020-00108-7

EJNMMI Radiopharmacy and Chemistry

RESEARCH ARTICLE Open Access

Automated, cassette-based isolation and formulation of high-purity [^{61}Cu]$CuCl_2$ from solid Ni targets

Johan Svedjehed[1], Christopher J. Kutyreff[2], Jonathan W. Engle[2,3] and Katherine Gagnon[1*]



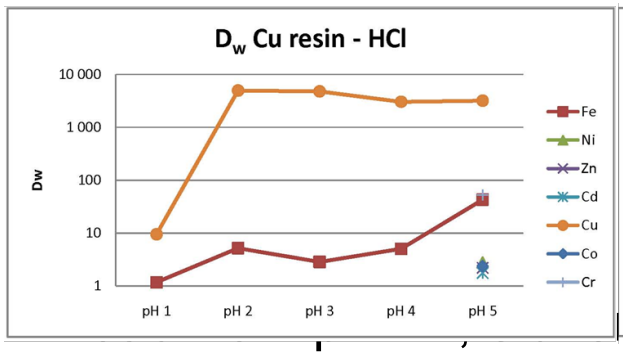
- Svedjehed et al. use of NaCl/HCl for better pH control of eluate
- Also being used for Zn separation
- Not applicable to solid Zn targets
- Higher activity version

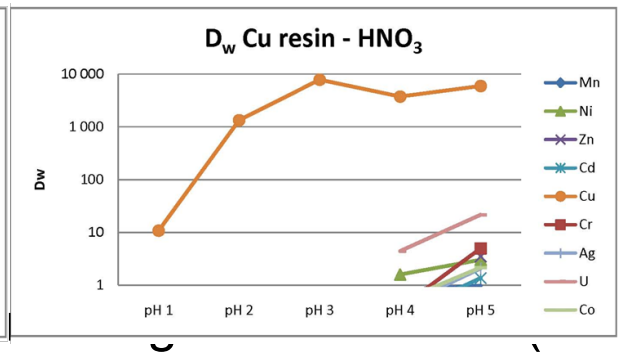
CU Resin

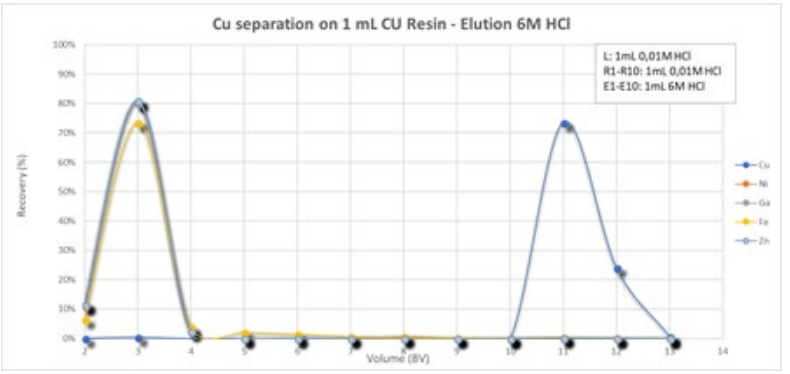
TK201 can not be used for Cu separation from Zn targets (e.g. Cu-67)

Use of oxime based CU Resin instead

High selectivity for Cu particularly with respect to Zn, Ni, Fe, Co,…







- Used for (large) solid **Zn** targets (=> Cu-67)
- Not ideal for solid Ni targets (usually high HCl) => TK201
  - Works for liquid targets (pH 2 – 3) => Fonseca et al.
  - Requires pH adjustment…
- Elution in high HCl not compatible with labelling/injection
  - Evaporation/redissolution or
  - Conversion to dilute HCl e.g. via TK201 (additional Zn removal) e.g. Kawabata et al.

Cu-67 at BNL (DeGraffenreid et al.)

Purification of ^{67}Cu and Recovery of its Irradiated Zn Target

A.J. DeGraffenreid[a] , R. Nidzyn[a], B. Jenkins[a], D.E. Wycoff[b], T.E. Phelps[b], A. Goldberg[a], D.G. Medvedev[a], S.S. Jurisson[b], C.S. Cutler[a]
[a]Brookhaven National Laboratory, C-AD/MIRP—Upton, NY (USA)
[b]University of Missouri, Department of Chemistry—Columbia, MO (USA)

Poster presented at ISRS 2017

- 13.7g Zn metal dissolved to give 312 mg $ZnCl_2$/mL solution at pH 2
- Loading of 60,6 mL => 18.9g $ZnCl_2$ onto 2.4g CU Resin column => 8 mL
- Rinse with 80 mL pH2 HCl
- Elution in 2 x 20 mL 6M HCl
- Evaporation to dryness
- Chemical yield ~100%
- Single column D_f for Zn ~10 000
  - Additional removal indicated
- Ideally further Zn and Co removal

Cu Resin

Nuclide	EOB Activity (mCi ± 1σ)	Recovery (%) Load w/ Quant. Transfer	pH 2 HCl Rinse	Acid #1	Acid #2
^{64}Cu	4700 ± 200	ND	ND	102	ND
^{65}Zn	41.0 ± 0.8	103	ND	0.04	ND
^{58}Co	63 ± 1	104	0.04	0.1	0.01

- Produced 143 mCi ^{67}Cu
- Quantitative recovery of radiocopper
- 99.5% radionuclidic purity—single column
- ICP-OES: 132.9 µg Cu and 1.3 mg Zn
  - Anion exchange column still needed to remove trace Zn
- Specific activity ^{67}Cu at EOB: 1.07 mCi/µg

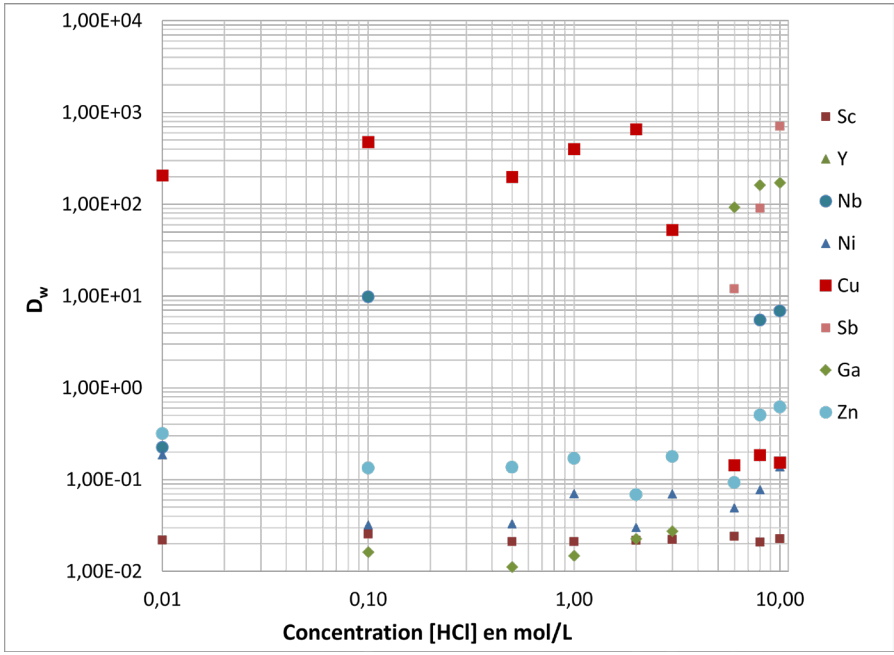
Cu Resin

Robust separation that could shorten the overall processing time to separate co-produced radionuclides and large quantities of Zn from radiocopper
Cation and anion exchange columns still needed to suitably purify radiocopper

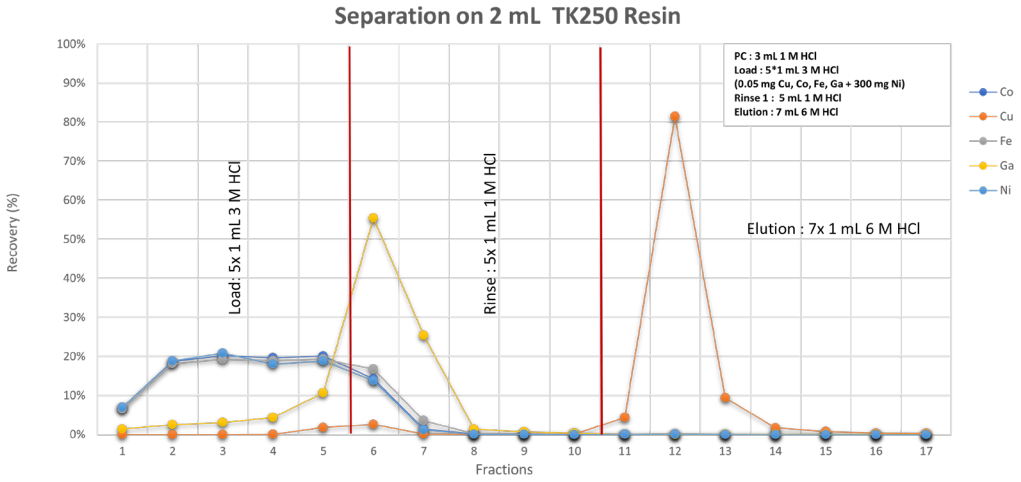
- Alternative to evaporation: Cu elution with 6M HCl directly onto TK201
- Cu elution from TK201 in dilute acid
- Optional: rinse with NaCl/HCl for better pH control

Upcoming: TK250 Resin

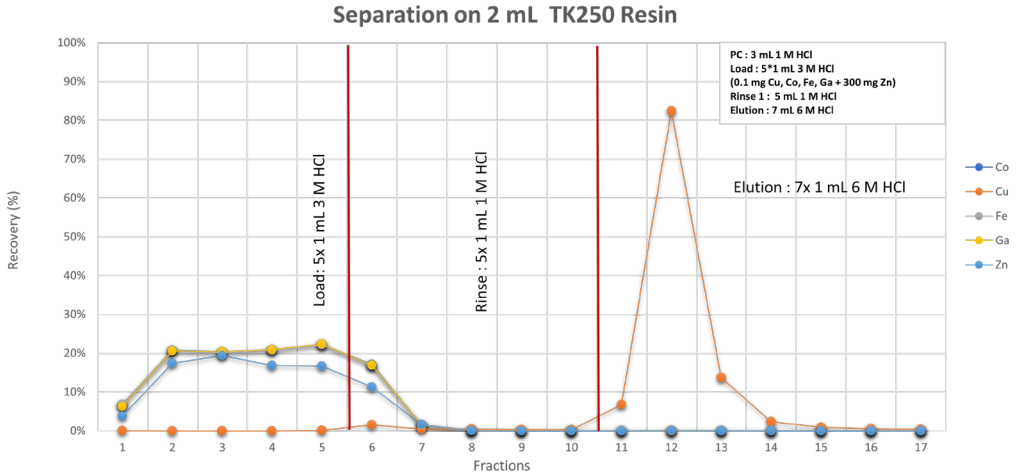
- CU Resin high selectivity for Cu over Zn but loading from pH >2 required
- Difficult to automize in case of solid Zn targets
- Upcoming TK250 Resin:
  - Cu retention from elevated acid up to 3M HCl
  - No selectivity for Ni **and Zn**
    - Tested up to 300mg each
  - Cu elution in 6M HCl
  - Rather low Cu capacaity (~0.13mg/g)



Dw values TK250 Resin, various éléments, HCl

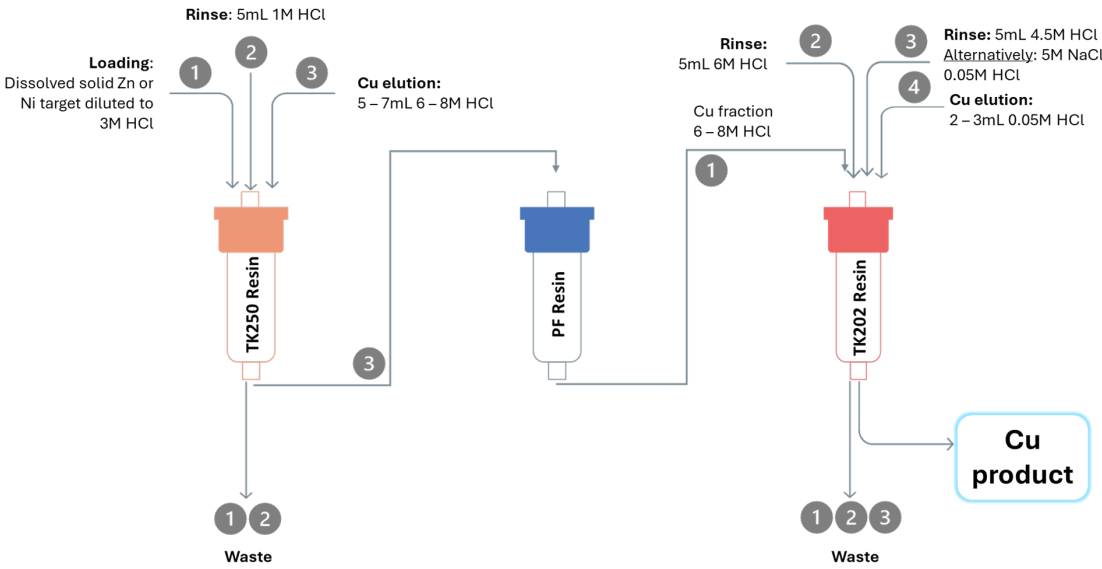


Cu separation from 300 mg Ni on 2mL TK250 Resin

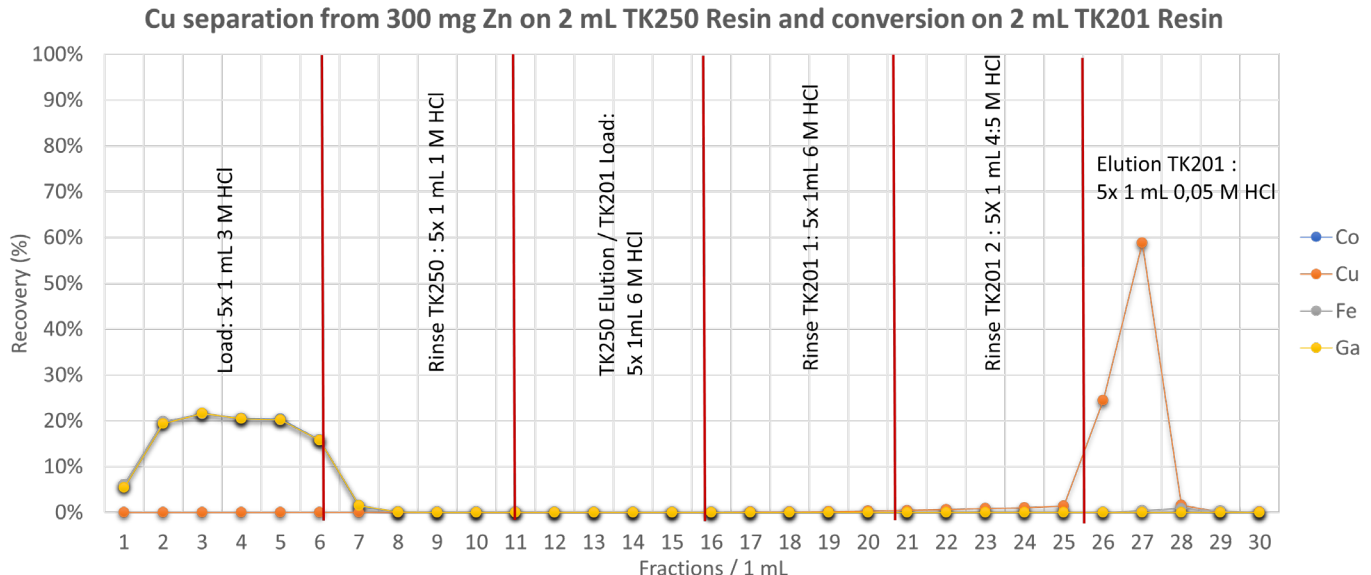


Cu separation from 300 mg Zn on 2mL TK250 Resin

Upcoming: TK250 Resin



- D_f typically >10^3 - 10^4
- 6M HCl to low HCl on TK201 Resin
- Prefilter or Guard Resin for organics removal
- Next steps:
  - Upscale and stability testing
- Integration in sequential separation of Cu and Ga from Zn targets e.g. with TBP Resin (Ga)

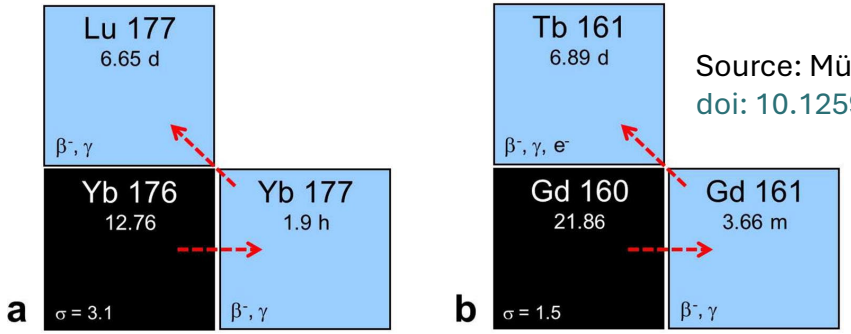


Lu-177 / Tb-161/55

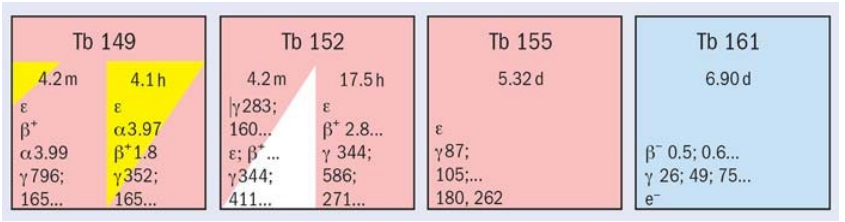
nca Lu-177 still more frequently used but Tb-161 getting strong interest

- Part of the ‘Swiss knife of nuclear medicine’ => Tb isotopes

Similar production for both



Source: Müller et al. 2018
doi: 10.1259/bjr.20180074



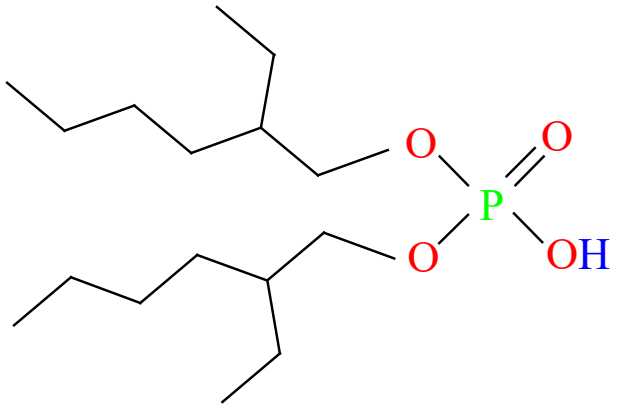
Terbium: a new ‘Swiss army knife’ for nuclear medicine
Source: https://cerncourier.com/a/terbium-a-new-swiss-army-knife-for-nuclear-medicine/

- Irradiation of several hundreds of mg or more
- Upscale on-going (incl. recycling) => typically 1g

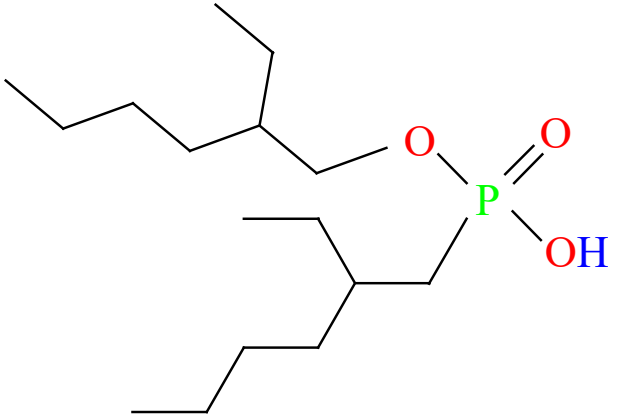
Prepacked PP columns

- **4cm x 30cm (375 mL)**, 2.5cm x 30cm,
  1.5cm x 30cm & 1.1cm x 30cm
- Connection: ¼’’ 28G, up to ~10bar
- QC/CoA per column (peak asymmetry) for TK211/2/3
- TK221 => dry packing

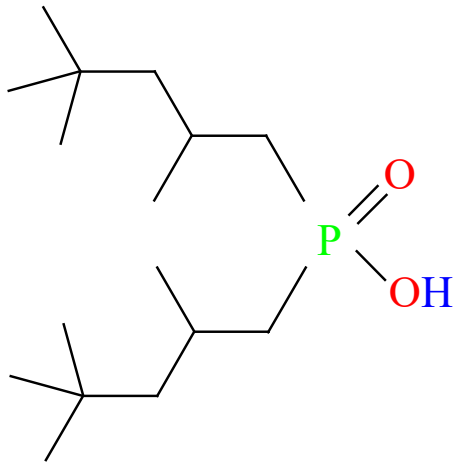
Lanthanide separation on TK211/2/3



HDEHP (LN)



HEH[EHP] (LN2)



H[TMPeP] (LN3)

Cyanex 572

$$M^{3+} + 3\overline{(HY)_2} \leftrightarrow \overline{M(HY_2)_3} + 3H^+$$

- Mixtures of different extractants
- Modified for higher radiation stability

TK212, TK211 and TK221 Resins

Increasing demand for separation from larger Yb, Gd,… targets

Resins exposed to high radiation throughout separation process

Desire to re-use columns several times

- Improvement of radiolysis stability

Feedback from earlier project => stability against radiolysis can be improved via:

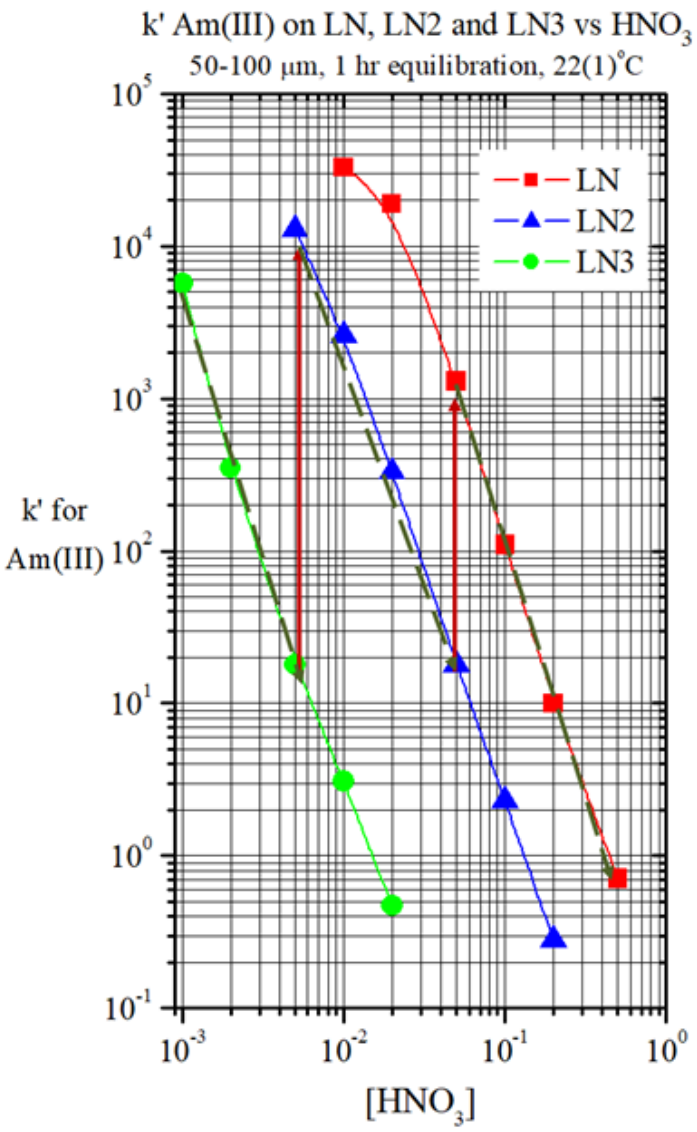
- Use of polymer containing aromatic groups as inert support
- Addition of radical scavenger (e.g. long chained alcohols) into stationary phase
- Increased amount of extractant and nature of extractant
- EtOH in aqueous phase

Applied to TK211/2/3, TK221/2, TK102,…

- Note: resins are more hydrophobic, require soaking in ≥20% EtOH for column packing

TK211/2/3 => standard ~30µm mean particle size, upcoming: 20µm

Sequential separations



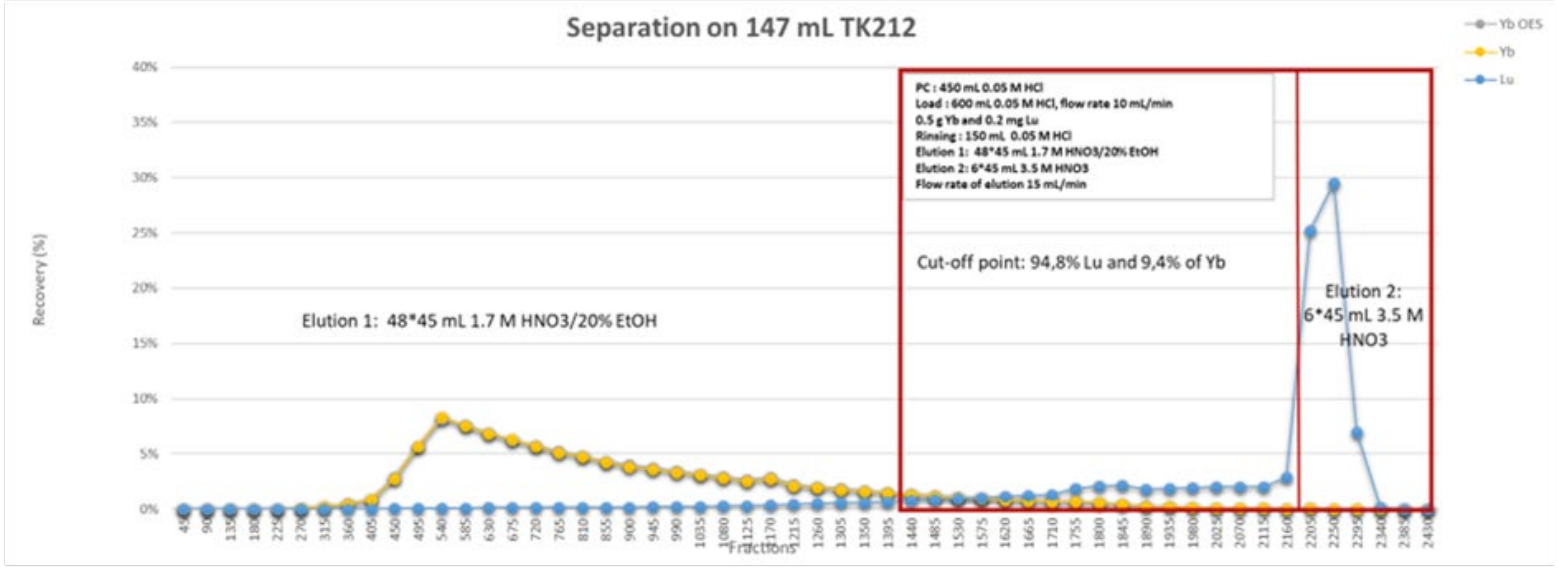
Lanthanide separations now main focus on TK212 and TK211.

- Better separation performance on-column than LN/LN2
- Especially for Yb/Lu and other complex systems with 10 – 20% EtOH

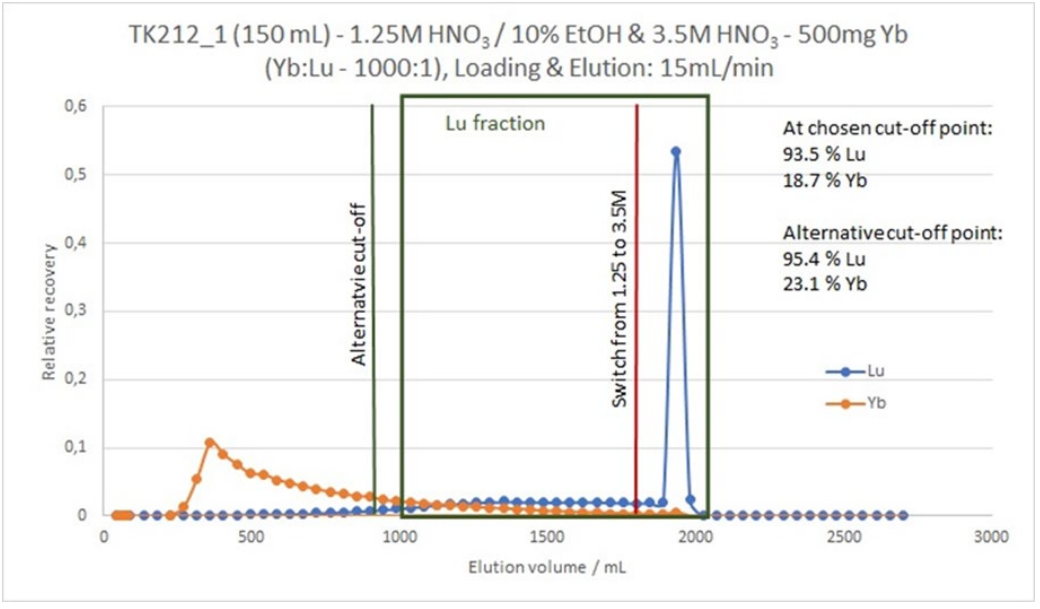
TK221 or DGA very useful for conversion of lanthanides from high HNO_3 (e.g. 3.5M HNO_3) to low acid (e.g. 0.05M) but small losses of Lu/Tb

Alternative: Direct load from TK212 to TK211

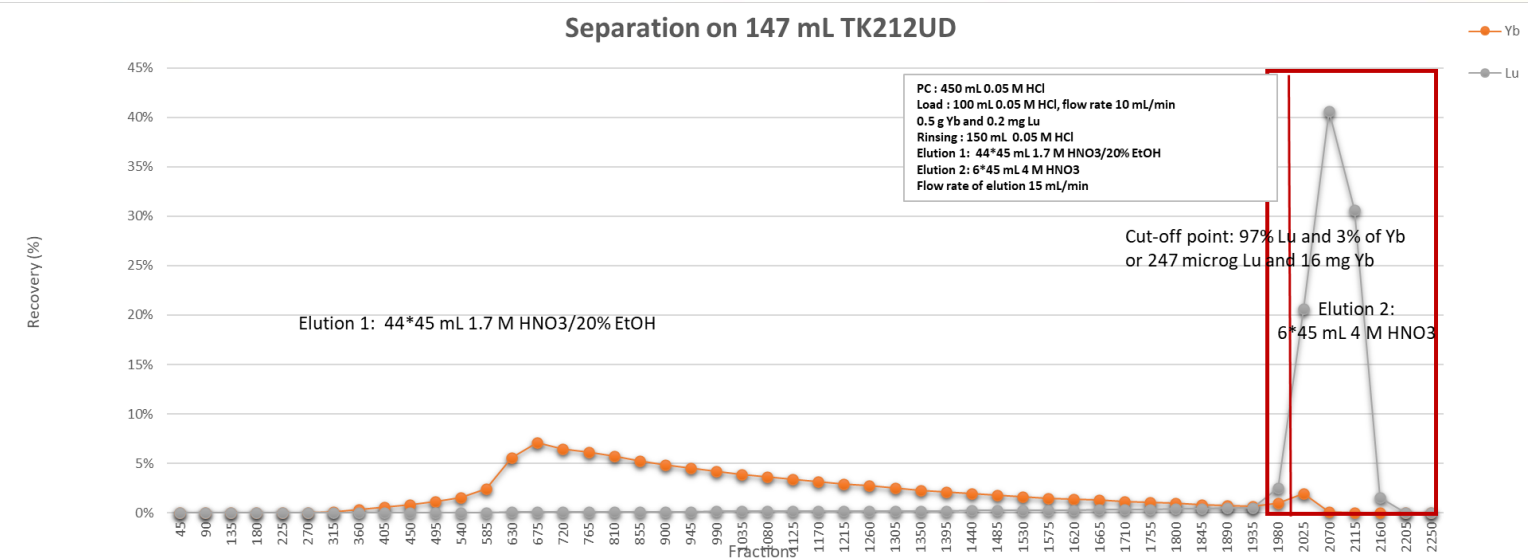
On-going improvement – amount of EtOH



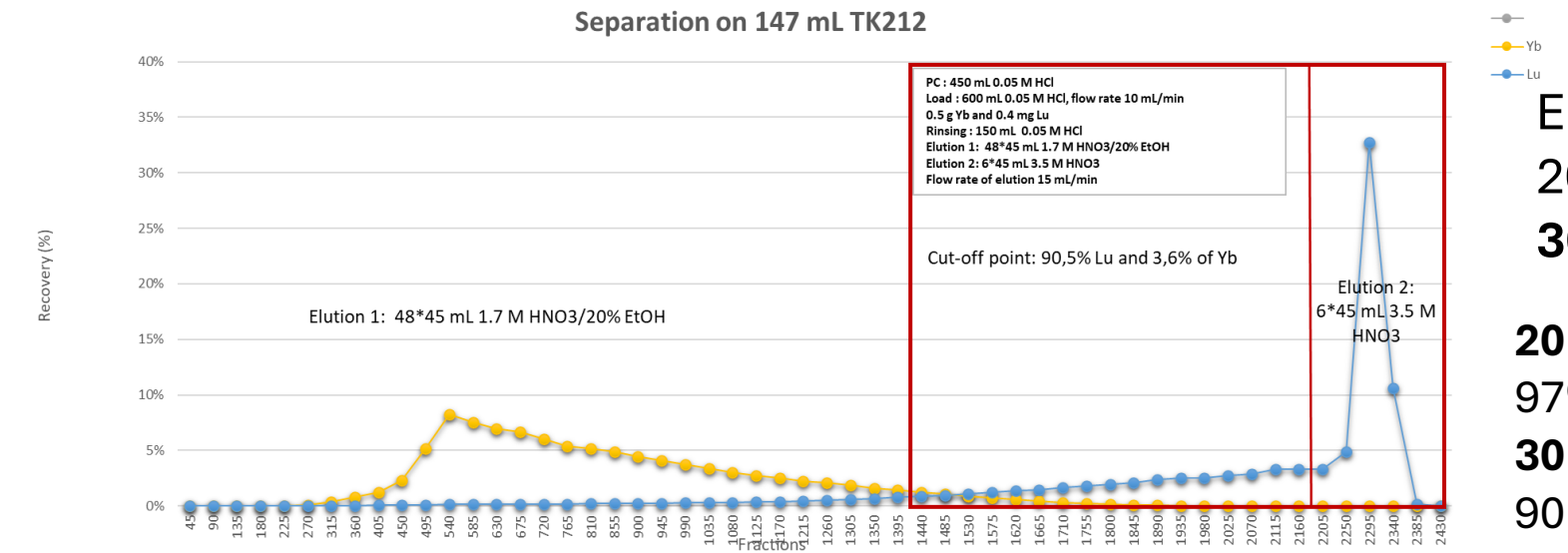
- Use of 1.7M HNO_3 / 20% EtOH
- Better Yb removal compared to 1.25HNO_3/10%EtOH
- Better Yb removal also improves separation on later columns
- Higher %-age of EtOH shifts peaks to higher elution volumes
- Higher acid to lower elution volumes / gain time



On-going improvement – Particle size – 20µm vs 30µm



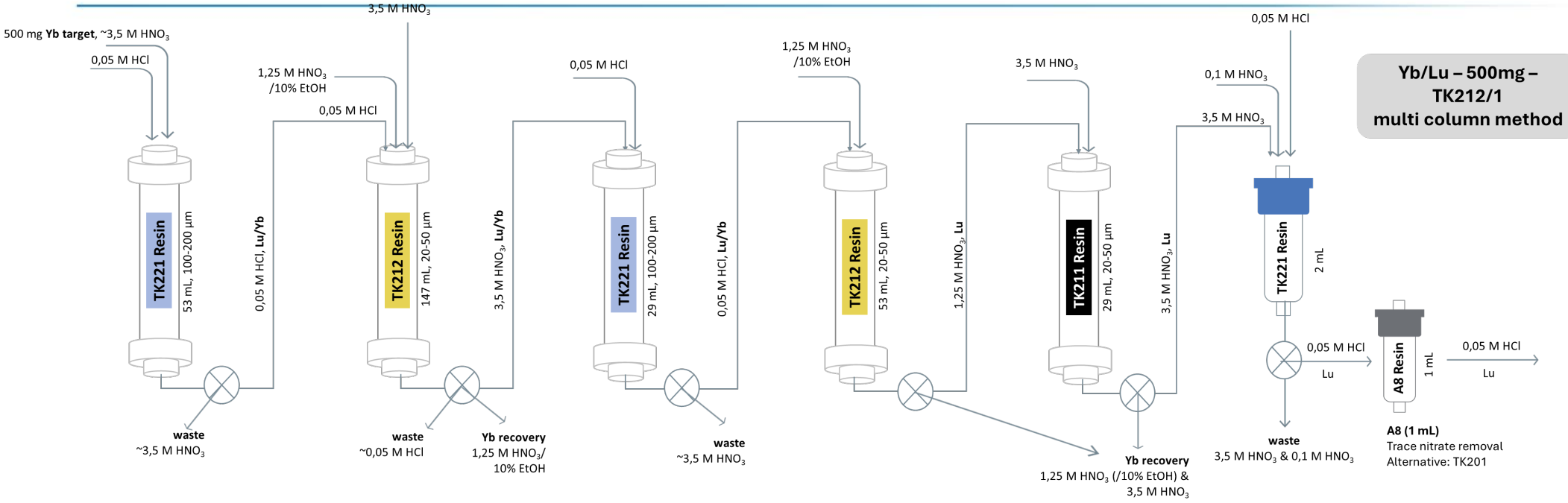
Elution with 1.7M HNO_3 / 20% EtOH – **20µm** particles



Elution with 1.7M HNO_3 / 20% EtOH – **30µm** particles

20µm at chosen cut-off:
97% Lu and 3% Yb
30µm at chosen cut-off:
90.5% Lu and 3.6% Yb
BUT higher pressure needed

Current ‘simplified’ method for Lu separation from 500 mg Yb – TK211/2 & TK221



Sequential separation step (direct load from TK212 onto TK211 for polish)

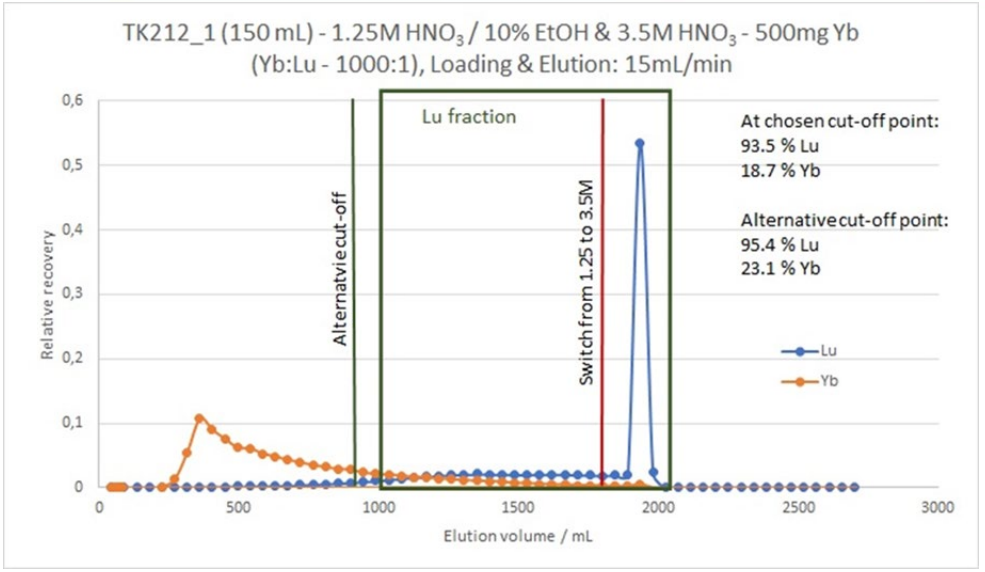
Unfortunately complete sequential TK213=>TK212=>TK211 didn’t work out

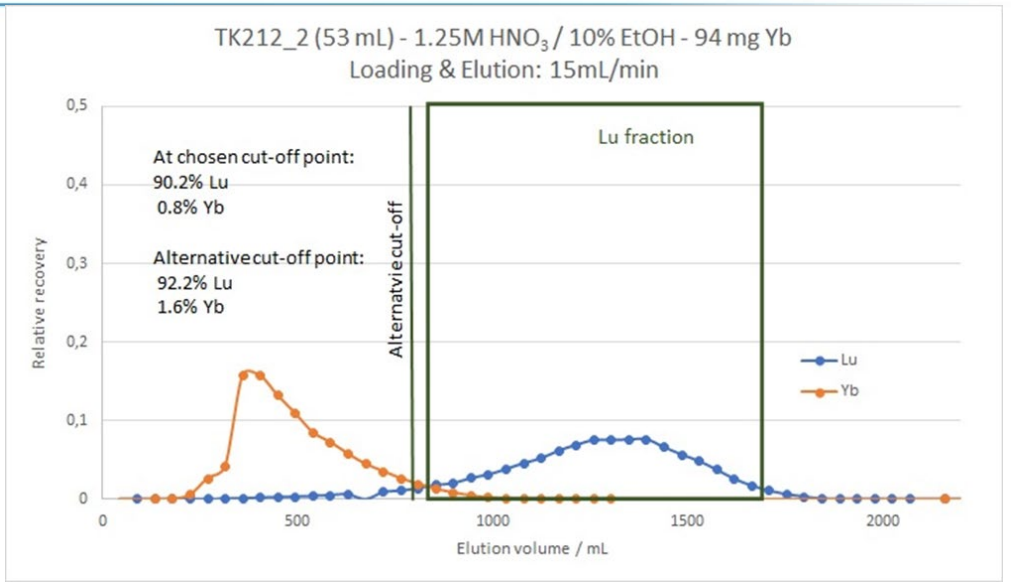
Can be upscaled (larger columns,…)

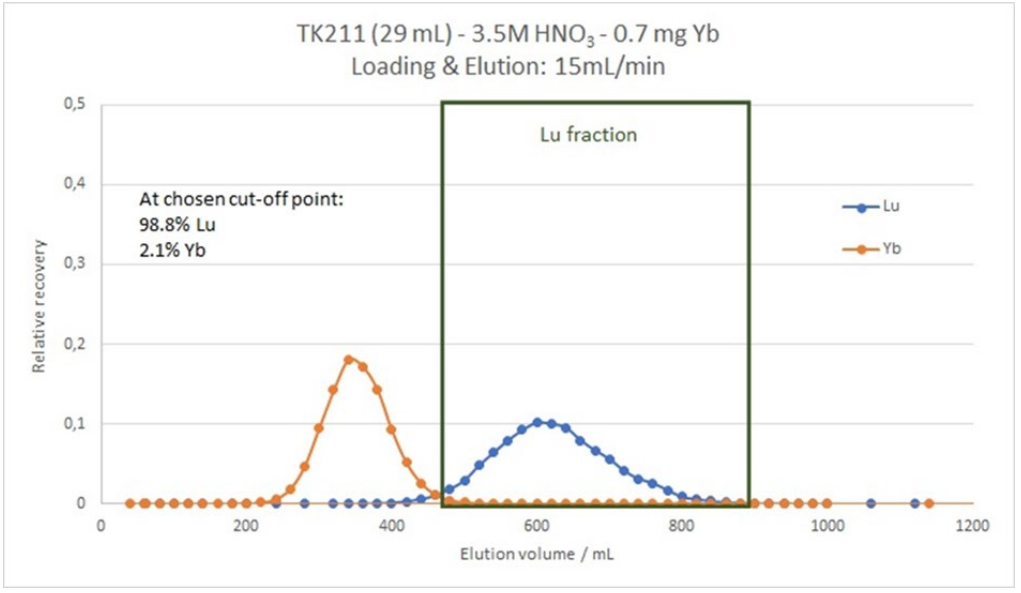
Further optimisation on-going

Upscale ongoing (now 4 – 5 g Yb)

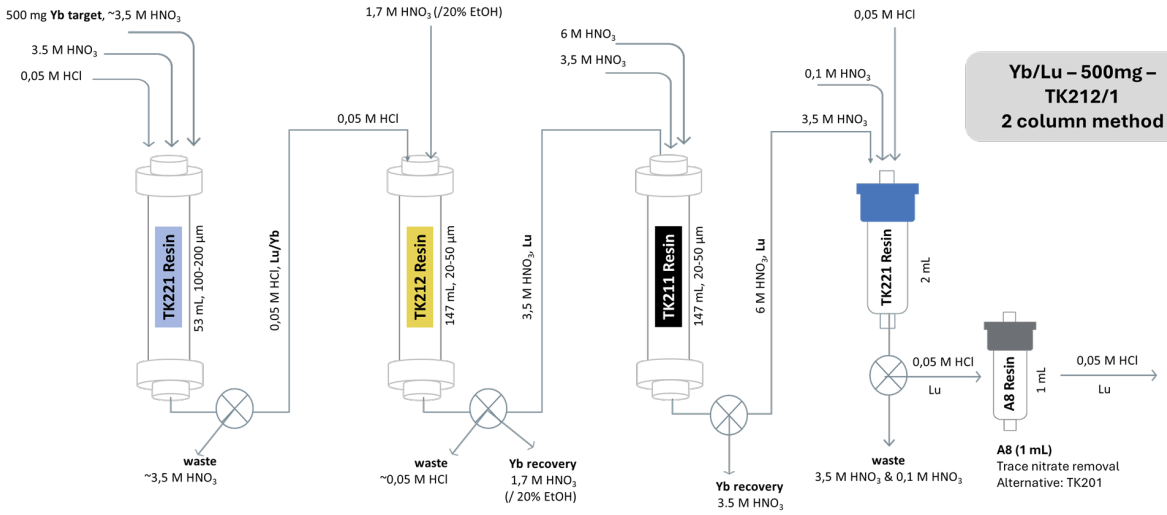
Current 500mg Yb target method







500 mg Yb: TK212/1 column approach



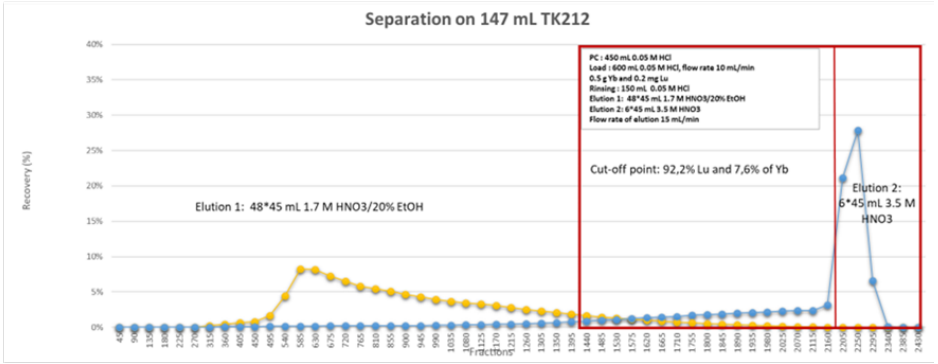
On-going work

Use of two 147mL TK212/1 columns instead of 3 TK212/1 columns+ TK221

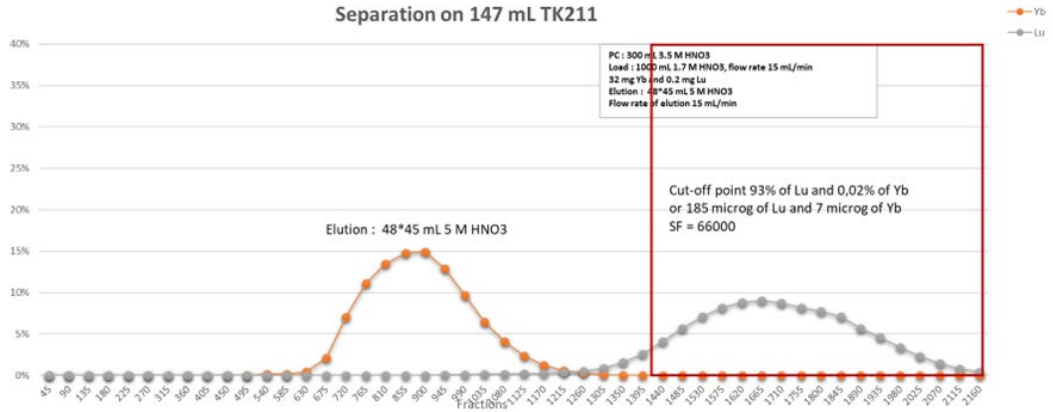
Faster and easier to automize

Better yields

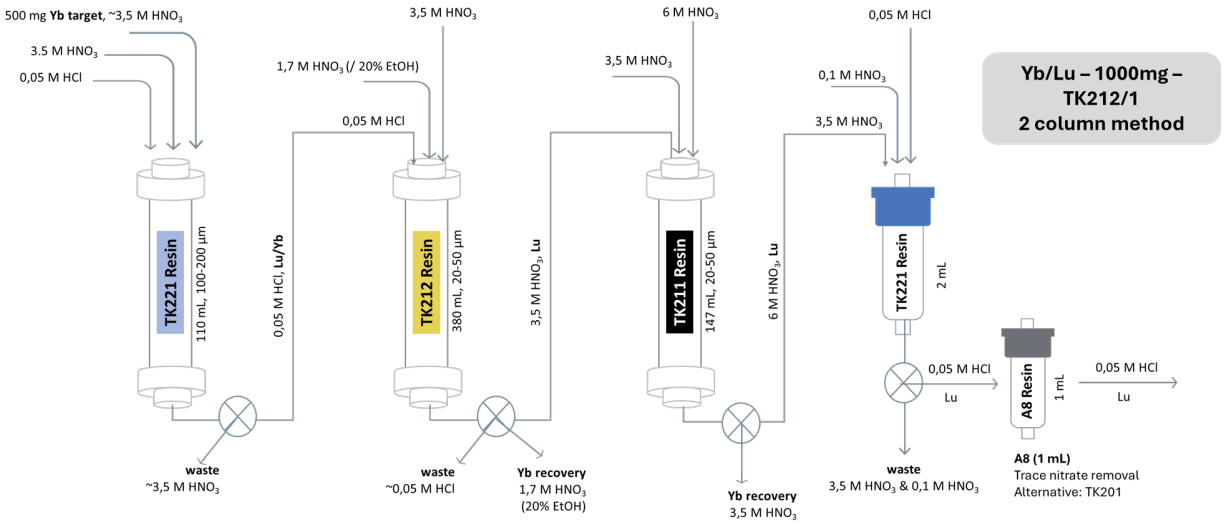
Also applicable to 1g targets (larger TK221 and TK212)



The 1st step separation on 147 mL TK212



1000 mg Yb: TK212/1 column approach



On-going work

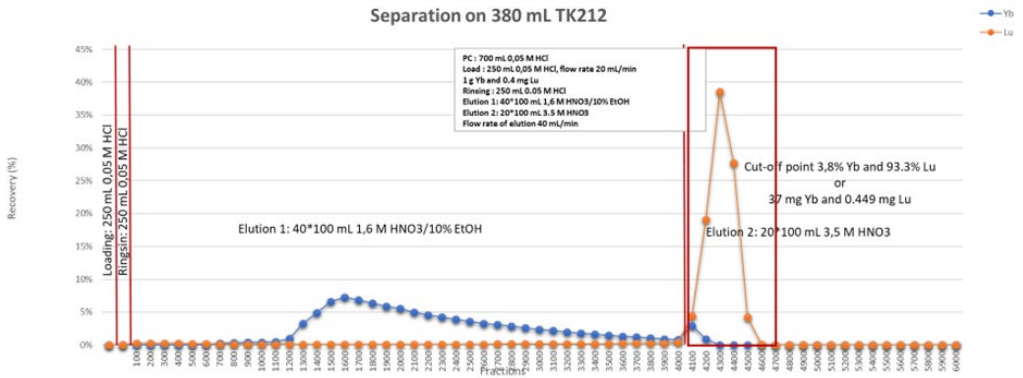
Larger TK221 column (min. 110 mL)

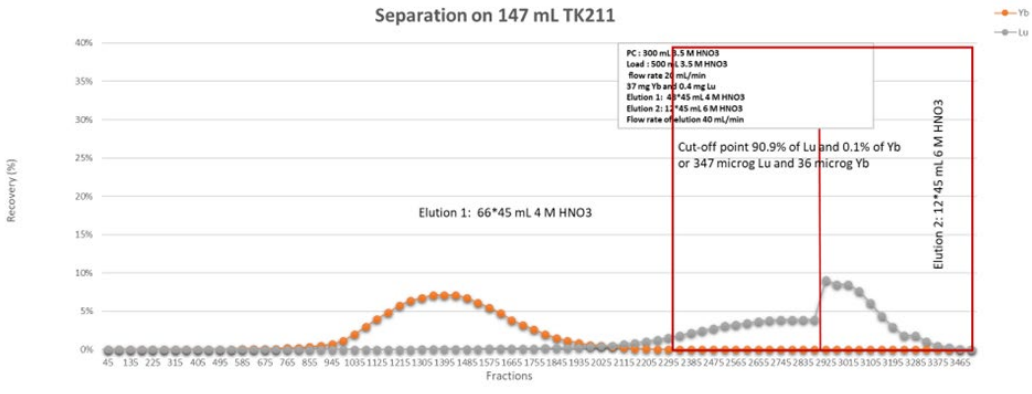
Use of one 380 mL TK212 and one 147mL TK211 columns Faster and easier to automize

Change of first two columns

Good separation on first column at 40mL/min

< 3mg Yb/mLresin





Tb separation from 1000 mg Gd targets

Irradiated target typically oxide => dissolved in >3M HNO_3

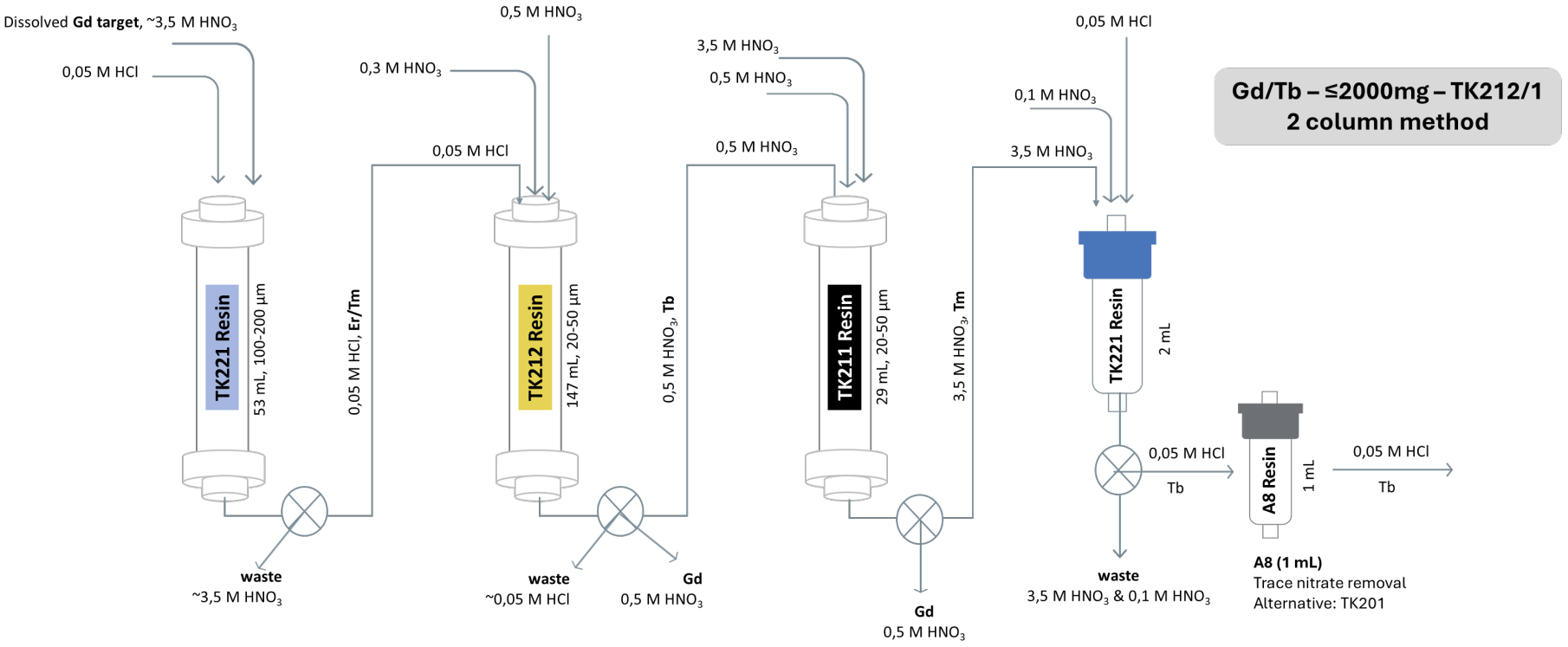
- For separation solution needs to be dilute acid

Conversion via TK221 Resin

Sequential separation on TK212/TK211

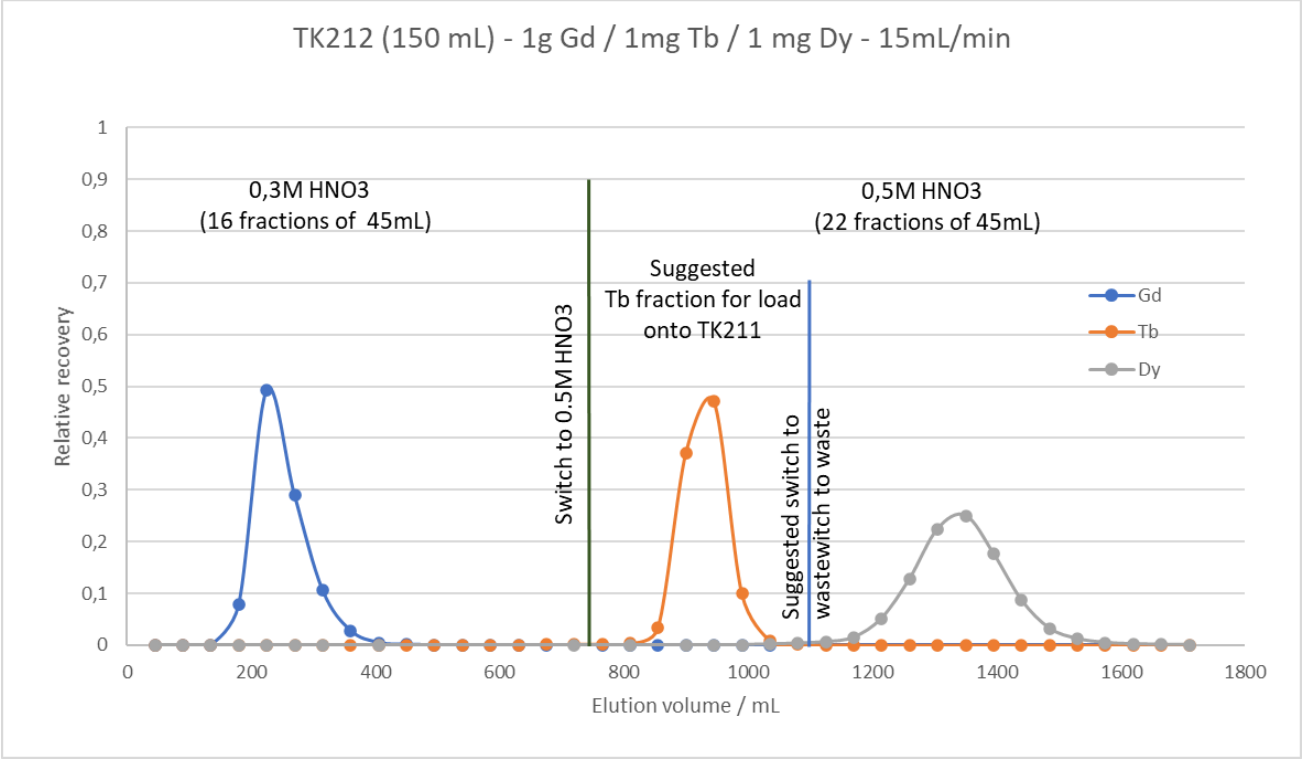
Final conversion to dilute HCl on TK221 + trace nitrate removal on AIX

Mainly Tb-161, also Tb-155



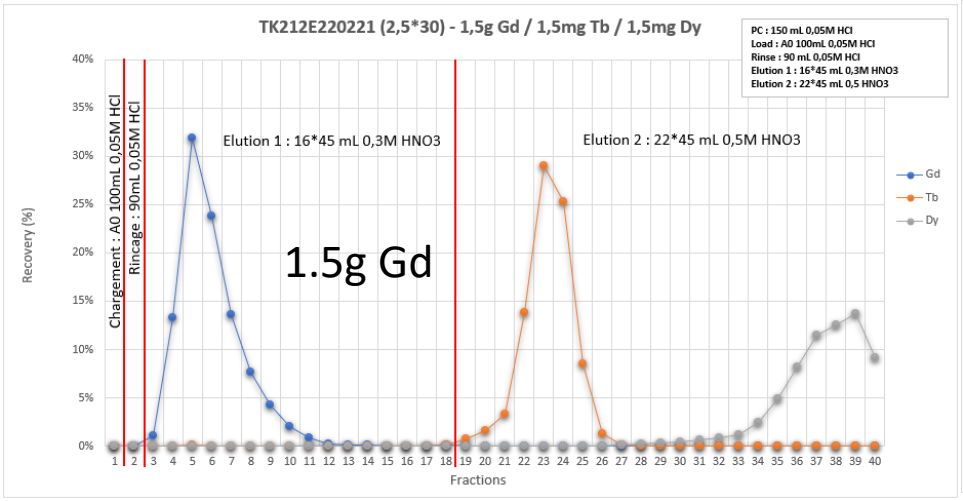
Tb separation from 1000 mg Gd targets

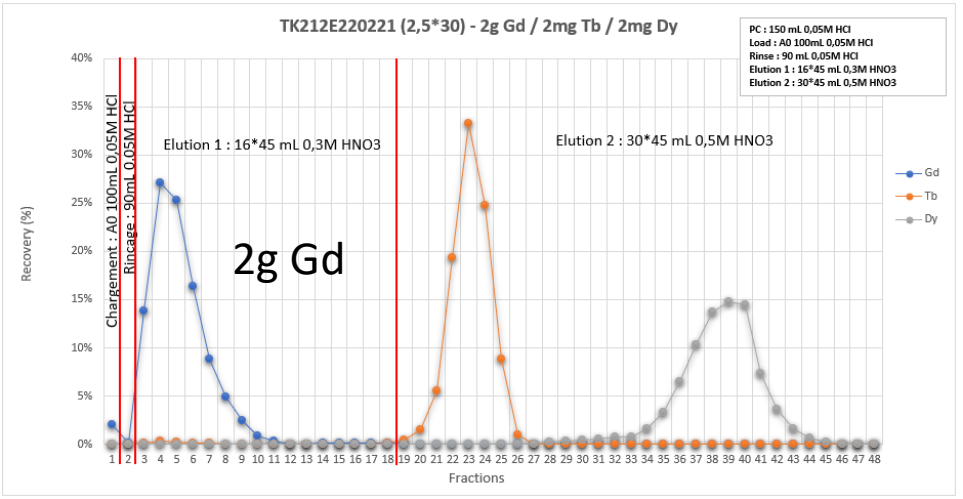
- Initial separation on TK212 – 150 mL column (30cm x 2.5cm)
- Allows for working with up to 2g of Gd
- Gd recovery => very expensive & difficult to find
- Tb separation from Gd and Dy – ideally using online detection
- Fine purification on TK211 (29 mL)

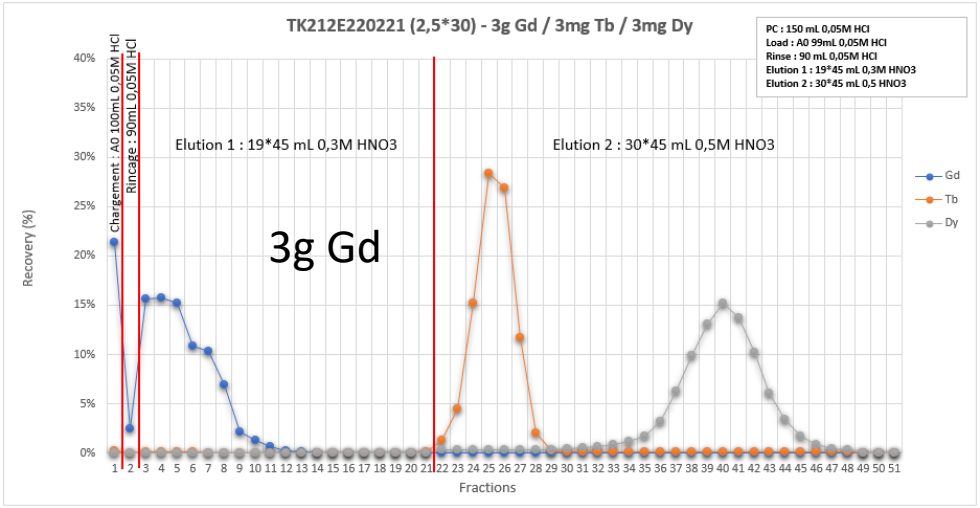


Tb separation from 1000 mg Gd on TK212 (147 mL column)

Increasing amouts of Gd

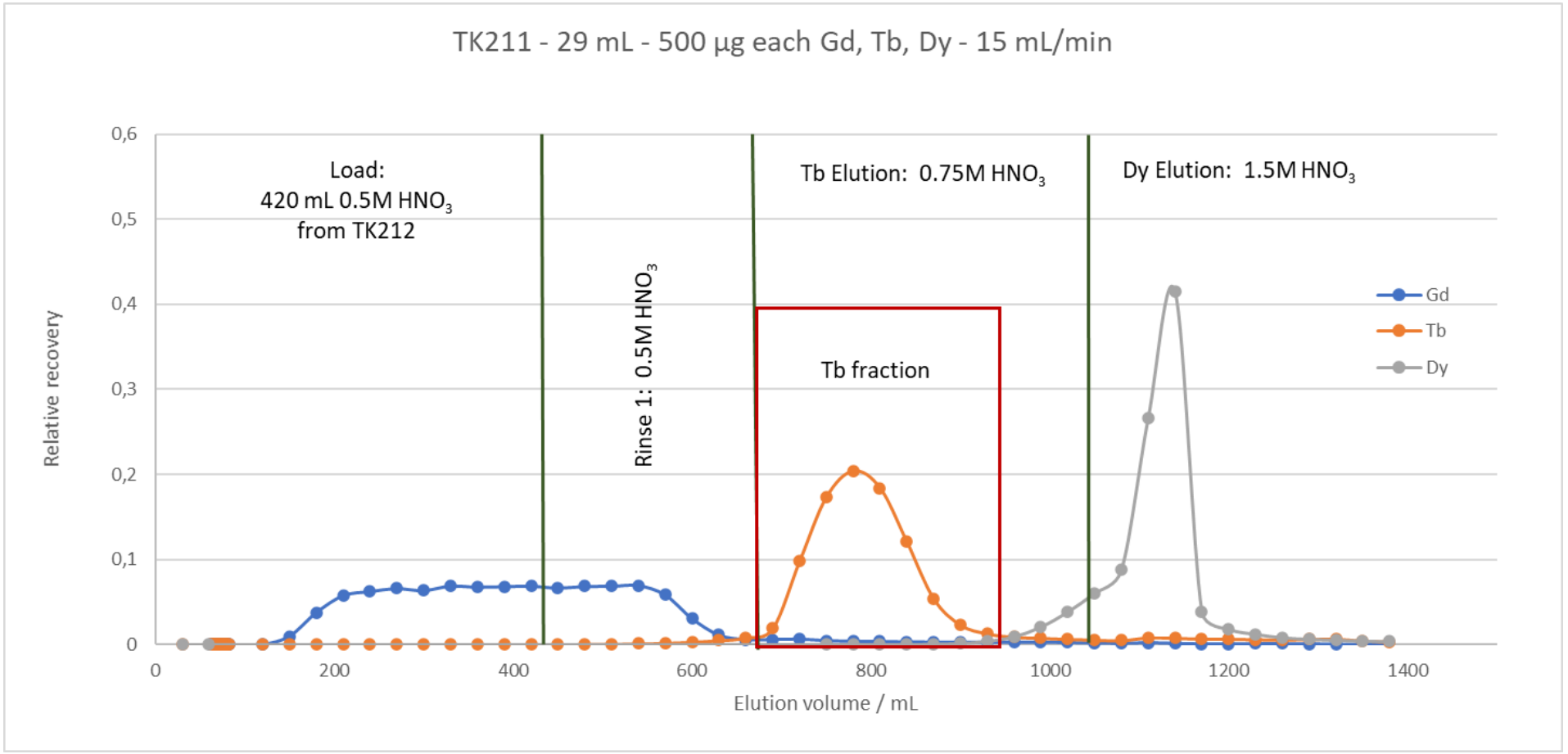






- On the same TK212 column
- More Gd => earlier elution
  - At 3g Gd start of breakthrough
  - More than 3g possible? Tb needs to remain retained…
- Little effect on Tb
- Small impact on Dy
- Tb / Dy sepration remains good.

Tb polishing on TK211

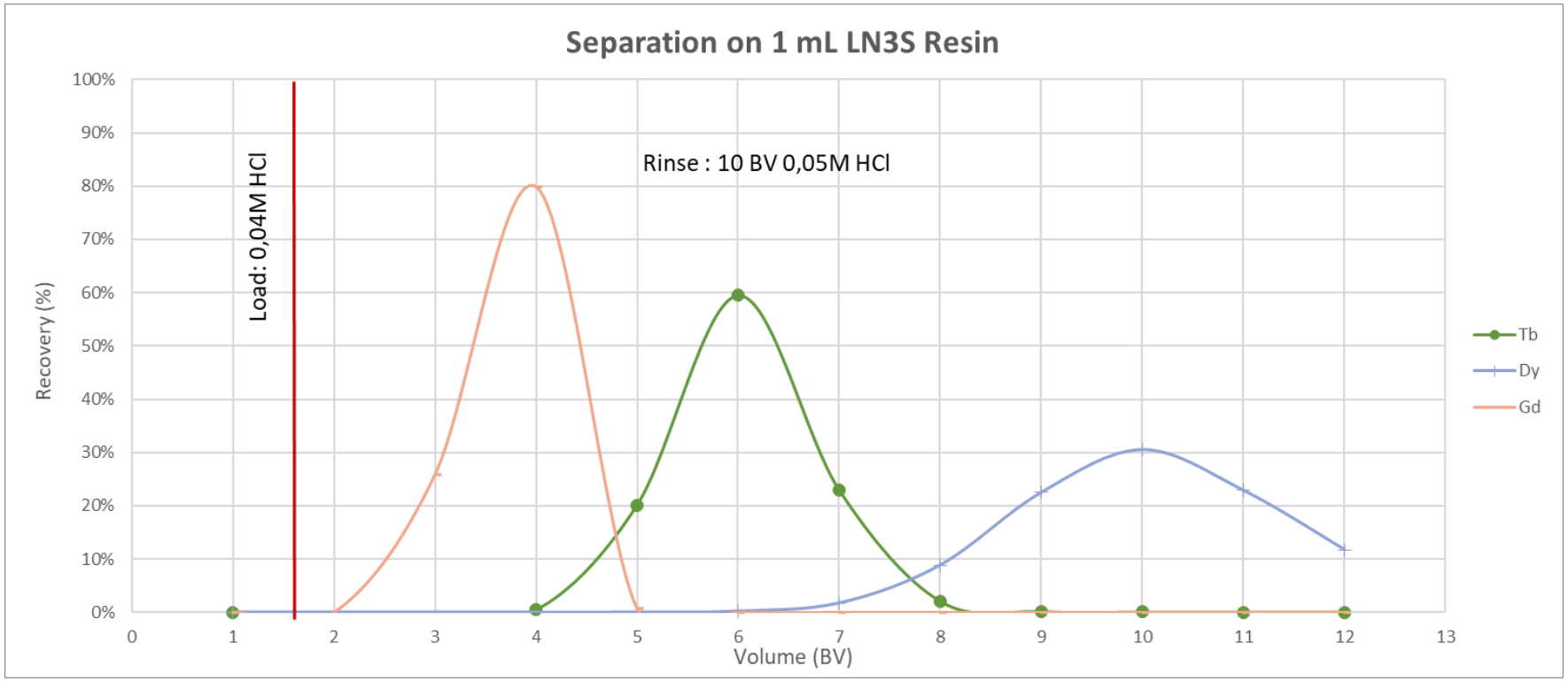


- Direct load of Tb fraction from TK212 onto TK211 (29 mL – 30cm x 1.1cm)
- Gd breakthrough during load & rinse with 0.5M HNO_3 (alternatively HCl)
- Tb elution (Dy sufficiently well removed before) preferably in **>3M HNO_3**
- Conversion to dilute HCl via TK221, A8 for nitrate removal

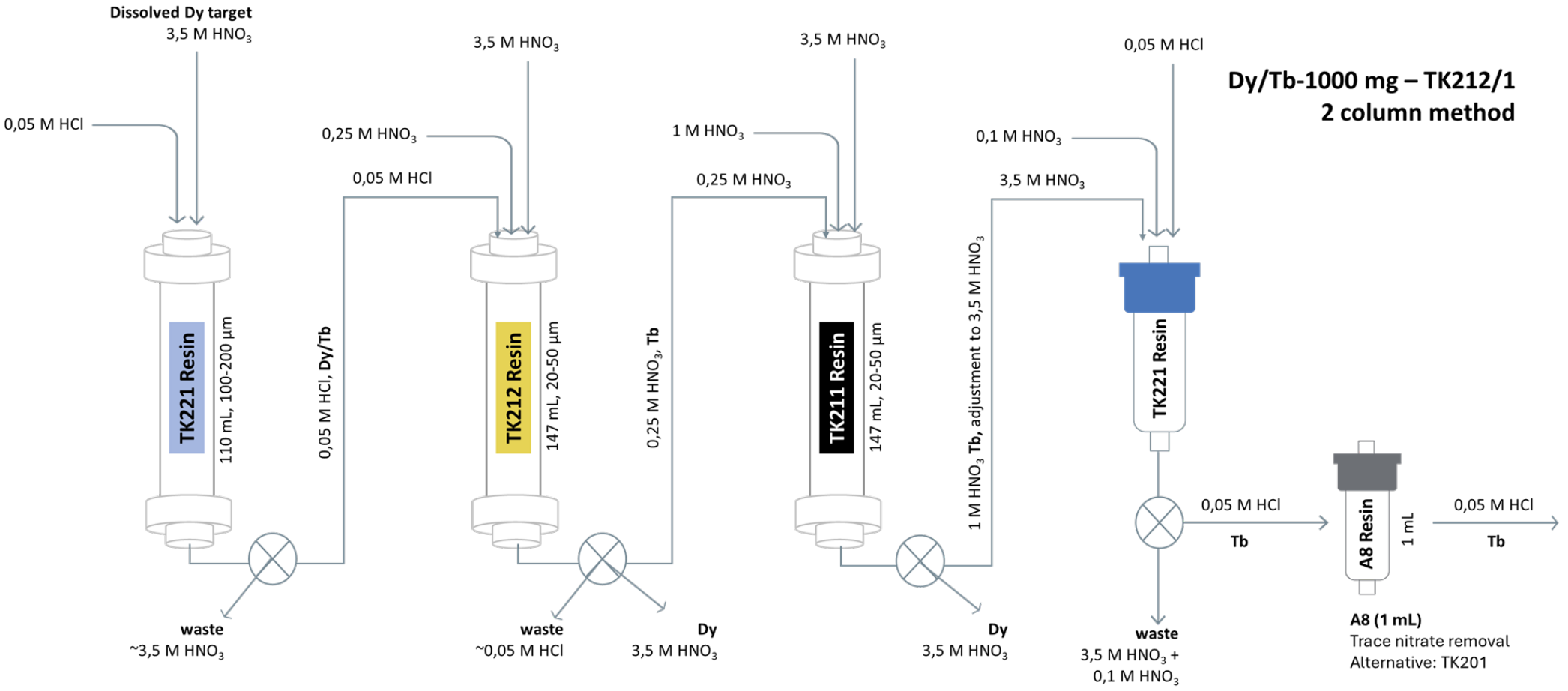
On-going: Tb/Dy separation

Request:

- Removal of Dy ingrown e.g. during transport
- Aim: rapid removal, no significant change of volume and acidity of Tb
- On-going work



Tb separation from 1g Dy targets



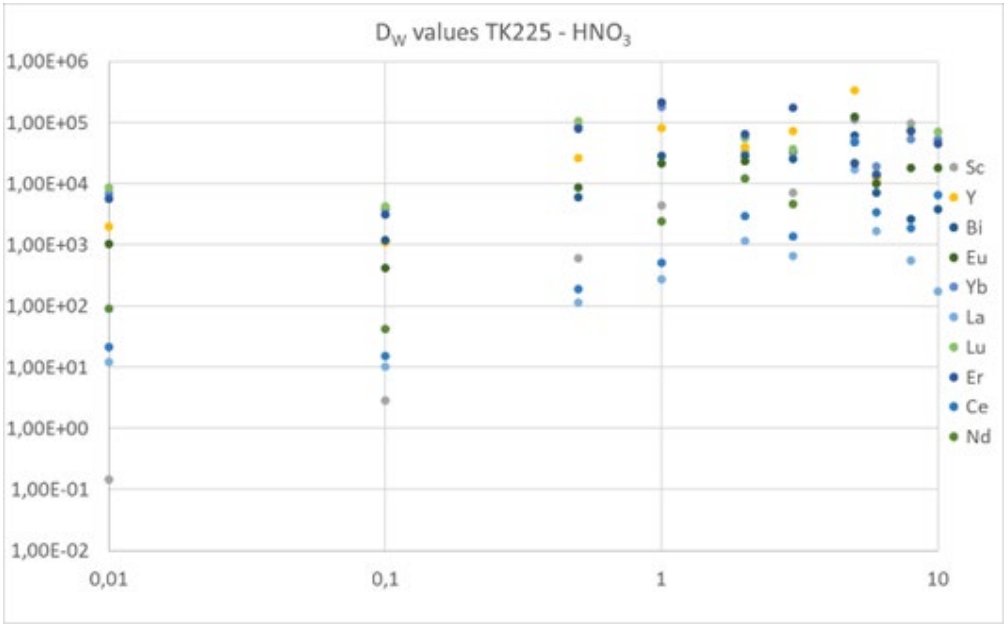
TK225 Resin

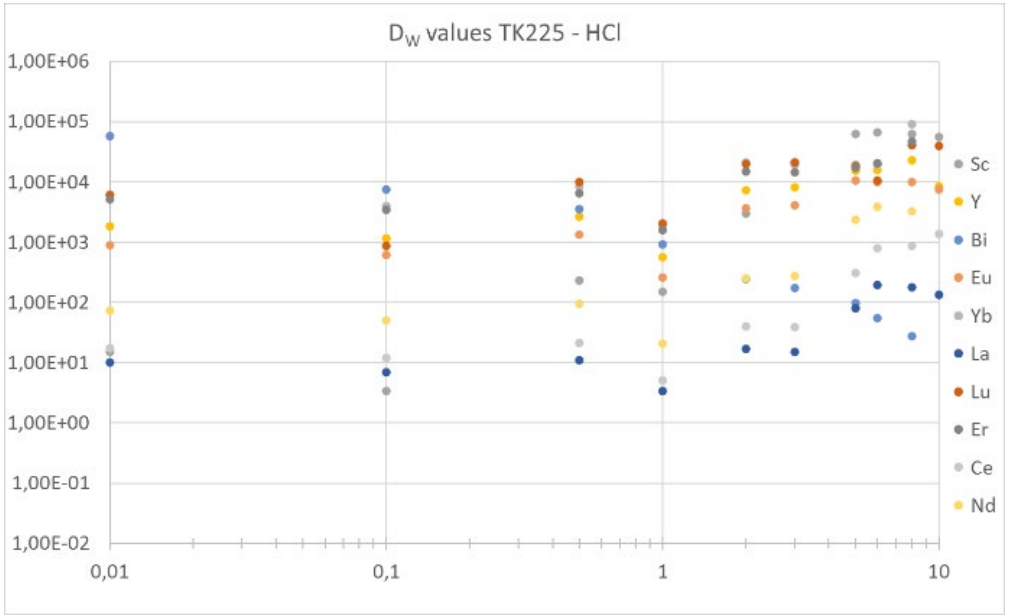
TO-DGA plus ionic liquid => originally failed experiment

Very high retention of lanthanides at medium to high acid

Especially heavy lanthanides also very well retained at low acid concentrations

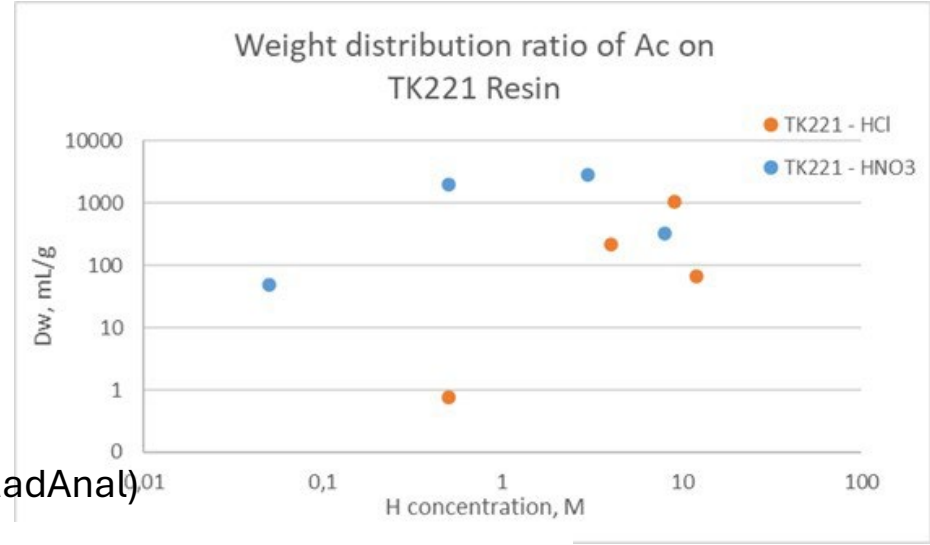
Main application: Removal of radiolanthanides from effluents





TK221/2 Resins – Ac Dw values

- Ac Dw data determination on-going
- Work with several groups
- Upcoming publication



CONFIDENTIAL

Data courtesy of N. Vajda (RadAnal)

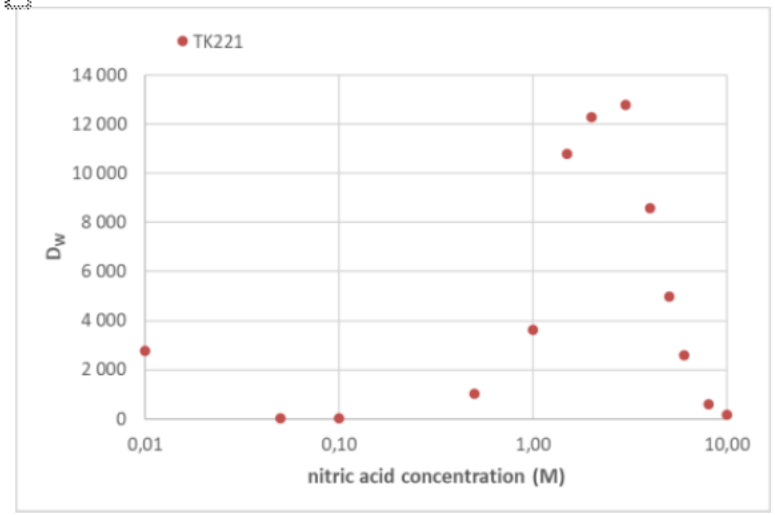


FIG. 1 The D_W values for ^{225}Ac between TK221 and nitric acid

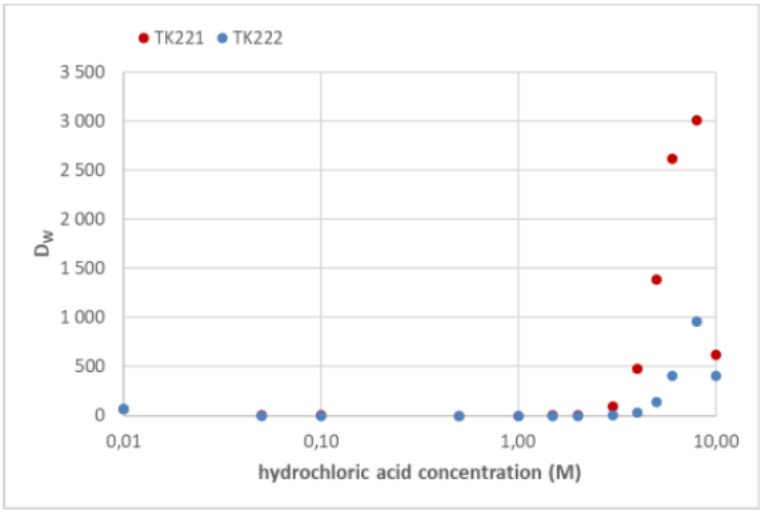


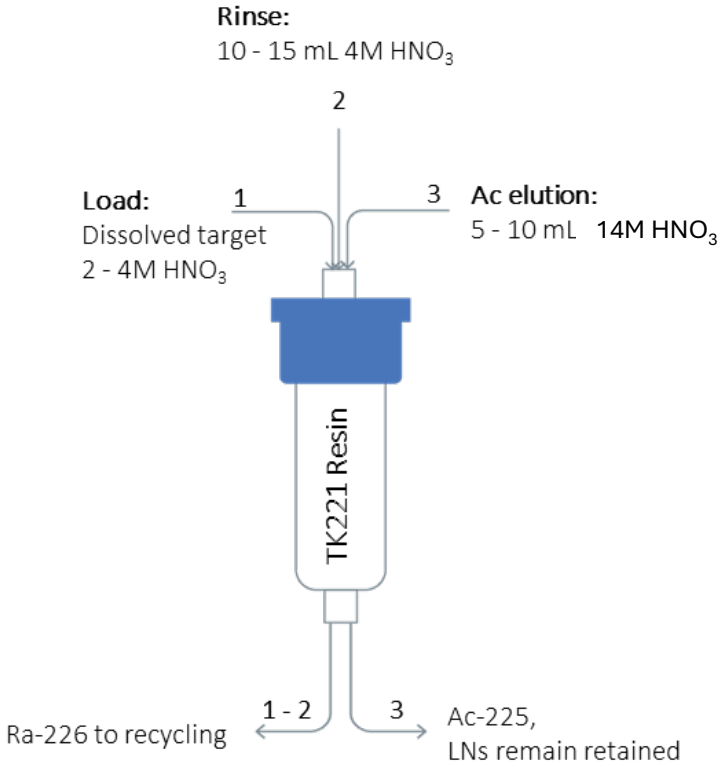
FIG. 2 The D_W values for ^{225}Ac between TK221 and TK222 and hydrochloric acid

Data courtesy of O. Lebeda (UjV Rez)

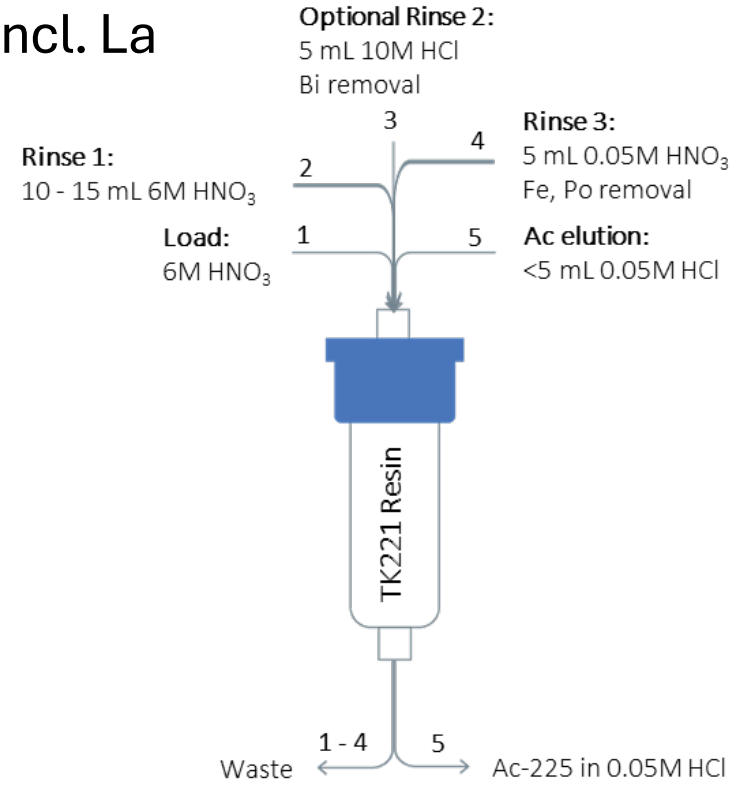
Ac-225 separation

Two TK221 cartridges for removal of impurities incl. La

- In case La can be excluded step 2 only

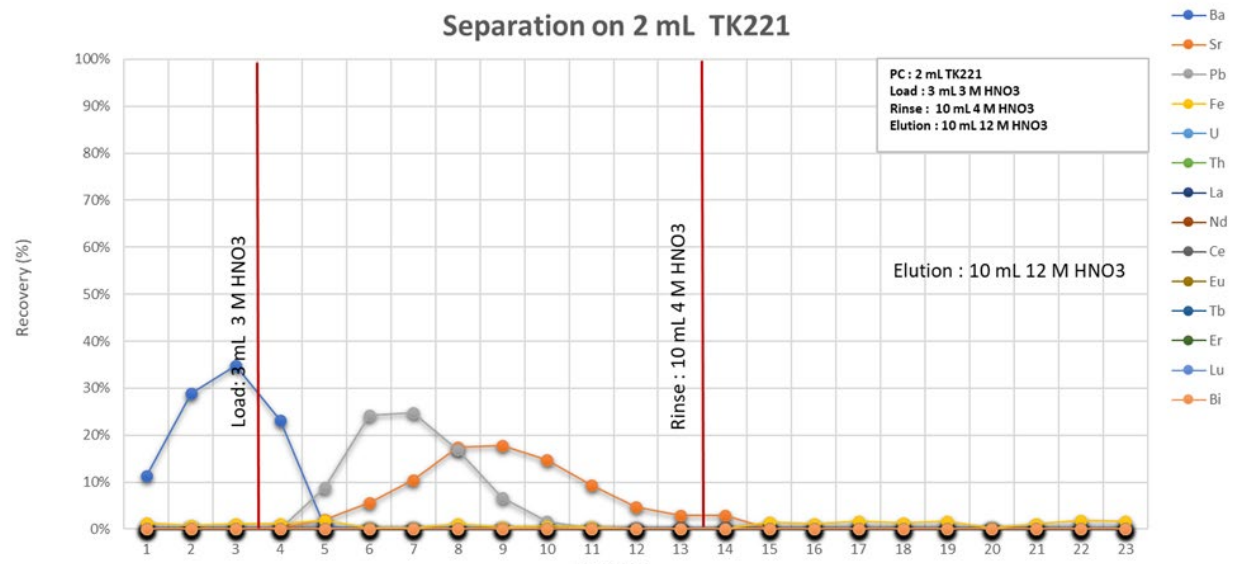


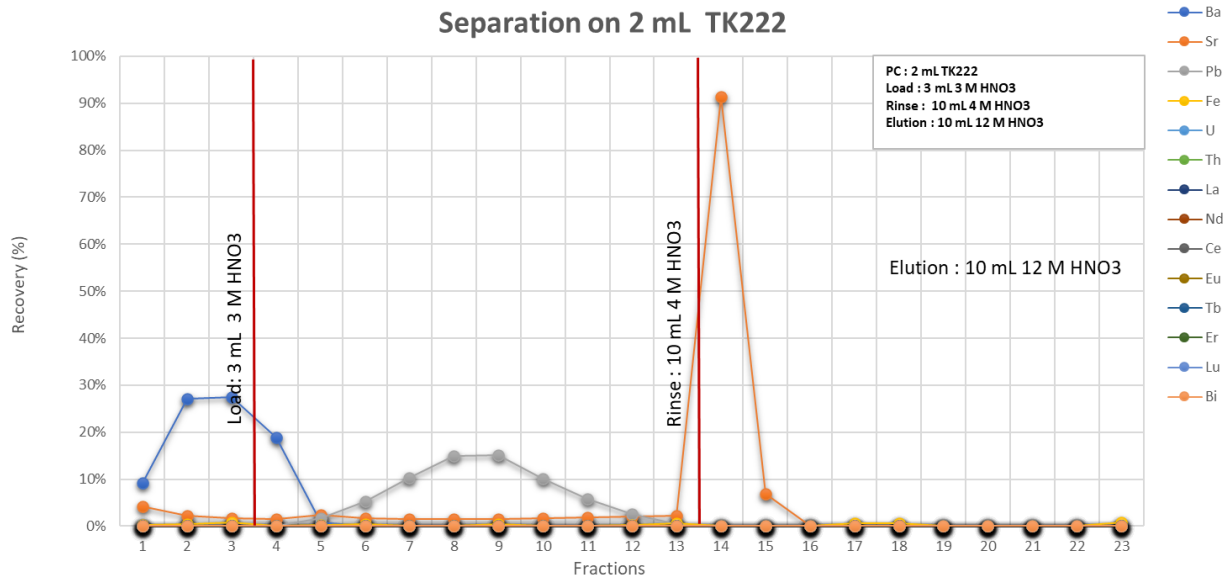
Step 1 TK221:
Target dissolved in 2 – 4M HNO_3 (2M prefered => Ra solubility)
Ra, Ba, Pb, Sr,... removal with 4M HNO_3
Ac elution in 14M HNO_3 (LNs retained)



Step 2 TK221:
2x diluted eluate from first TK221
Rinse with 6M HNO_3 and opional rinses with:
10M HCl => Bi removal and
0.05M HNO_3 (Fe, Po removal) => can be inverted
Ac elution in 0.05M HCl

TK221 Resin – Ac separation – step one





- In case LN need to be removed
- Two step procedure

First Ac / LN separation

TK221

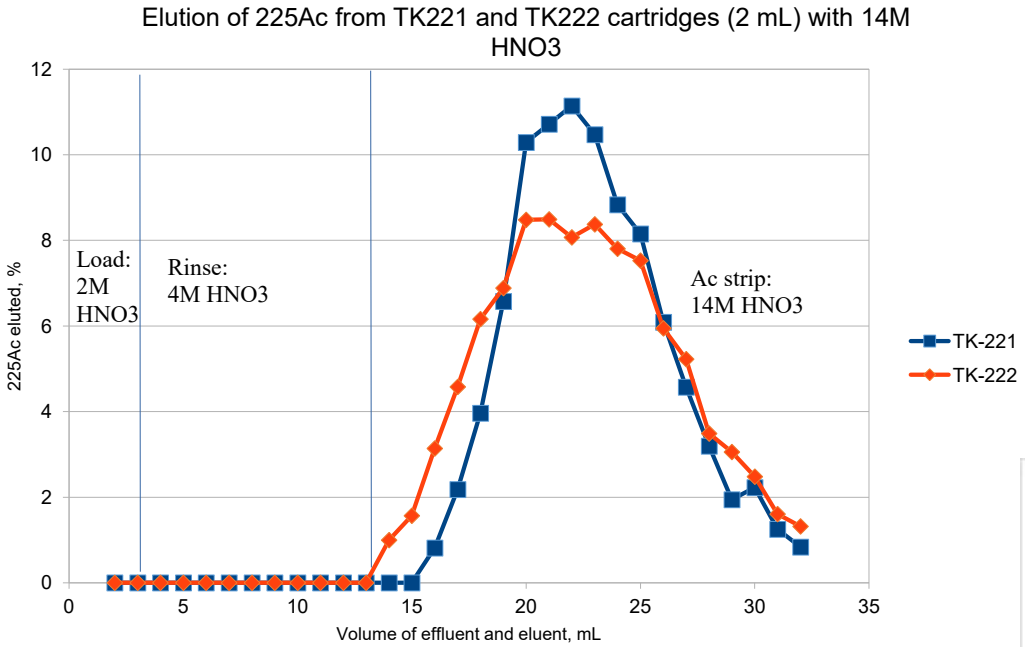
- Load from elevated HNO_3
- Ac elution in very high HNO_3
- LNs, U, Th retained
- Particular attention to Pb/Sr
  - Elution in 4M HNO_3

TK222

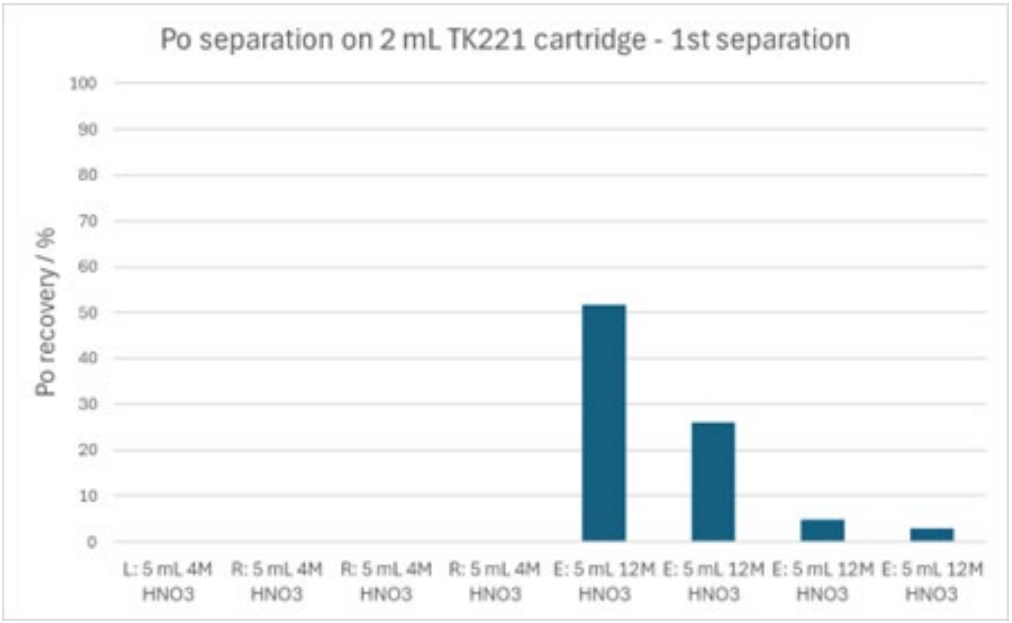
- Load from elevated HNO_3
- Ac elution in very high HNO_3
- LNs, U, Th retained
- Particular attention to Pb and Sr
  - Pb Elution in 4M HNO_3
  - Sr elution in 12M HNO_3

TK221 prefered option

Ac and Po behaviour – step 1



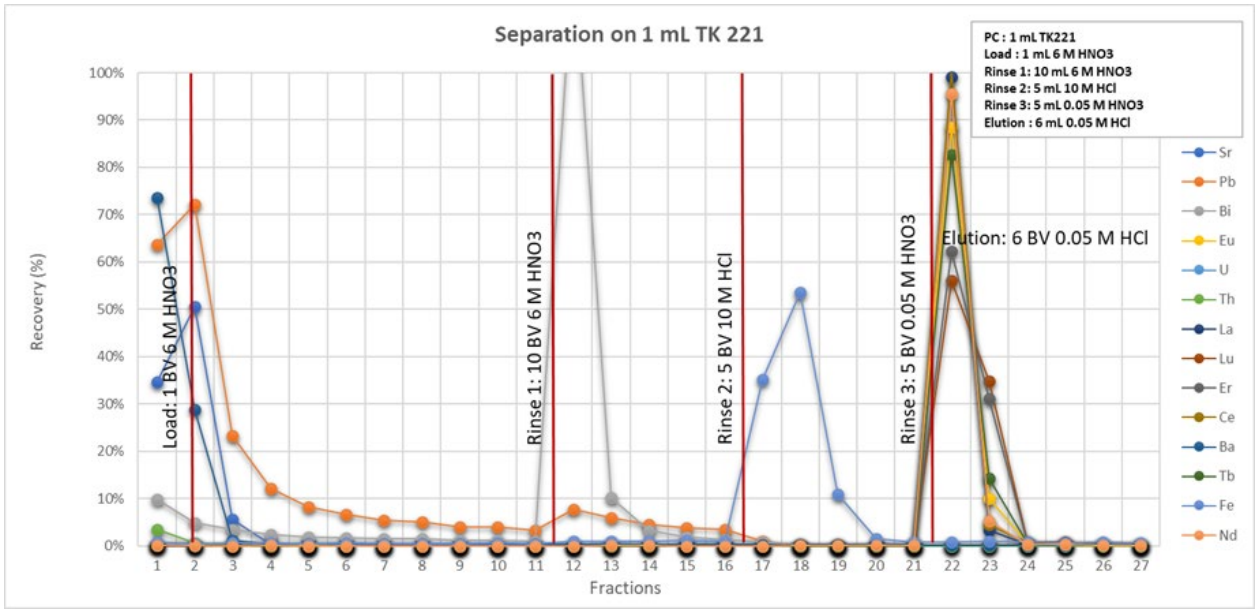
Ac elution in 14M HNO_3
Similar profiles for TK221 and TK222
Requires ~20 mL
Dilution by x2 before loading onto second TK221 or TK222

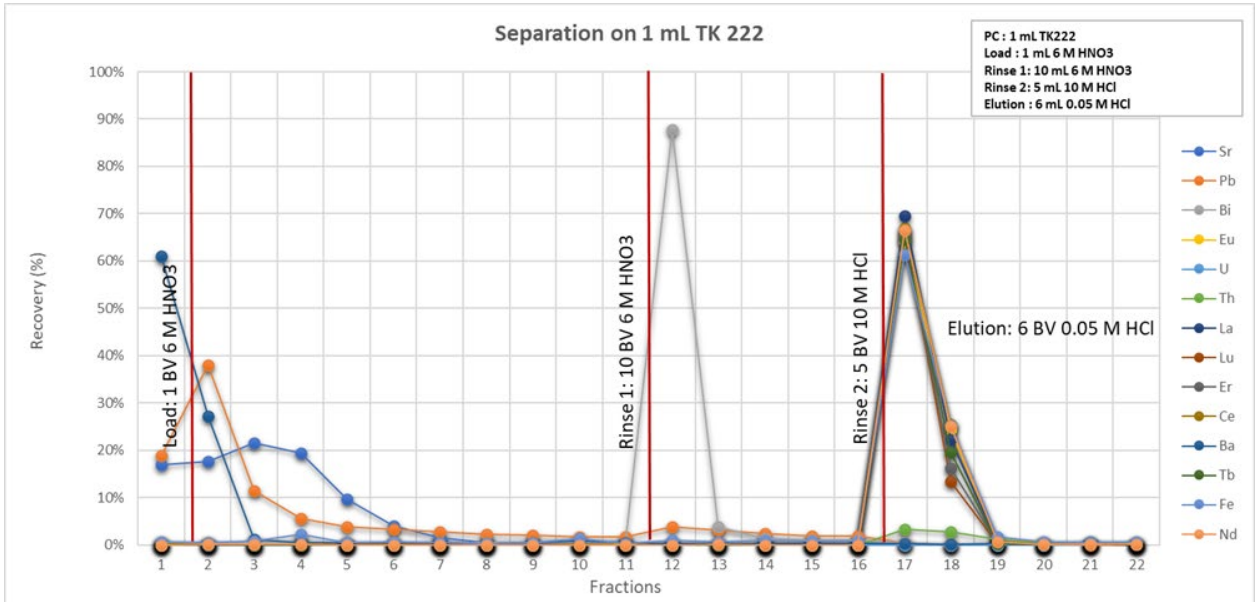


Po co-elutes with Ac
To be considered on second TK221/2

All data courtesy of Nora Vajda (Radanal)

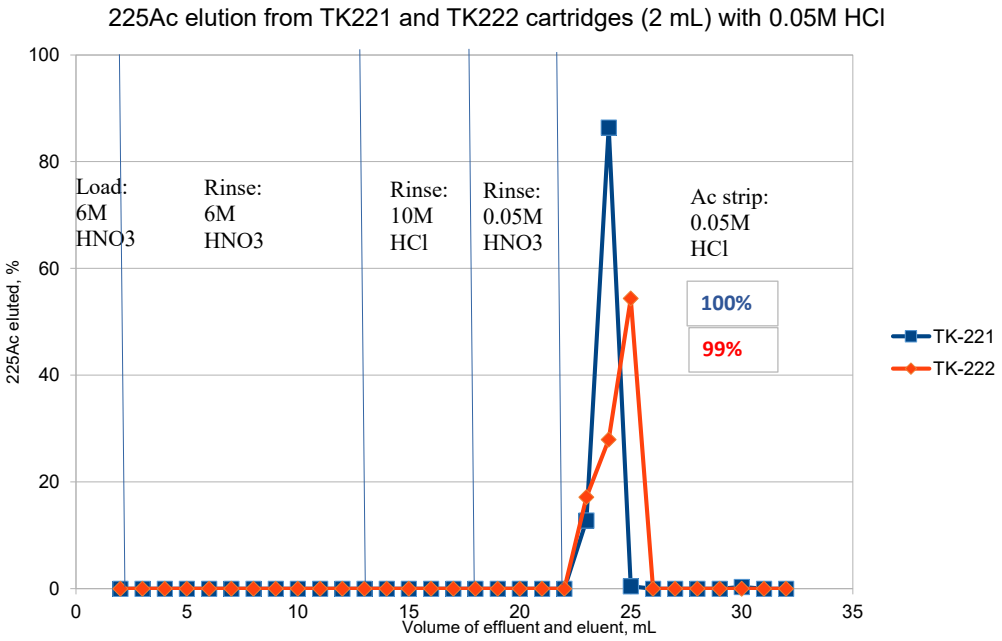
TK221 Resin – Ac separation – step two





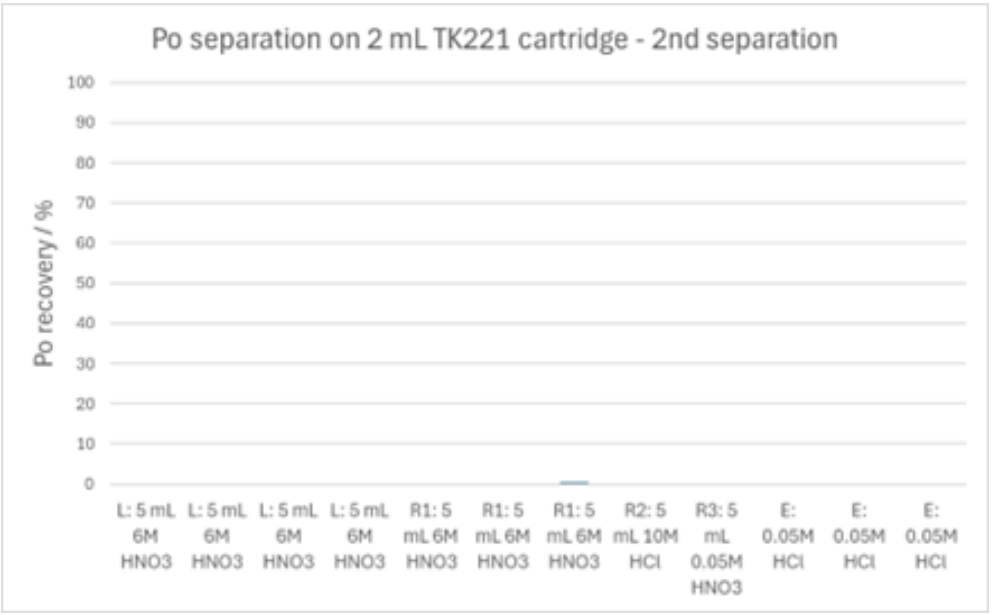
- Second separation
- TK221
  - Dilute x2 => load
  - Bi removal 10M HCl
  - Fe removal in 0.05M HNO_3
  - Ac elution in 0.05M HCl
  - Important: Lanthanides need to be removed upfront (1st TK221)
- Alternative: TK222
  - Sharper Ac elution
  - No rinse with 0.05M HNO_3
  - Only in case of absence of Fe
- TK221 prefered in case of presence of Fe

Ac and Po elution – step 2



All data courtesy of Nora Vajda (Radanal)

- Sharp Ac-225 elution from TK221 and TK222
- Note: 0.05M HNO_3 rinse only performed on TK221 (Fe removal not possible on TK222) so elution was performed directly after 10M HCl rinsing step => delays Ac elution.
- W/o this step Ac elution from TK222 very sharp



Po remains retained on TK221, no elution

Ac elution from TK221 and TK222

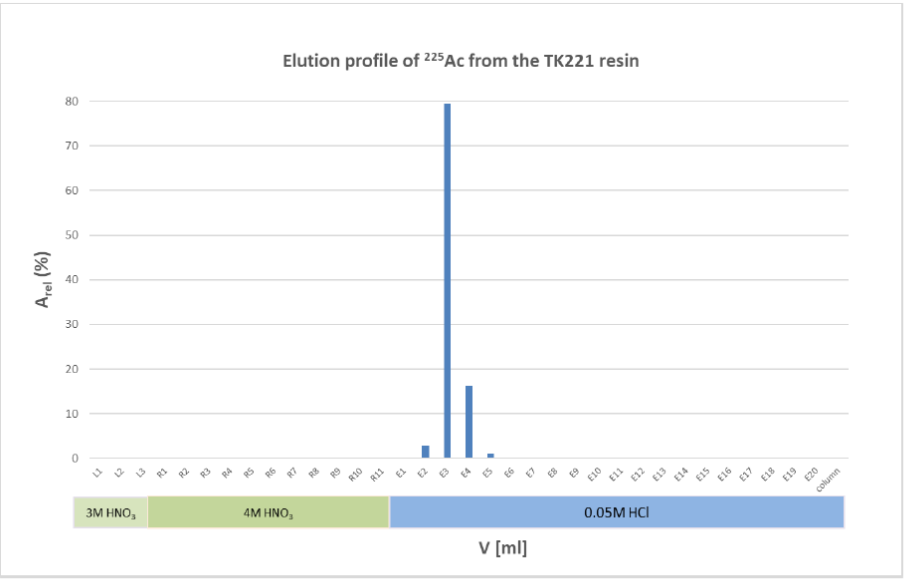


FIG. 3 Elution profile of ^{225}Ac loaded on the TK221 column in 3M nitric acid, rinsed with 4M nitric acid and eluted into 0.05M hydrochloric acid

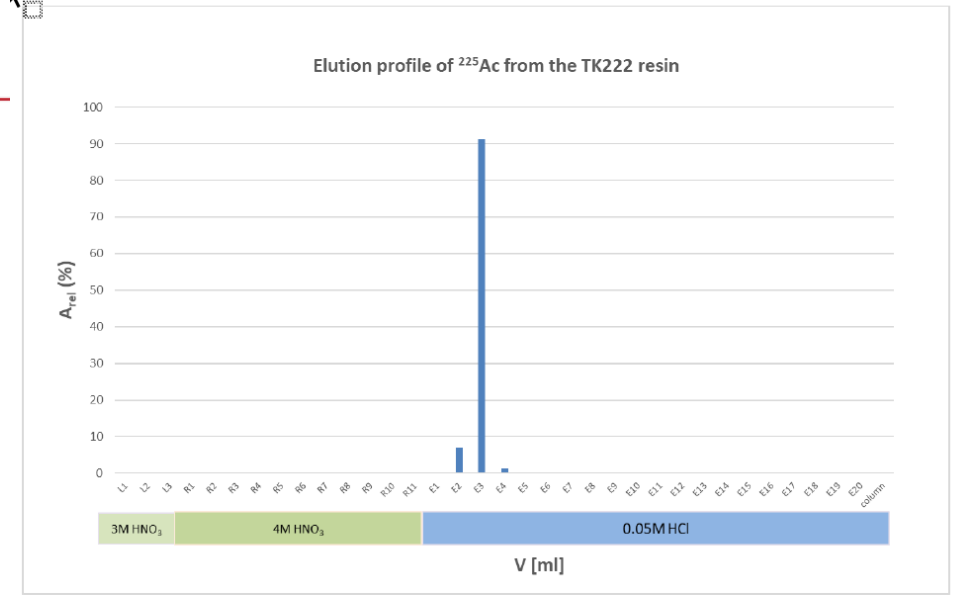


FIG. 4 Elution profile of ^{225}Ac loaded on the TK222 column in 3M nitric acid, rinsed with 4M nitric acid and eluted into 0.05M hydrochloric acid

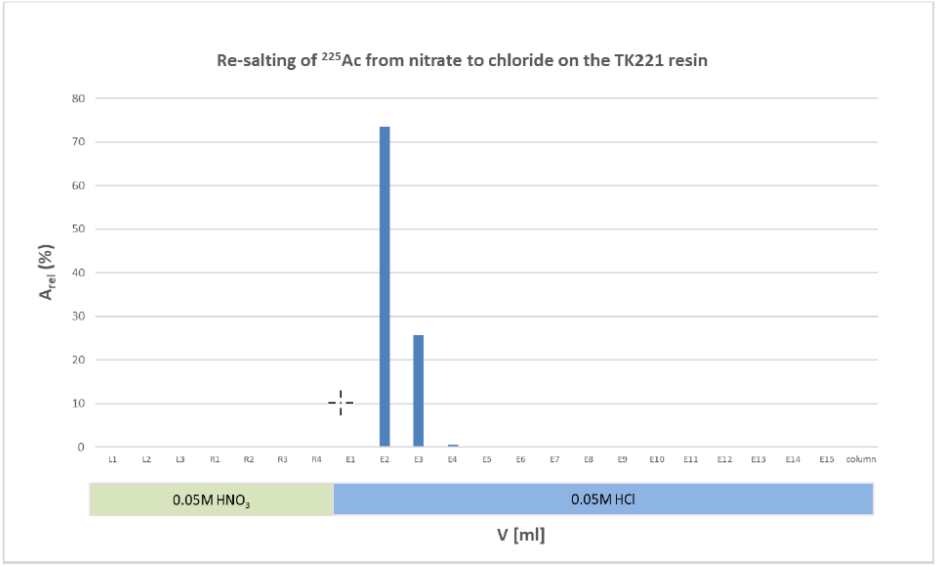


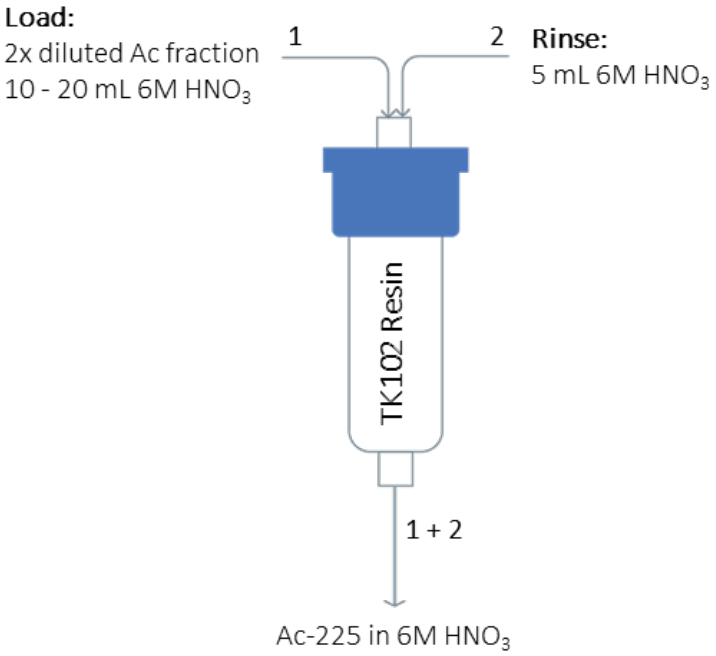
FIG. 5 Re-salting of ^{225}Ac loaded on the TK221 column in 0.05M nitric acid and eluted into 0.05M hydrochloric acid

- Sharp Ac elution from TK221, even sharper from TK222
- 'Resalting' from Ac nitrate to chloride form possible on TK221 (not TK222)
  - Load from 0.05M HNO_3, elution in 0.05M HCl

All data courtesy of O. Lebeda, Rez

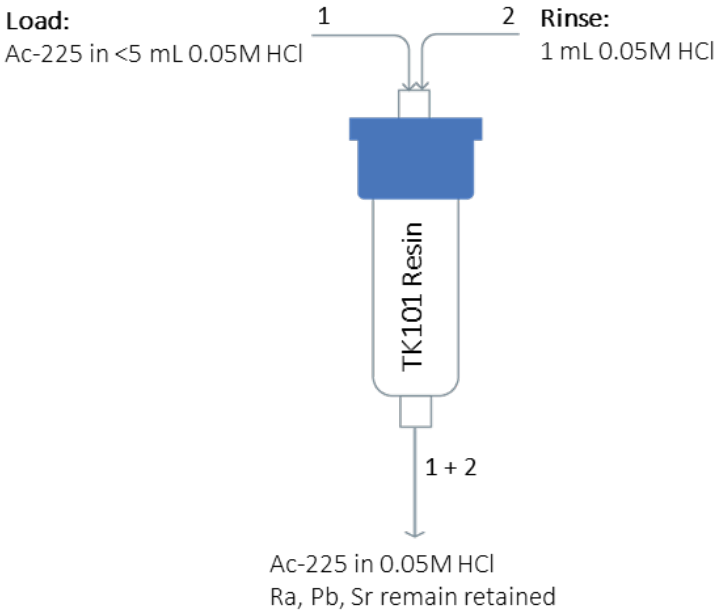
Ac-225 separation – Optional additional purification

Optional:
Pb removal on TK102



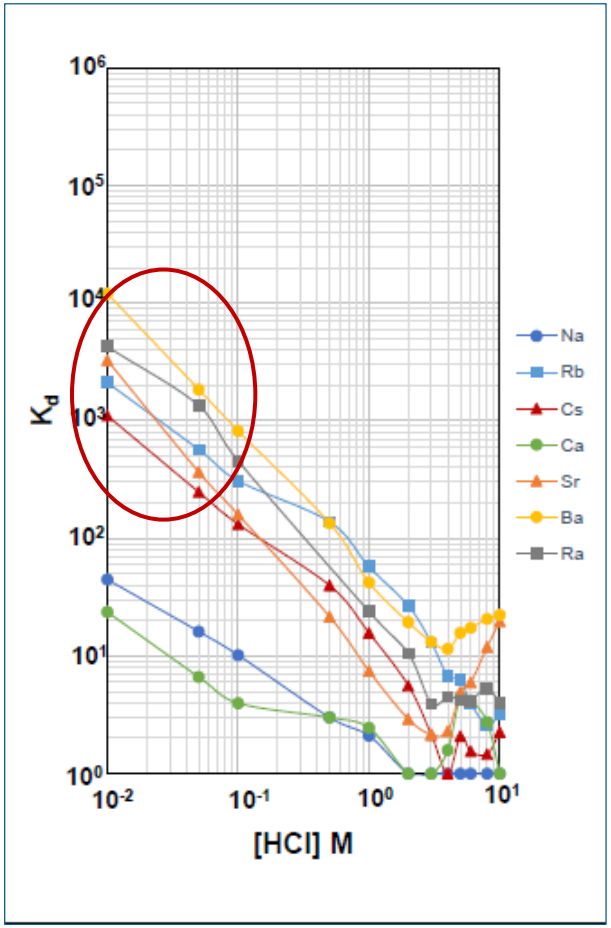
Optional Pb removal step (TK102)
Eluate of step 1 dilute by x2
Load through TK102
Pb and Sr retained, Ac passes through

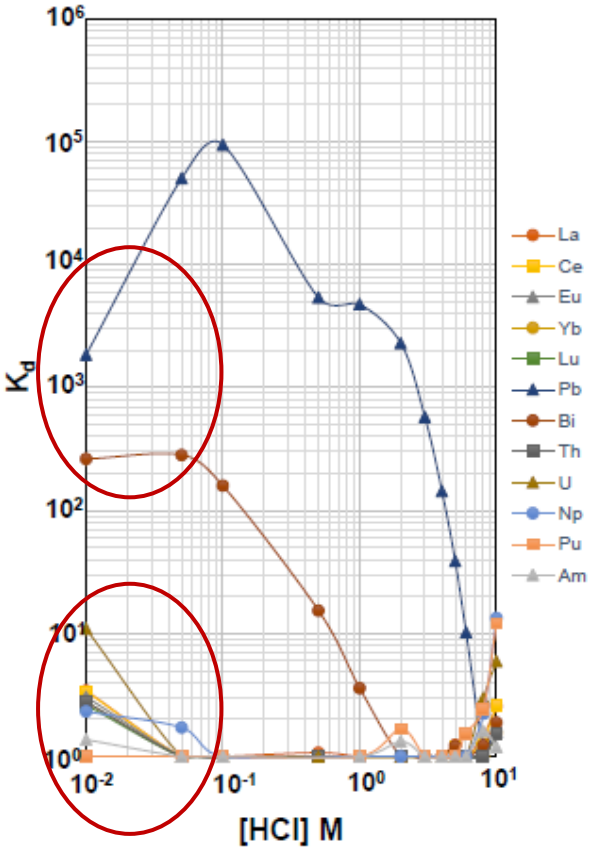
Optional:
Ra, Pb, Sr, Ba removal on TK101



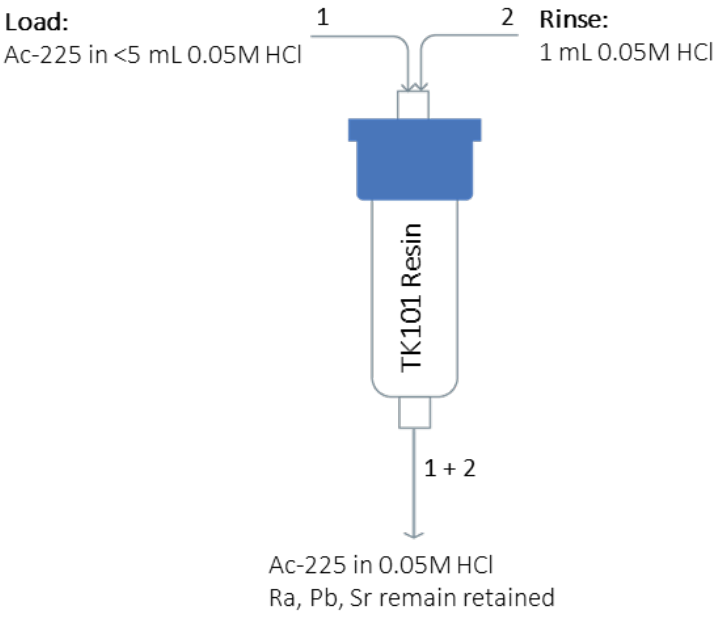
Optional Pb, Ra, Sr,... removal step (TK101)
Pass Ac fraction (0.05M HCl) through TK101
Ac passes through, Ra, Pb, Sr,... retained

Optional: TK101 purification step





Optional:
Ra, Pb, Sr, Ba removal on TK101



Data courtesy of B. Russel (NPL)

Optional Pb, Bi, Ra, Sr,... removal step (TK101)
Pass Ac fraction (0.05M HCl) through TK101
Ac passes - Ra, Pb, Sr, Bi,... retained

Ra purification / recycling

Needles and other Ra sources often contain Pt, Ir, Au, Ba besides Ra.

Ra generally present as $RaSO_4$

Suggestion: Work-up following Matyskin et al.

Destruction of the needle, generally cutting (higher losses) or dissolution in aqua regia

Conversion of $Ra(Ba)SO_4$ via heating with Na_2CO_3 solution

- $RaCO_3$ recovered as solid
- Soluble in dilute acid => dilute HNO_3 final acidity <0.1M HNO_3
- Alternative: EDTA => use of e.g. AC Resin to pull Ra out of EDTA at pH4

Ra purification on TK101/2 possible

At-211

- Requests for cartridge based separation of At from Bi targets in HNO_3. Resin approach already used by Burns et al. (3-octanone)
- Eriksen et al. showed At separation from Bi possible in HNO_3 via LLX using Octanol (=> TK400 Resin)
- Tereshatov et al. tested several extraction chromatographic resins for At separation from Bi incl. TK400
- At elution via alcohol (removal of org. phase + At from resin)
- TK400 and three additional resins currently being tested (“TK401”, “TK402”, TK200) – standard and new support => improvements possible?
    - Gagnon et al. PEG Resin (=> TK202?)
- Elution via NaOH possible?
- At still active in labelling reactions?
- Currently shipping samples
- Also working on resins for Rn-211/At-211 gen.

DGA Sheets

TO-DGA (normal DGA) and TEH-DGA (branched DGA) impregnated Whatman TLC paper

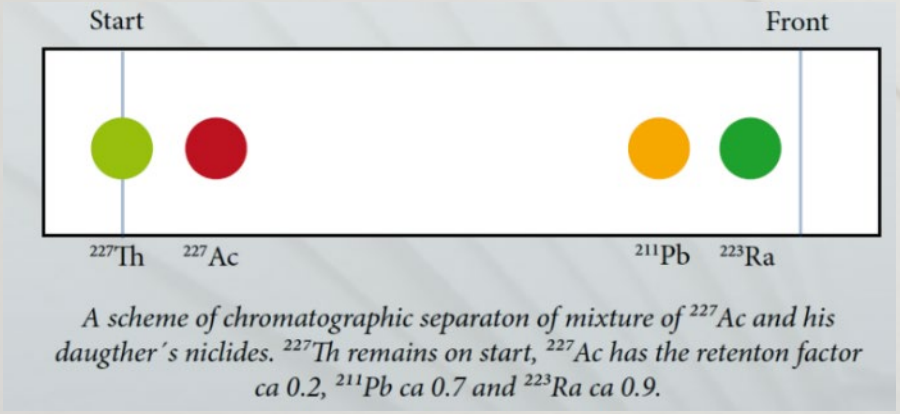
- Developed at CVUT (Kozempel et al.)
- Now also iTLC based (iSheets)

QC of radionuclides and generator eluents

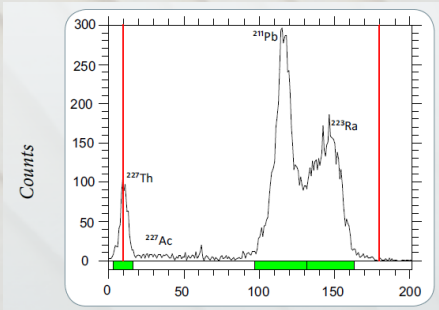
(p.ex. Ra-223, Ac-225/Bi-213, Pb-212, Ge-68/Ga-68 …)

- TLC scanner or radiometer/LSC or HPGe after cutting

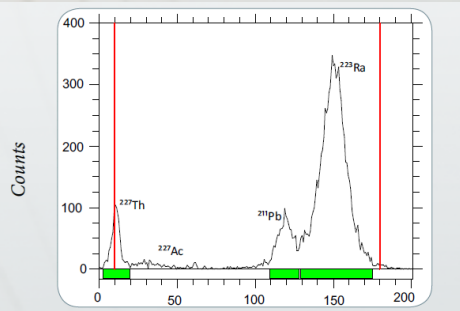
Run under acidic conditions => radionuclidic purity



A scheme of chromatographic separaton of mixture of ^{227}Ac and his daugther´s niclides. ^{227}Th remains on start, ^{227}Ac has the retenton factor ca 0.2, ^{211}Pb ca 0.7 and ^{223}Ra ca 0.9.



Radiochromatogram measured immediately after separaton. Low abundant radiatons of ^{227}Ac were not detected.



Radiochromatogram measured one hour afer separaton. Decay and ingrowth of ^{211}Pb is clearly visible.

More types of sheets under development (selectivities, geometry, support)

- ZR, TK201,...
- 2D TLC for radionuclide screening ?

DGA Sheets - Ra

DGA-SHEETS technical note - Quality control of labelled Ra compounds

Radio-instant thin layer chromatography (radioTLC) can be used to assess complex formation of Ra isotopes with a stable ligand such as biologically stable radiocomplex with macropa, which can stably chelate $[^{223}Ra]Ra^{2+}$ with a radiolabelling efficiency of >95%.
The complexation is carried out at room temperature in metal-free ammonium acetate buffer (0.1 M, pH 6). Aliquots from these radiolabeling reactions were collected at various time points and analyzed by radioTLC to evaluate complex formation.
The TLC is performed using DGA impregnated TLC sheets (DGA Sheets) as the stationary phase and **0.1 M NaOH** as the mobile phase. Under these conditions, free $[^{223}Ra]Ra^{2+}$ remained at the baseline (R = 0), while the complexed species migrated with the solvent front (R = 1) [1].

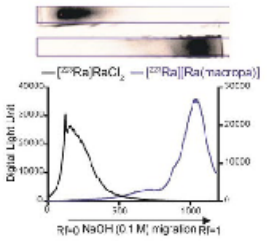


Fig. 1 Formation of $[^{223}Ra][Ra(macropa)]$ under migration of $[^{223}Ra]RaCl_2$ (top) and $[^{223}Ra][Ra(macropa)]$ (bottom) on DGA-coated chromatographic strips. [1]

Buffered solutions

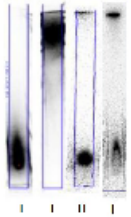


Fig. 2 TLC autoradiographic readings of $[^{223}Ra][Ra(macropa)]$ (10 mM), DOTA (10 mM) and EDTA (5mM) migrated on DGA-coated TLC using a NaOH (0.1 M) mobile phase.
I. $[^{223}Ra]RaCl_2$ migration (Rf≈0)
II. $[^{223}Ra][Ra(macropa)]$ (Rf ≈ 1)
III. ^{223}Ra tentatively chelated with DOTA showing unsuccessful radiolabeling (85% remained unchelated)
IV. ^{223}Ra partially chelated with EDTA (65% remained unchelated). [1]

Serum

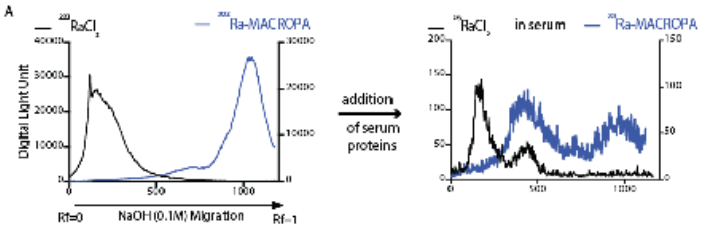


Fig. 3 TLC profiles of pure $[^{223/224}Ra]RaCl_2$ and labeled macropa in PBS (left) and in human serum (right). $[^{223}Ra]RaCl_2$ (black trace) and $[^{223}Ra][Ra(macropa)]$ (blue trace) mixed in serum were poorly separated, questioning the suitability of the DGA sheets to detect Ra decomplexation in serum. Weak ionic interactions of $[^{223}Ra]Ra^{2+}$ or $[^{223}Ra][Ra(macropa)]$ with proteins may occur and result in the inability of TLC to clearly separate each species. [1]

[1] Abou, D. S., Thiele, N. A., et al (2021). Towards the stable chelation of radium for biomedical applications with an 18-membered macrocyclic ligand. Chemical Science, 12, 3733-3742

TrisKem International, 3 rue des Champs Géons, 35170 BRUZ
www.triskem.com

Based on publication by Abou et al.

Free Ra vs macropa labelled Ra

0.1M NaOH

Ra remains fix (R_f=0), labelled compound moves (R_f=1)

CU iSheets

Poster presented at Terachem 2022 (Svedjehed et al.)

QC of Cu radiolabeled peptides (labeled vs free Cu)

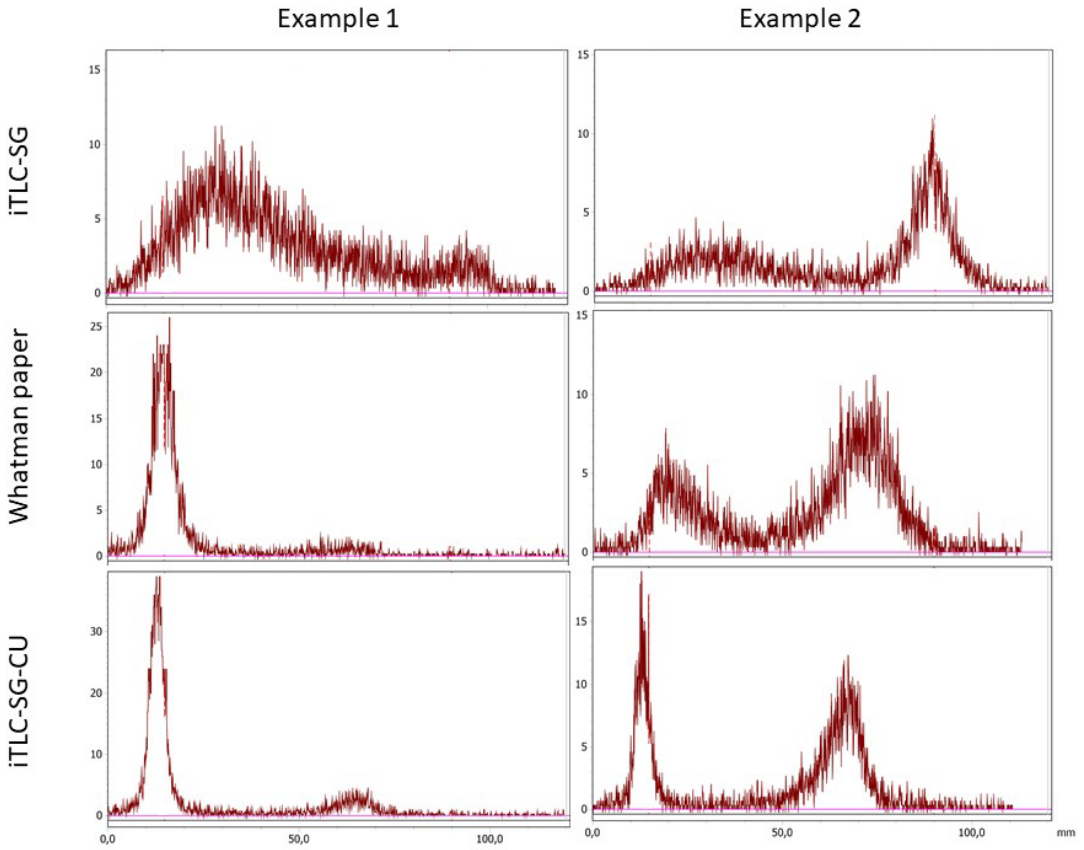
- Shown: [^{61}Cu]Cu-NOTA-octreotide

Spotting/run on three different papers after labeling:

- Whatman and iTLC without modification and
- CU extractant impregnated iTLC paper.

Both iTLC paper (impregnated/non-impregnated) developed in less than 10min, Whatmn took 25 – 30 min.

CU extractant impregnated iTLC paper showed superior resolution

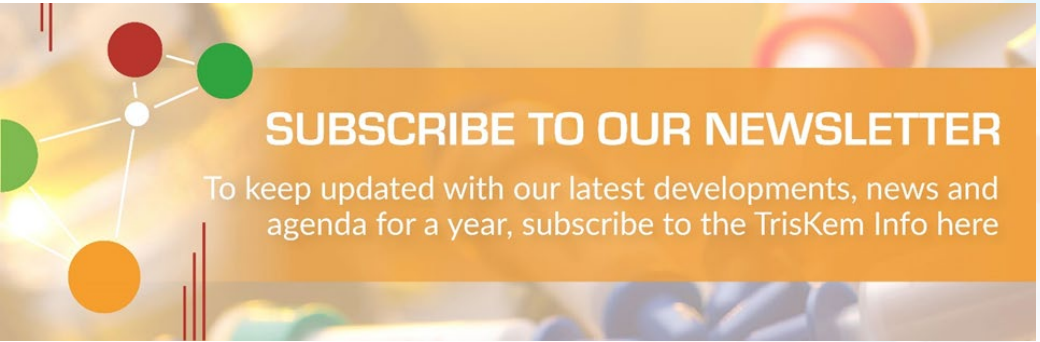


- Other systems under development/testing

Some other on-going projects

- Improvement of radiolysis stability
- Additional ‘Sheets’
- Removal of free RN from reaction mixtures
- Further upscale of radiolanthanide separations
- Other radiometals
  - Auger (Sb, Pd, Hg, Ag,…), Mn, V…
- At separation
  - Resin optimisation, Rn-211/At-211 generator,…
- Decontamination
  - Effluents and reaction wastes
- Other geometries
- Fate’ of RN in the environment and bioassay
  - Separation methods
  - Mainly longer lived RN (=> therapy)
    - Ac-225/7, Lu-177(m), radioiodine,…
  - Quantification

Thank you for your attention!



TRISKEM
Expertise in Separation Chemistry