TrisKem International

Overview and new Developments RadPharm & on-going R&D

TKI UGM at CARM 2023

Steffen Happel
22/02/2023

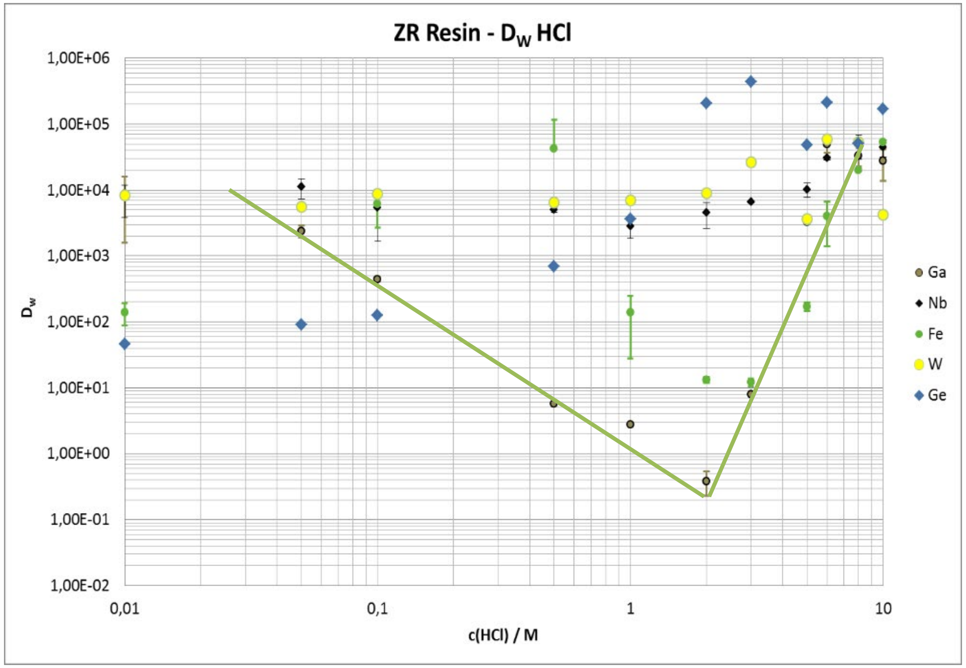
TRISKEM
Expertise in Separation Chemistry

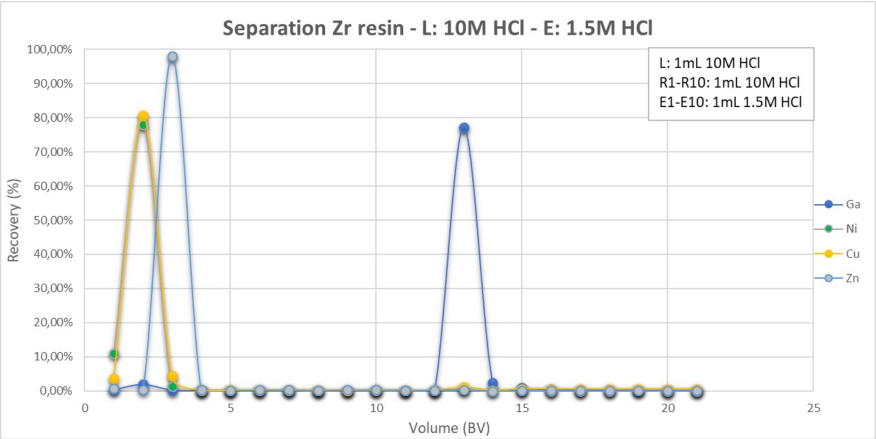
Overview

- ZR Resin
  - Ga-68 from Zn targets
  - Ge-68 from GaNi targets
- Cu-61/4/7
  - TK201 Resin
  - CU Resin
- Radiolanthanides
  - Tb-161 from Gd targets
  - Lu-177 from Yb targets
  - TK225 Resin
- TK221 Resin
- TK222 Resin
- Ra-226
- TK202 Resin
- Quality Control – Sheets
- Other on-going R&D

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

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Rodnick et al. EJNMMI Radiopharmacy and Chemistry (2020) 5:25
https://doi.org/10.1186/s41181-020-00106-9

EJNMMI Radiopharmacy and Chemistry

RESEARCH ARTICLE Open Access

Cyclotron-based production of ^{68}Ga, [^{68}Ga]$GaCl_3$, and [^{68}Ga]Ga-PSMA-11 from a liquid target

Melissa E. Rodnick[1], Carina Sollert[2], Daniela Stark[3], Mara Clark[1], Andrew Katsifis[3], Brian G. Hockley[1], D. Christian Parr[2], Jens Frigell[2], Bradford D. Henderson[1], Monica Abghari-Gerst[1], Morand R. Piert[1], Michael J. Fulham[4], Stefan Eberl[5*], Katherine Gagnon[2*] and Peter J. H. Scott[1*]

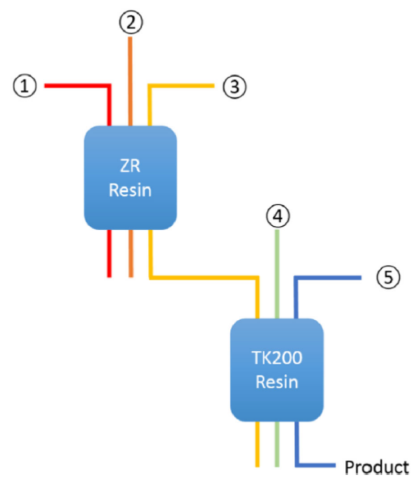


Fig. 4 Two-column approach for ^{68}Ga chemical separation

Table 1 High level schemes of [^{68}Ga]$GaCl_3$ purifications

	Scheme A*	Scheme B
① ZR Load	< 0.1 M HNO_3	
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)

- J. Kumlin et al.
- ZR, LN & TK200 for solid targets
  - High Ga-68 activities
  - ARTMS/Odense: 10 Ci production
- One column separation possible using TK400 Resin => solid targets
  - Ga retention on TK400 from high HCl
  - No Zn retention
  - Faster flow than ZR Resin
- W. Tieu et al. use of single TK400 cartridge for solid Zn targets
- Svedjehed et al. use of TK400/A8/TK200 for solid Zn targets

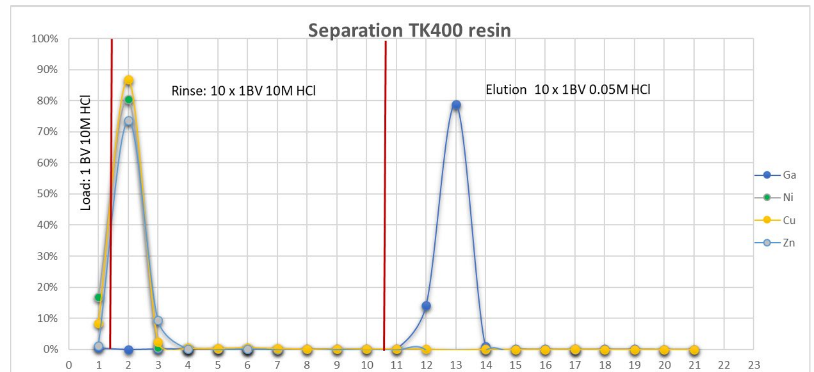
Demystifying solid targets: Simple and rapid distribution-scale production of [^{68}Ga]$GaCl_3$ and [^{68}Ga]Ga-PSMA-11

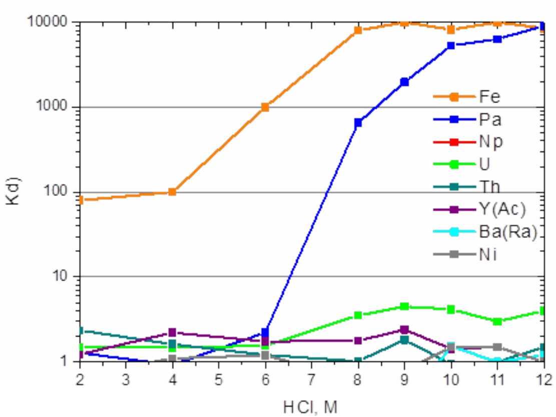
Johan Svedjehed, Martin Pärnaste, Katherine Gagnon *

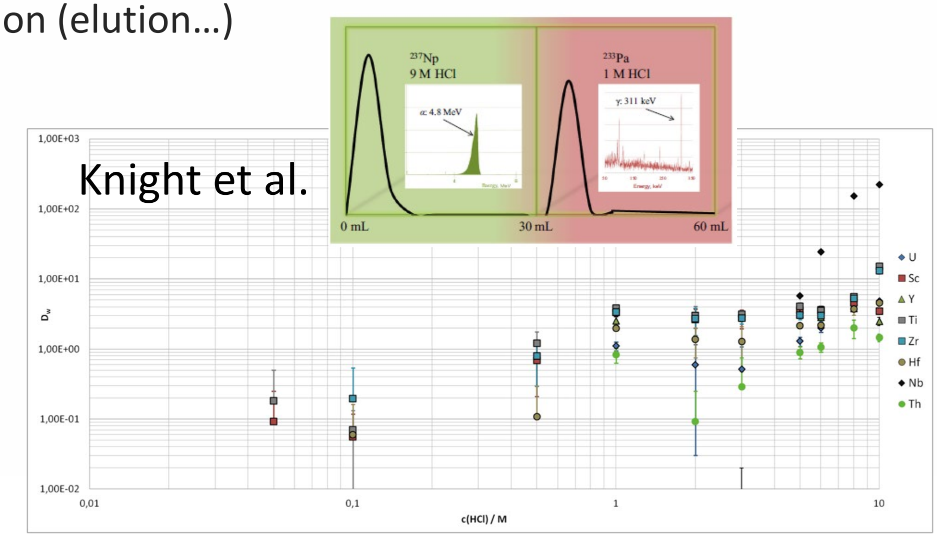
Cyclotrons and TRACERcenter, GEMS PET Systems AB, GE Healthcare, Uppsala, Sweden

TK400 Resin

- Long chained alcohol – initial work by A. Knight et al.
- Main application: **Pa separation** (Pa-231 by MS/Pa-230 for medical use)
  - NPL (no selectivity for AC, Ra, Pb,…=> Pa-230 purif.)
- Other applications:
  - Also retains Mo, Nb, **Fe**, **Ga**, Po
  - **Ga removal from Cu-67**
  - **Fe, Nb removal from Zr on TBP**
  - **Can replace TBP Resin in Cu-61/4 separation**
  - **Ga separation from Zn at high HCl**
  - Nb separation from Zr possible (Nb-90)
  - Under further testing for At separation (elution…)







Ge-68 separation from GaNi or GaCo

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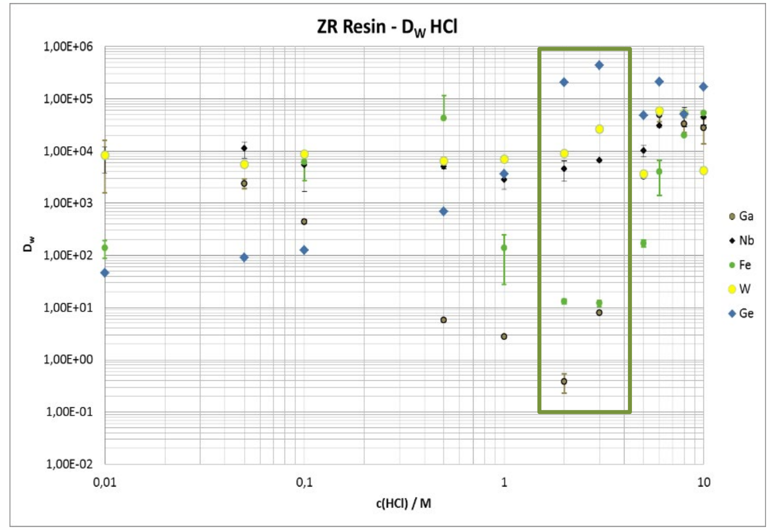
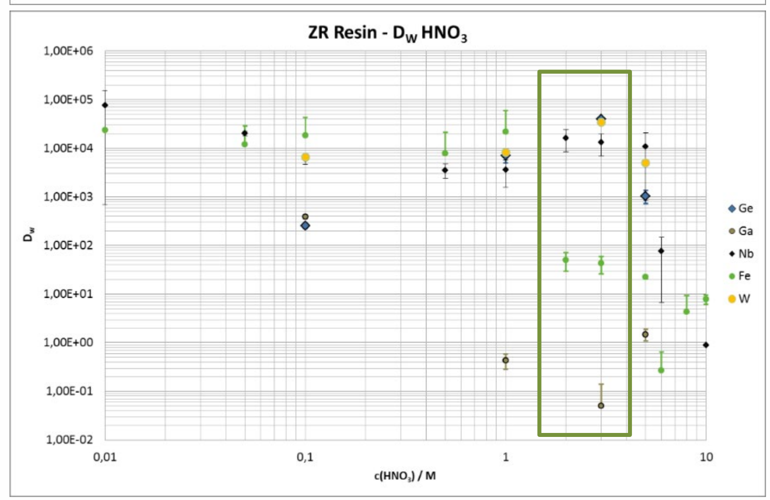
- Loading from HNO_3, HCl or $\mathbf{H_2SO_4}$ possible
  - Target dissolution in H_2SO_4
- Cold tests on >5g GaNi
- First cycle on ZR (**2 mL ZR Resin cartridge**):
  - Load/rinse from ≥5M H_2SO_4
  - High Ge retention/purification from Ga, Ni & Co
  - Elution: 0.1M citric acid (pH 3)
- Second cycle on ZR (**1 mL ZR cartridge**):
  - Adjustment of eluate to ≥5M H_2SO_4
  - Load/rinse from ≥5M H_2SO_4
  - Elution with 0.1M citric acid (pH 3)
- Conversion step (**2 mL Guard Resin cartridge**):
  - Acidification to 9M HCl, load onto Guard Resin
  - Ge/Ga selectivity => further purification
  - Rinse with 9M HCl
  - Elution with water/0.05M HCl => pH!





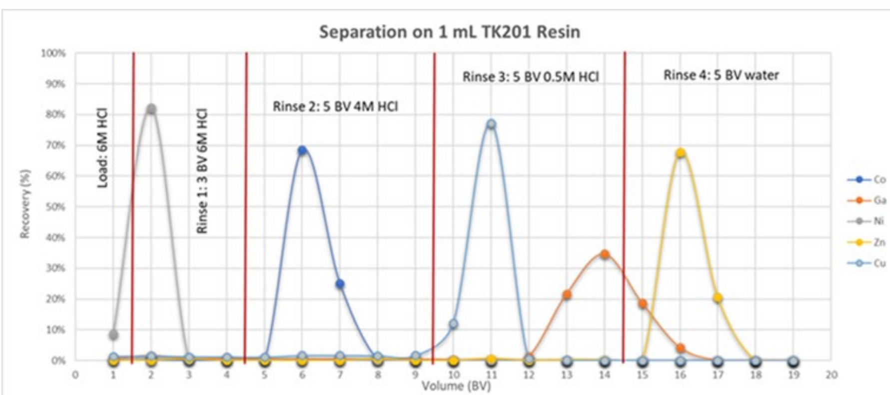
Important for high amounts of Ge: pre-rinse of GR with EtOH, then water necessary!

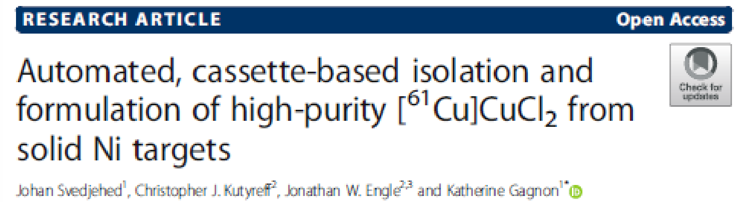
On-going: replace citric acid by warm water?

Cu-61/4 separation on TK201

- Cu-64 separation from solid Ni-64 targets
  - Target dissolution in high HCl
  - Load and rinse at 6M HCl
    - Ni removal and recovery/recycling
  - Co elution with 4 – 5M HCl => Co separation?
  - Cu elution with 0.5M HCl
    - Zn remains retained (Ga and Fe partially co-elute)

    => requires further treatment

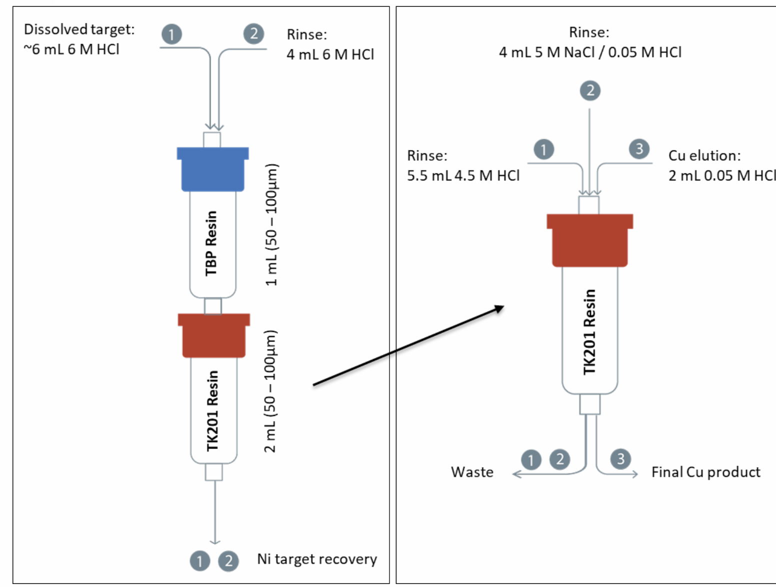




RESEARCH ARTICLE Open Access

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*]



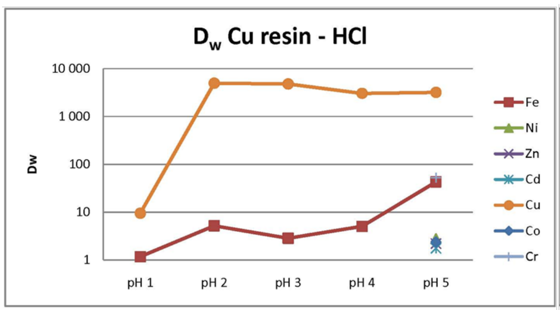
- Improvements:
  - Preferred alternative: Use of TBP (or TK400) upfront for Fe/Ga removal

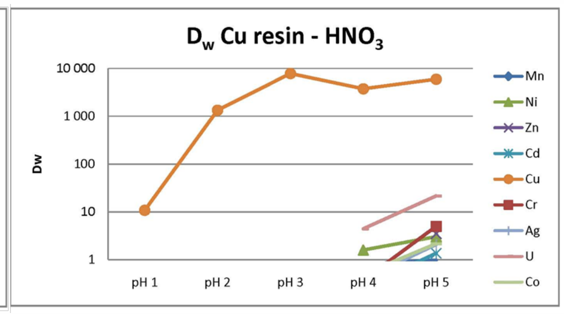
  => allows for Cu elution in 0.05M HCl

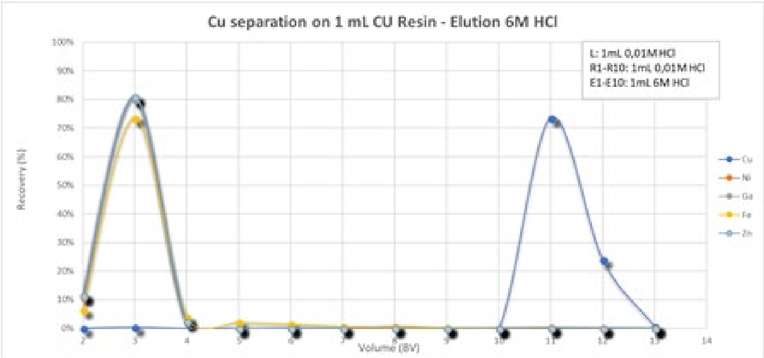
  - May also be used for Zn separation
  - **Co separation from Ni targets**
  - Several options possible:
    - 2x TK201 for elution in dilute HCl
    - TBP/TK201 elution in NaCl/dilute HCl

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,… Ga requires attention







- Load from pH >2, elution in high mineral acid (2 – 8M)
  - 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.
  - 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.
    - **Brühlmann et al. CU/TK400/TK201 for improved Ga removal**

Article

Production of GMP-Compliant Clinical Amounts of Copper-61 Radiopharmaceuticals from Liquid Targets

Alexandra I. Fonseca [1], Vítor H. Alves [1,2], Sérgio J. C. do Carmo [1,3], Magda Silva [1], Ivanna Hrynchak [1], Francisco Alves [3,4], Amílcar Falcão [1,5] and Antero J. Abrunhosa [1,3,*]

Article

Cyclotron-Based Production of ^{67}Cu for Radionuclide Theranostics via the ^{70}Zn(p,α)^{67}Cu Reaction

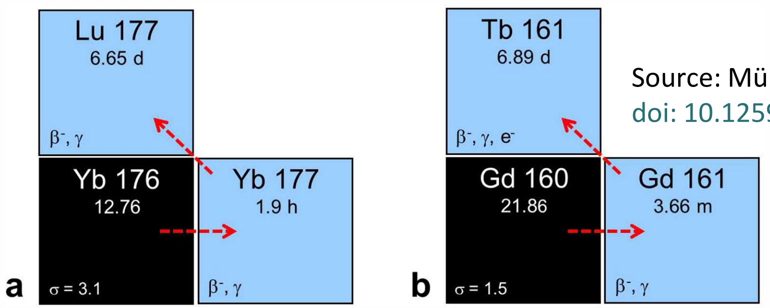
Santiago Andrés Brühlmann [1,2], Martin Walther [1,*], Martin Kreller [1], Falco Reissig [1], Hans-Jürgen Pietzsch [1], Torsten Kniess [1] and Klaus Kopka [1,2,3,4]

Ongoing: TK201/CU/TK201

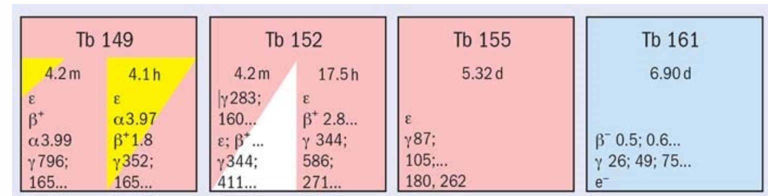
- Use of CU Resin still possible for solid Ni targets?
  - Should result in very high purity Cu…
  - **TK201/CU/TK201 method**
  - Use of 2 mL TK201 for Cu 'conversion' and matrix removal
    - Ni passes through.
      - No TBP needed (Fe/Ga removal on CU Resin)
    - Modified TK201 rinse (HCl/NaCl) is key!
    - Cu recovered in acetate buffer (pH >2)
  - Cu eluate can then directly be loaded onto 1 mL CU Resin cartridge for further purification (Zn, Fe, Ga, Ni removal).
  - Cu Elution with 6M HCl onto e.g. 0.3 mL TK201 for conversion and further concentration
  - Initial test OK, now further optimisation on-going (volumes) then hot testing

Lu-177/Tb-161

- 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

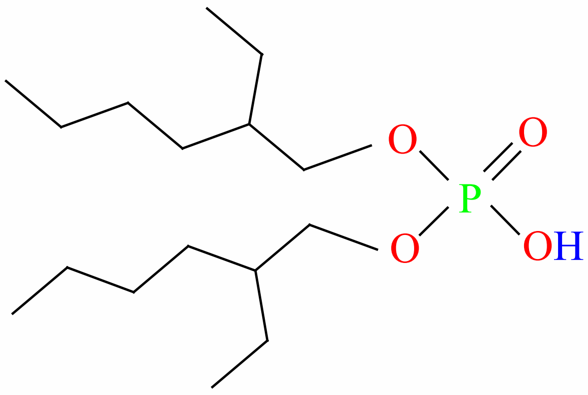


Terbium: a new ‘Swiss army knife’ for nuclear medicine
Source: https://cerncourier.com/a/terbium-a-new-swiss-army-knife-for-nuclear-medicine/

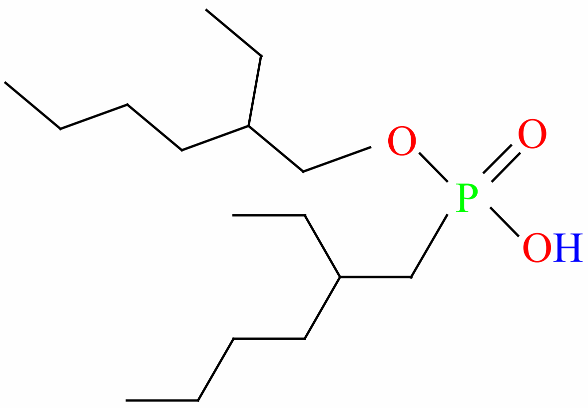
  - Irradiation of several hundreds of mg or more
  - Upscale on-going (incl. recycling) => typically 1g
  - Improvement of recycling

- Prepacked PP columns now starting to be available
  - 4cm x 30cm, 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

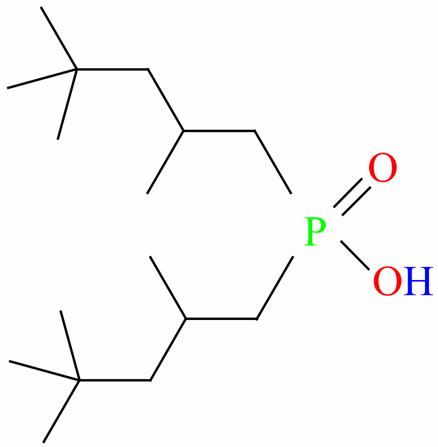
Lanthanide separation on TK211/2/3



HDEHP (LN)



HEH[EHP] (LN2)



H[TMPeP] (LN3)

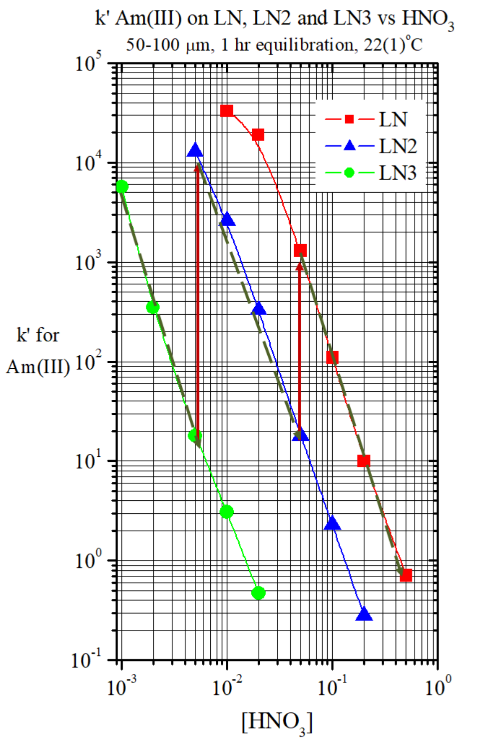
Cyanex 572

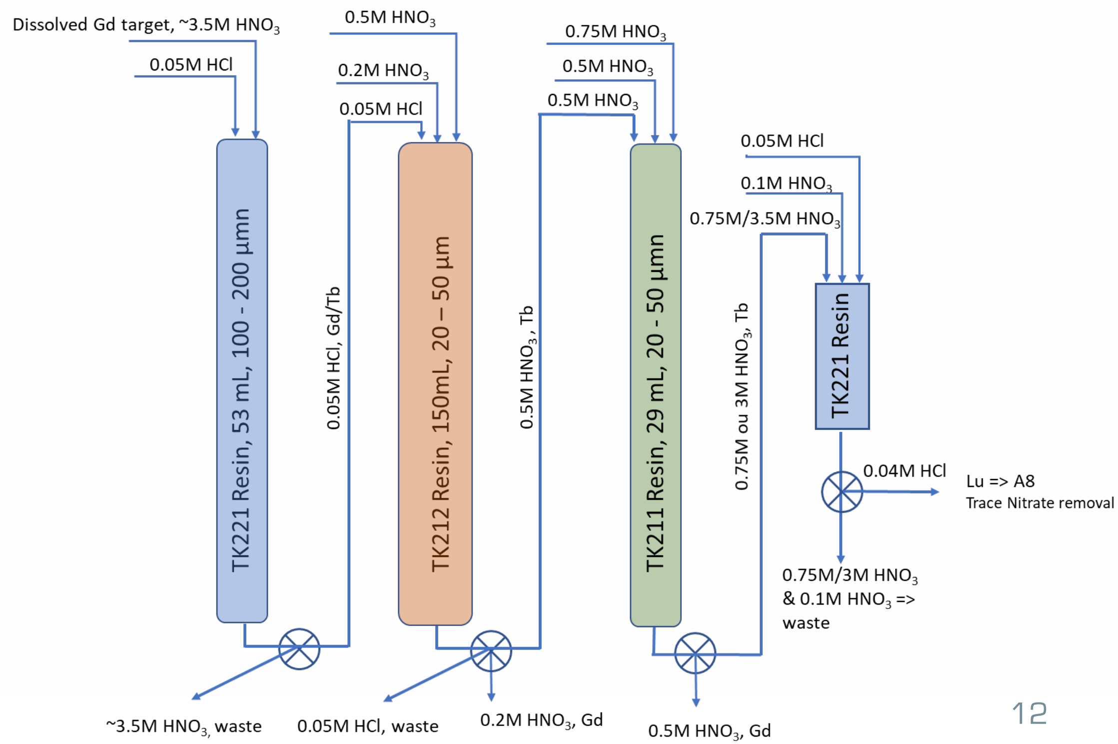
$$M^{3+} + 3\overline{(HY)_2} \leftrightarrow \overline{M(HY_2)_3} + 3H^{+}$$

- Mixtures of different extractants
- Optimized for high radiation stability
- Capacity

Tb separation from 1000 mg Gd targets

- Irradiated target typically oxide => dissolved in >3M HNO_3
- Conversion via TK221 Resin **(TK222 work in progress => elution in dilute HNO_3 possible but requires higher volume)**
- **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

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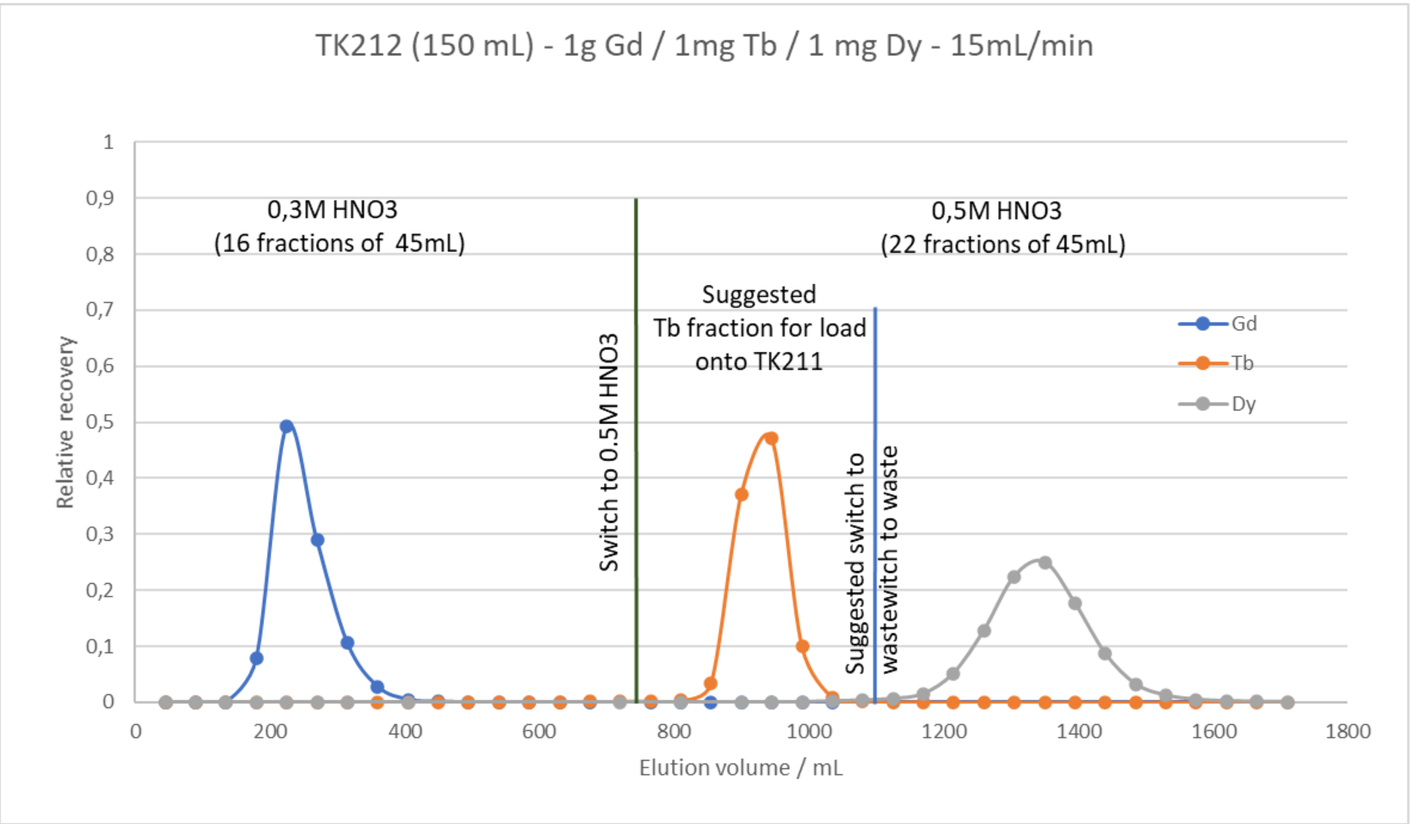
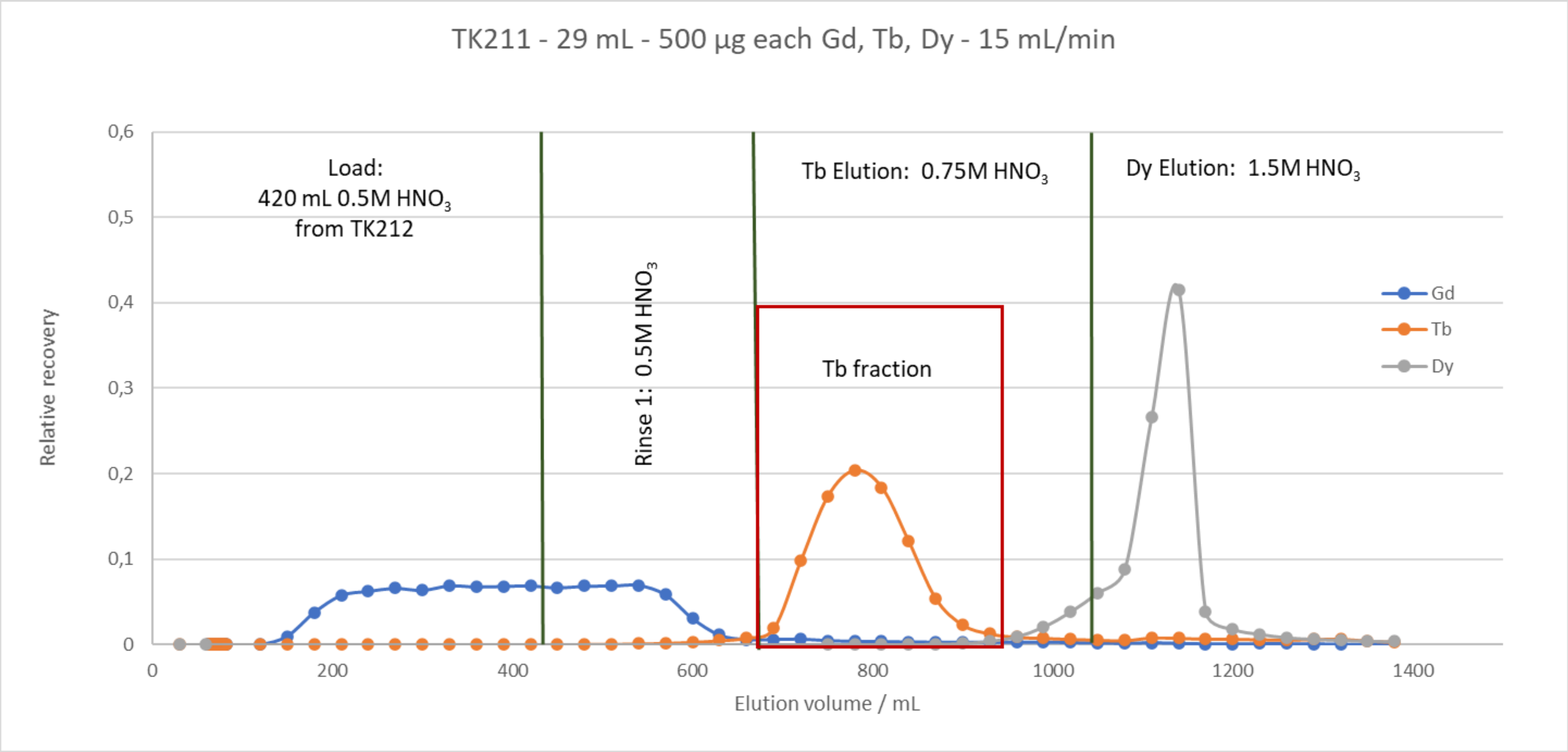
- Initial separation on TK212 – 150 mL column (30cm x 2.5cm)
- Gd recovery => very expensive & difficult to find
- Tb separation from Gd and Dy – ideally using online detection
- Fine purification on TK211 (29 mL)



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

Tb purification 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: cartridge for Dy removal from Tb before use**

nca Lu-177 from Yb targets

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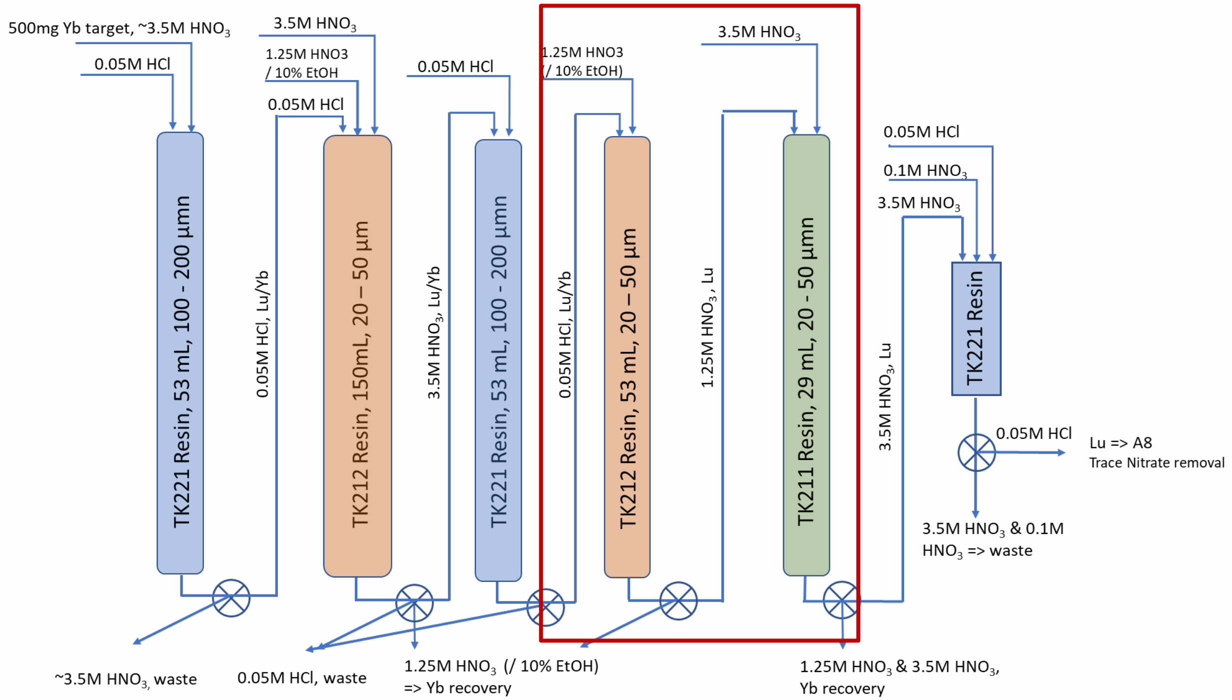
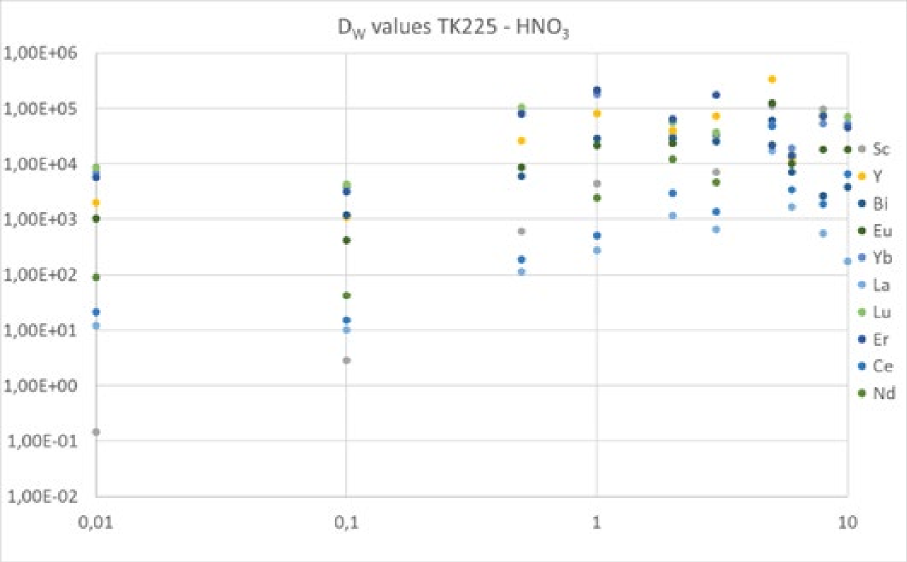
- Typically 500mg – 1g Yb targtes
  - 1g requires larger first column, rest of the separation is identical to 500 mg method

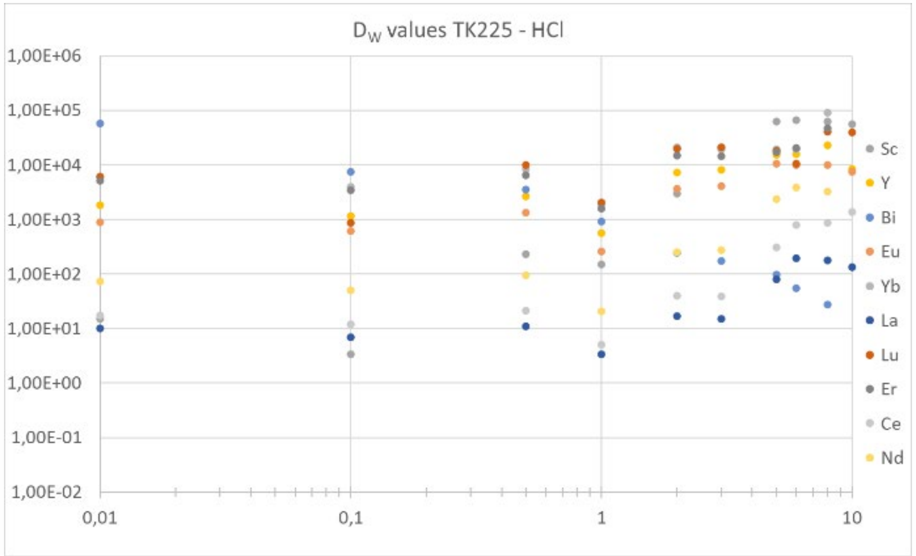


- Sequential separations may be emplyed, too
- Remains more difficult than Tb/Gd
- **Addition of 10% EtOH improves separation**
  - Also useful in analytical applications => Warwick et al.

TK225 Resin

- TO-DGA plus ionic liquid
- 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**

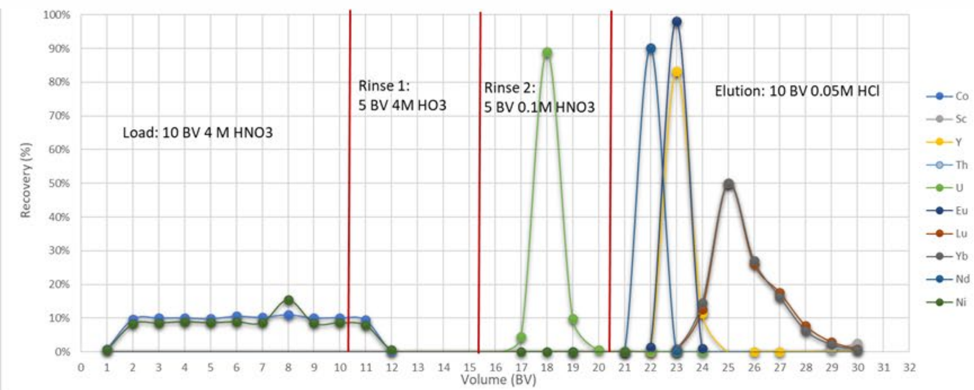




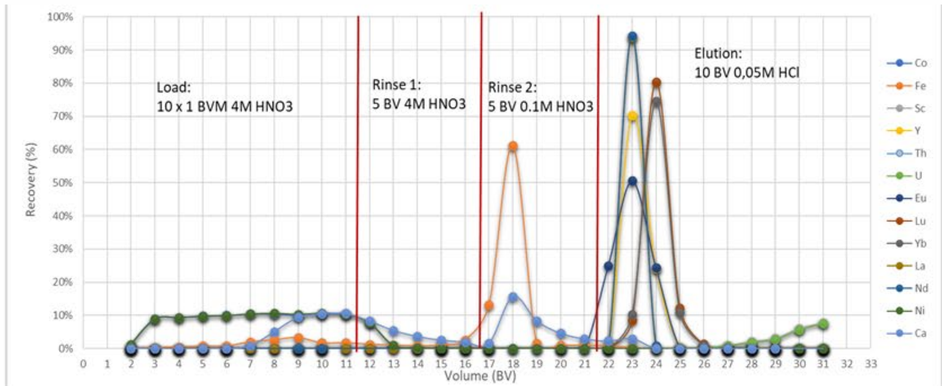
TK221 Resin

- DGA well suited for ‘conversion’ and purification (Ca, Al, Fe,… removal)
  - Convert Lu from high nitric acid to dilute HCl
- Elution of heavy lanthanides at as low volumes as possible
  - small volume prefered => high activity concentration
- TK221 Resin
  - DGA / phosphine-oxide, improved radiolysis stability (inert support, scavanger,…)
  - Better La and U retention than DGA and higher Am than TRU => paper N. Vajda et al.
  - Lu & Tb eluted in small volume in dilute HCl => drawback, no group RE separation possible

DGA Resin

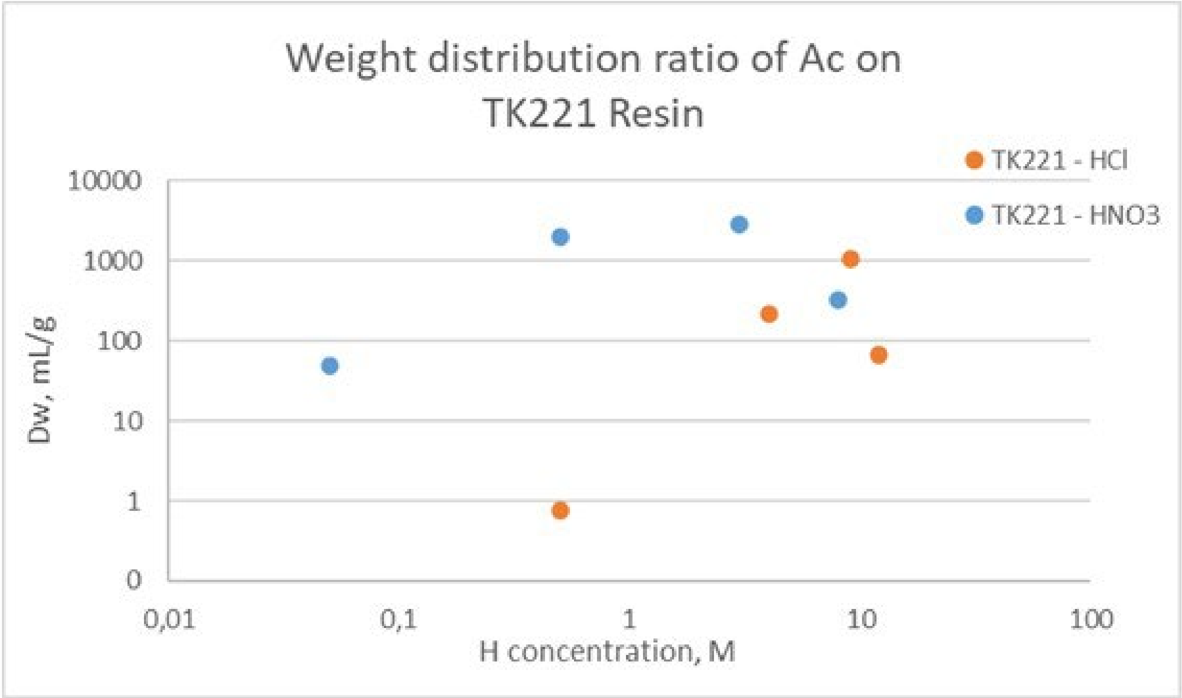


TK221 Resin



- **Use in Ac separation? High interest in Ac-225 from irradiated Ra-226 targets**

TK221 Resin – Ac separation

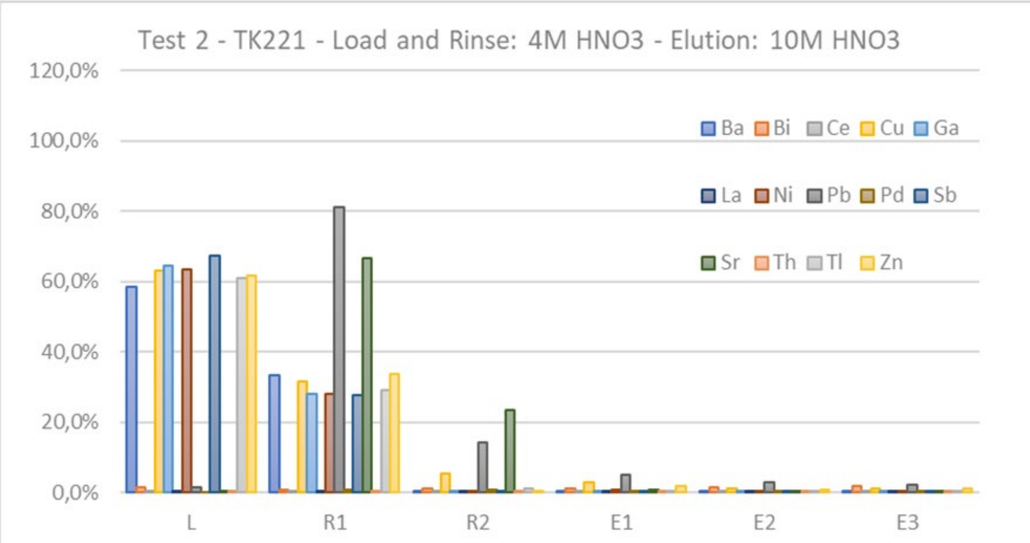


Data courtesy of N. Vajda (RadAnal)

- On-going work
- HNO_3
  - High Ac retention from high to low HNO_3
  - Elution in 0.1 – 0.05M HNO_3 **not** possible
    - Different from DGA
  - Uptake at low HNO_3, elution in HCl?

- HCl:
  - High retention of Ac on at elevated HCl
  - D_W drops at very high HCl
    - LN/Ac separation?
  - Elution in dilute HCl possible

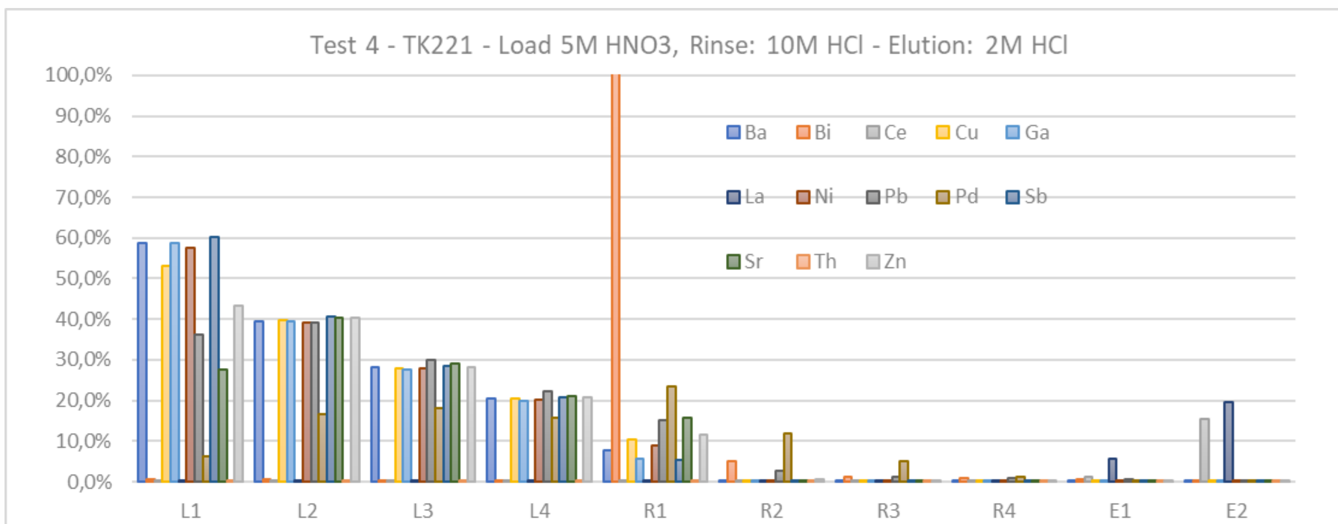
TK221 Resin – Ac separation



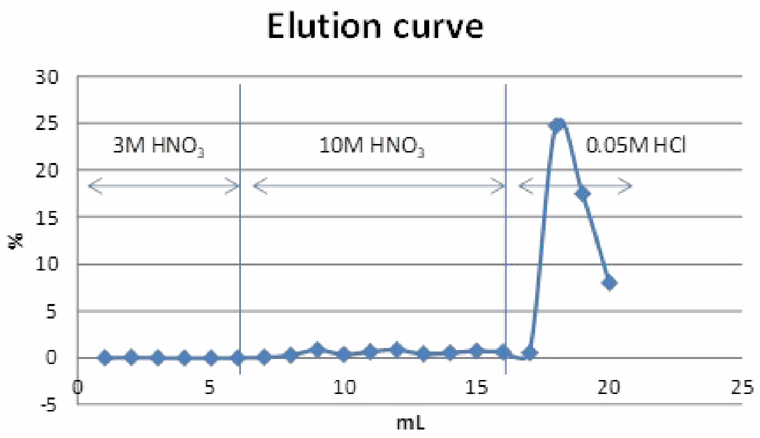
- In case LN need to be removed
- Two step procedure

- First TK221
  - Load from e.g. 4M HNO_3
  - Ac elution in very high HNO_3
  - LNs retained
  - Particular attention to Pb/Sr

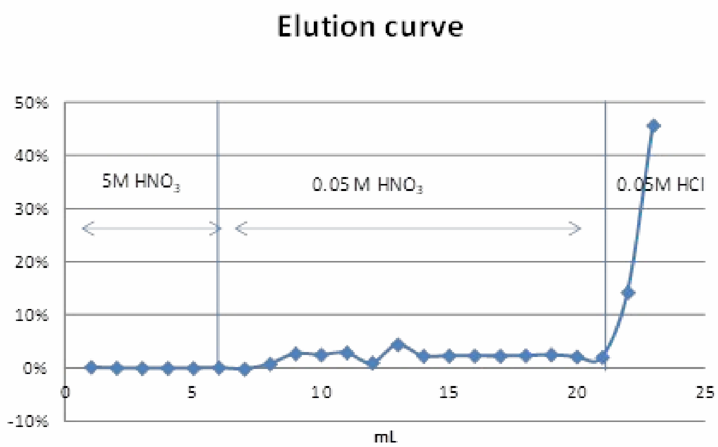
- Second TK221
  - Dilute x2 => load
  - Bi removal 10M HCl
  - Ac elution in 0.05M HCl
  - Additional purification on TK101
- Alternative: TK222
  - Sharper elution?



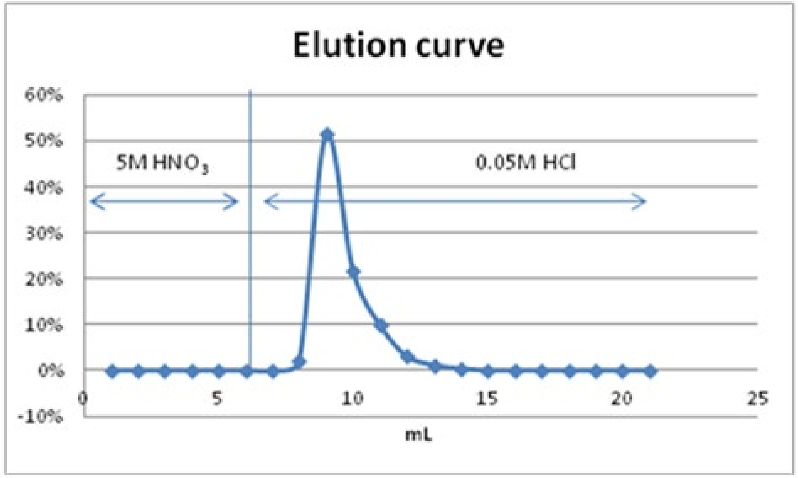
TK221 Resin – Ac separation



Elution of Ac from TK221 cartridge with 10M HNO3, 1mL TK221 column, data courtesy of N. Vajda et al.



Elution of Ac from TK221 cartridge with 0.05M HNO3, 1mL TK221 column, data courtesy of N. Vajda et al.

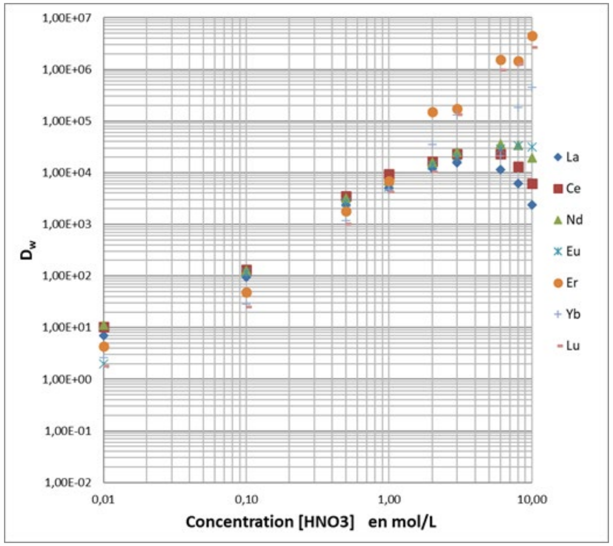


Elution of Ac from TK221 cartridge with 0.05M HCl, 1mL TK221 column, data courtesy of N. Vajda et al.

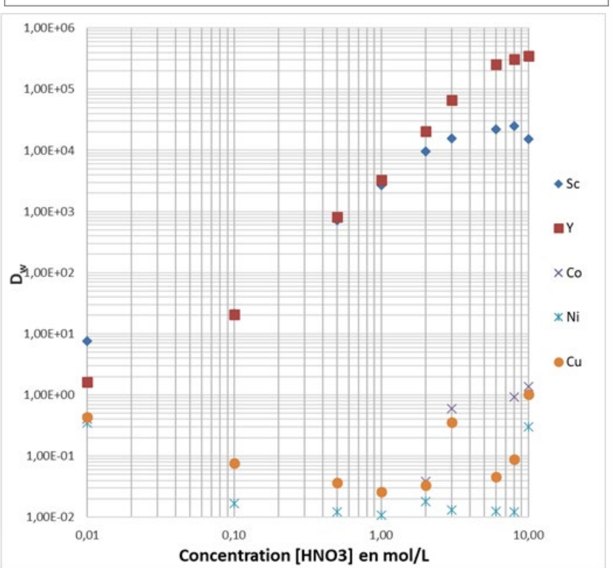
– Other than DGA, N no Ac elution from 10M HNO_3
– Ac/LN separation requires min. 12M HNO_3
  => Ac eluted, LNs retained
– No Ac elution in 0.05M HNO_3
– Elution in 0.05M HCl possible
– TK222 => sharper elution in dilute HCl?

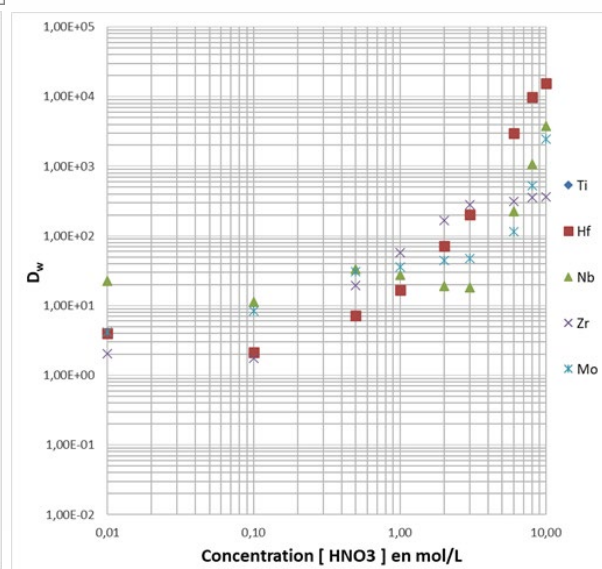
TK222 Resin – HNO_3

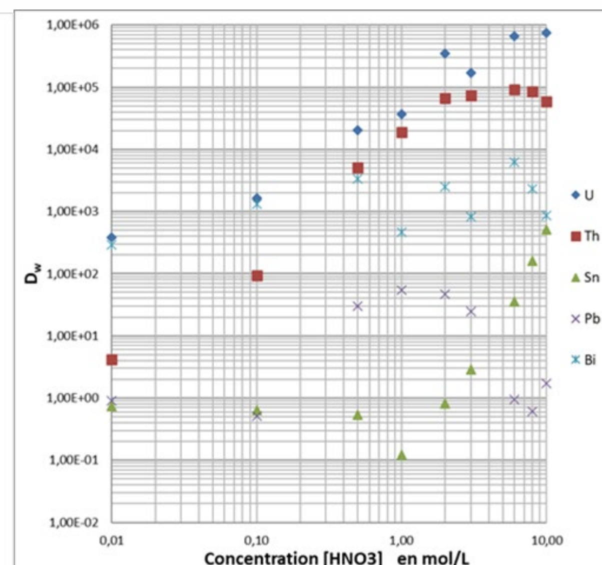
Expertise in Separation Chemistry



- TEH-DGA and phosphine oxide
- High retention of trivalents , U, Th, Zr, Hf in HNO_3
- D_W for Ac in HNO_3 work in process
- Ac elution studies on TK222 in work (HNO_3 and HCl)
- L/M REE elution in dilute HNO_3 possible?

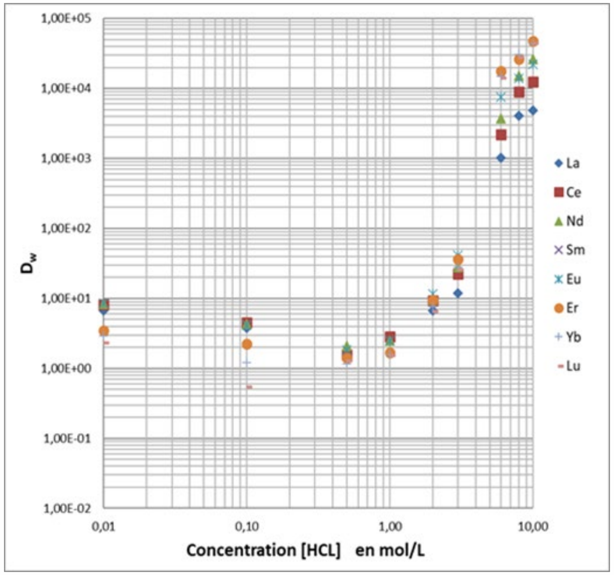


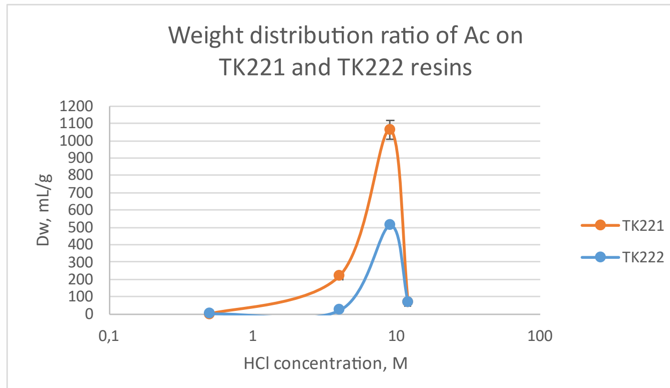




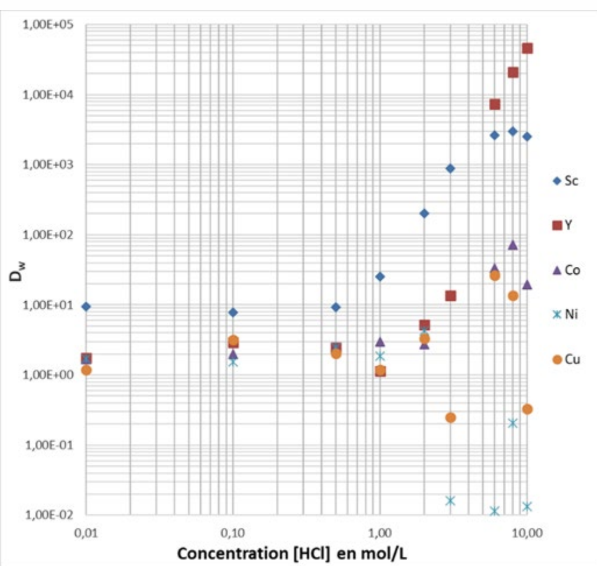
TK222 Resin - HCl

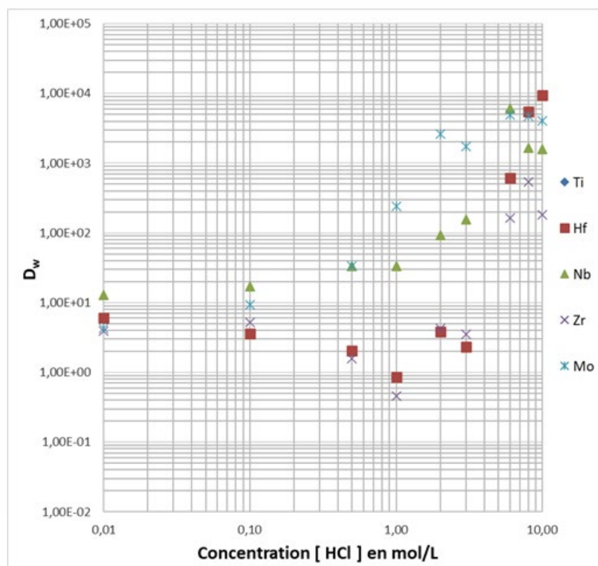
- High retention of trivalents, U, Th and Zr at high HCl
- Beside U: elution in dilute HCl

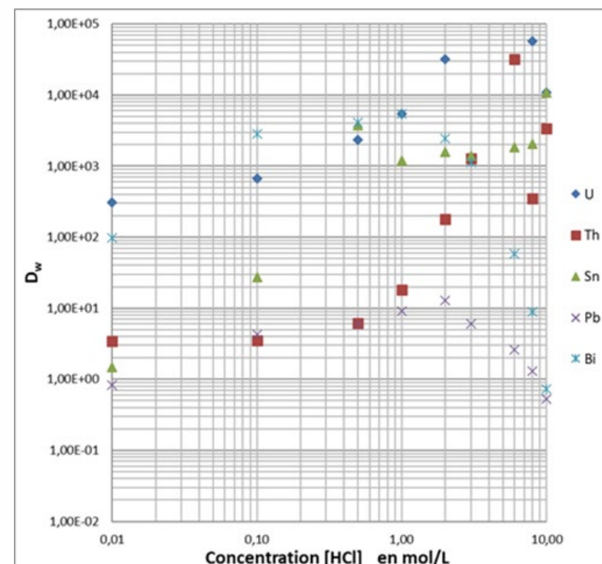




- Y and Sc separation to be tested
- Ac Retention on TK222 (and TK221) high up to 8 – 9M HCl, then drop => Ac/LN separation at very high HCl?







TK221/2 Lu separation

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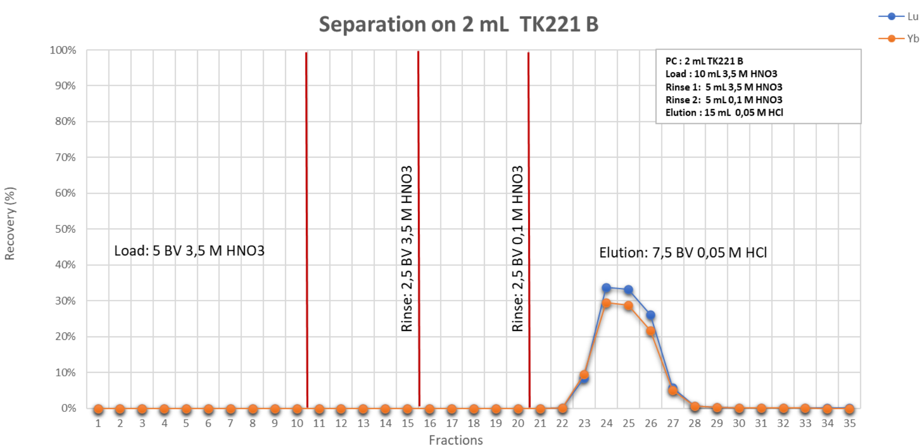

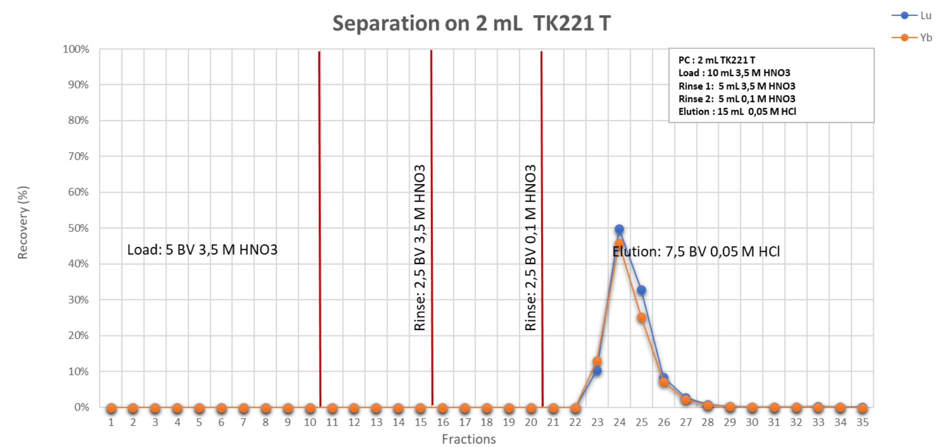

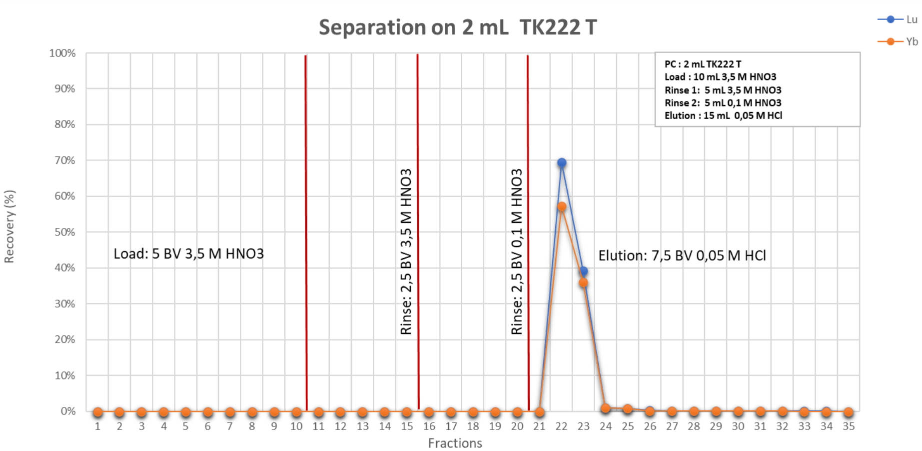

- New T grade (50 – 100 µm) TK221 allows for elution in smaller volumes compared to B grade (100 – 200 µm)
- TK222 (T grade) allows even sharper Lu elution
- Interest for ca Lu-177?
- For use in nca Lu-177: verify TK222 allows loading >hundreds of mL solution

TK221/2 Lu separation

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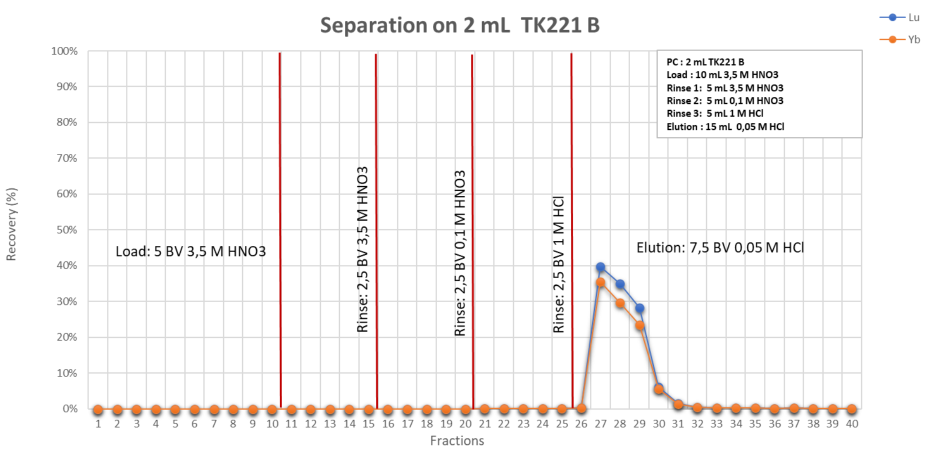
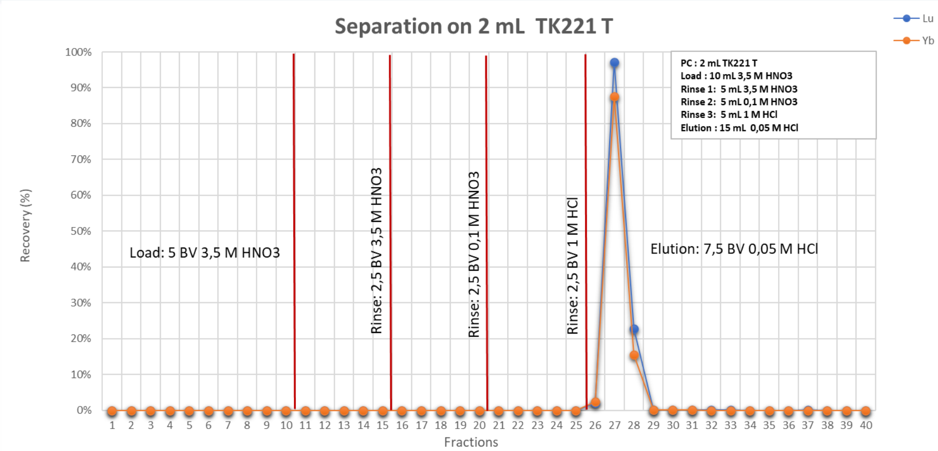
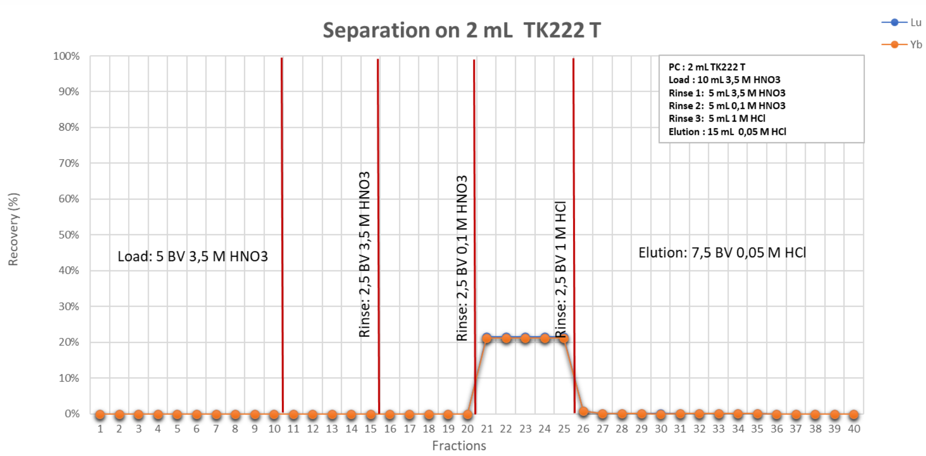
Expertise in Separation Chemistry





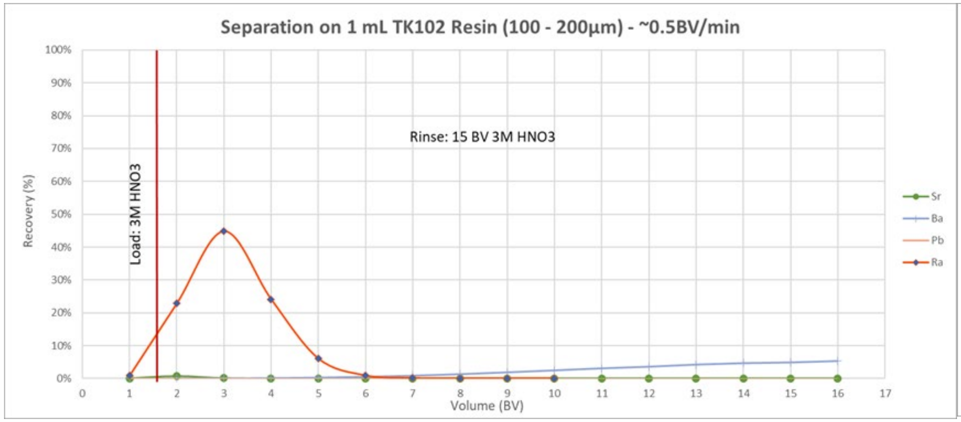


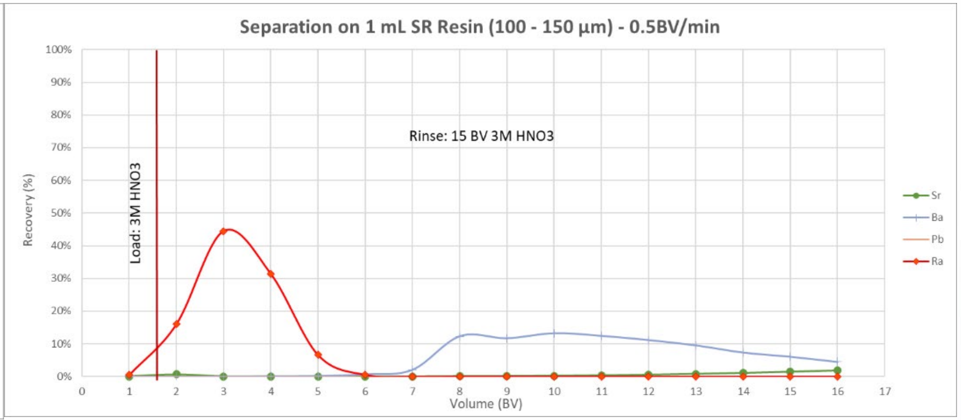
- Adding additional HCl rinse (here 1M HCl) after 0.1M HNO_3 rinse results in sharper Lu elution on TK221
- Removal of NO_3^-
- Not compatible with TK222 => requires 3M HCl or higher => pH of final product…

Ra purification / recycling

- Work on crown-ether based resin for Ra ongoing
  - Aim: Ra retention from acidic/high NO_3^- matrices, high capacity
- Ra initial purification and recycling after irradiation
  – Exact methods depending on impurities present

  => Ideal case: only remove impurities, leave Ra in solution
  - TK221 (or DGA) => other alpha emitters et al.
  - TK102 for Ba, Pb and Sr removal from 3M HNO_3
    – Low organics bleeding (hydrophobic solvent)





Ra purification / recycling

- In case Ra needs to be purified on-column (e.g. dissolved Ra needles) => Use of TK101 for Ra retention / purification
  - Test against Chelex, CEX, TK100
- TK101 => similar to TK100 but ionic liquid replaces HDEHP
  - Both based on same crownether as SR Resin
  - TK100 developed for Sr and Pb uptake also between pH ~2 and 7 (DGT)

    ⇒ Wagner et al. TK100 discs

    ⇒ Retains wide range of elements
  - Replacing HDEHP by ionic liquid (=> TK101 Resin) allows for retention of Pb, Sr, Ba, Ra,… from pH ~2 – 7 without extensive extraction of other elements

TK101 - Radium

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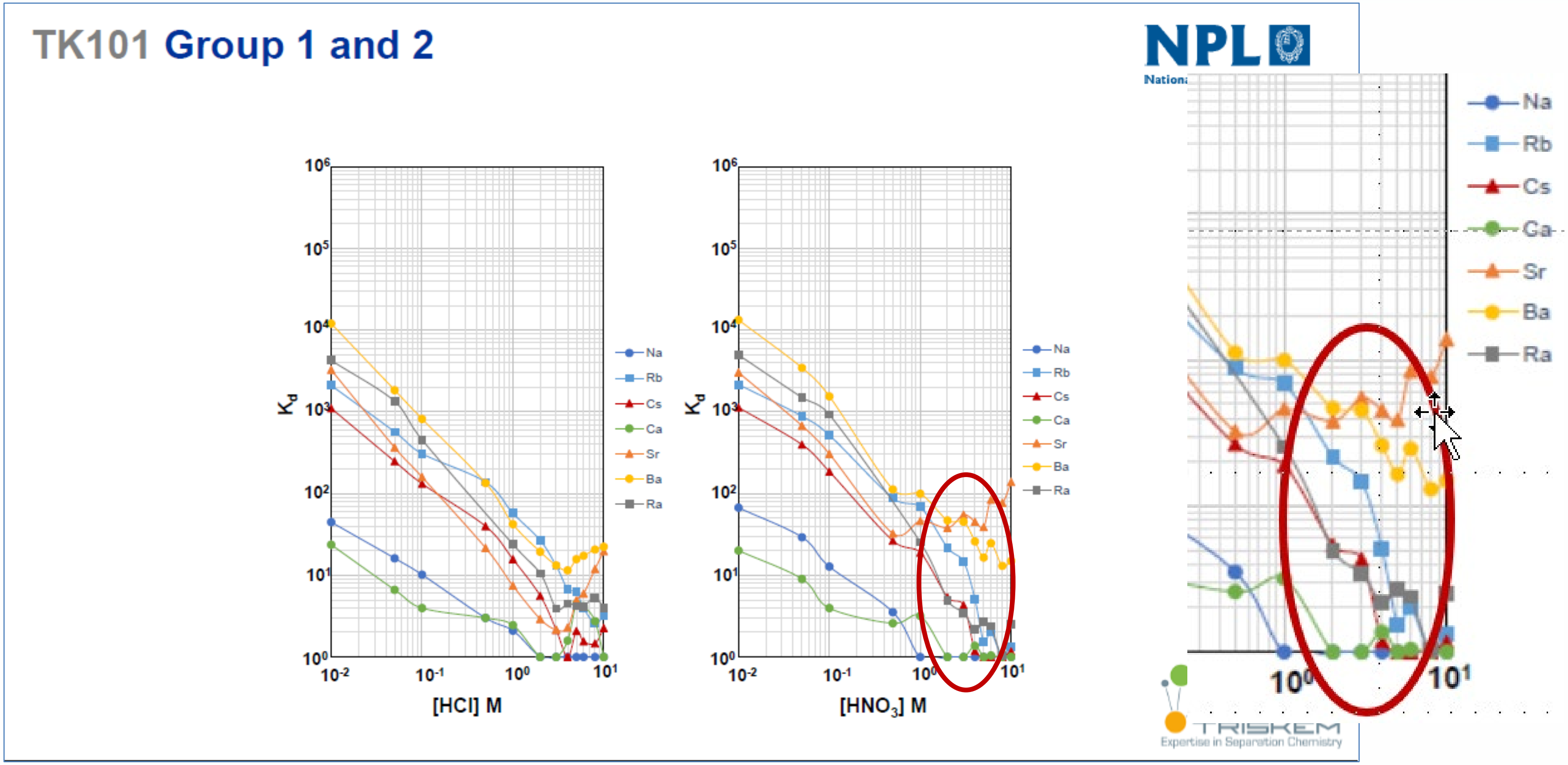
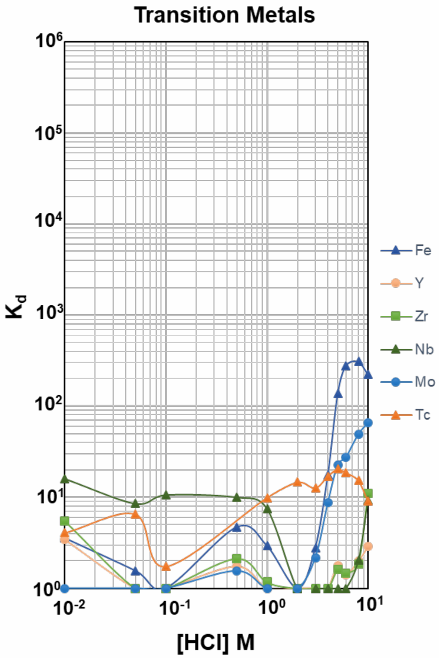
Expertise in Separation Chemistry

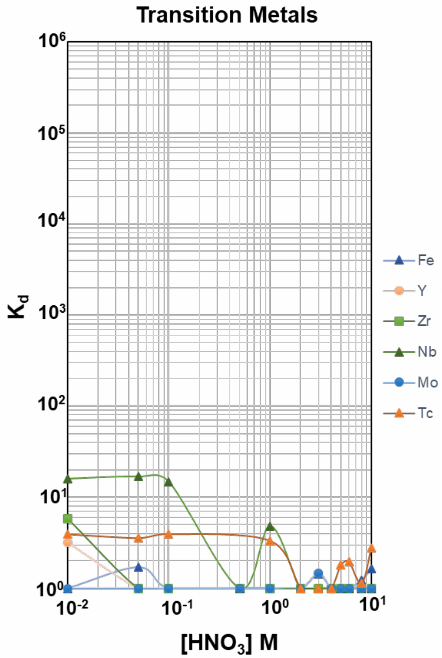


Data provided by
Russel et al. (NPL)

- Ra retention from water/dilute acid up to ~0.5M HNO_3/HCl
- At higher conc. selectivity closer to SR Resin/TK102 Resin

TK101 Resin





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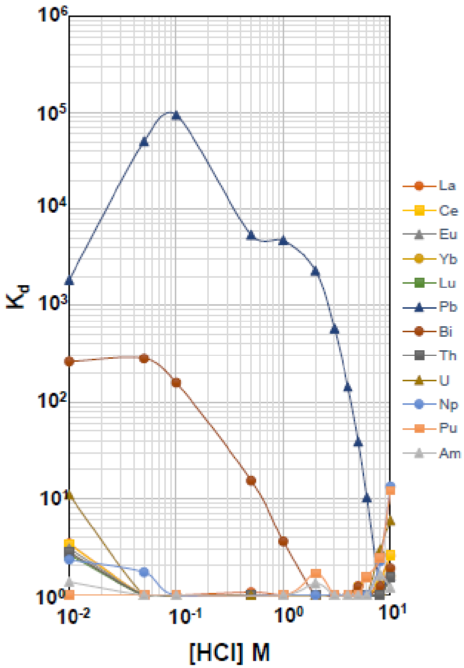
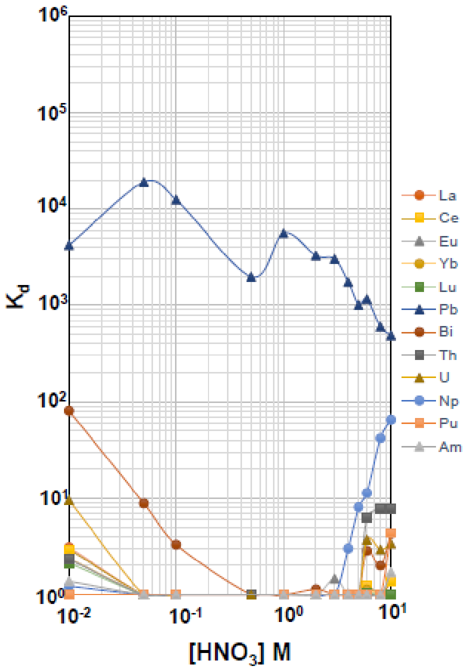
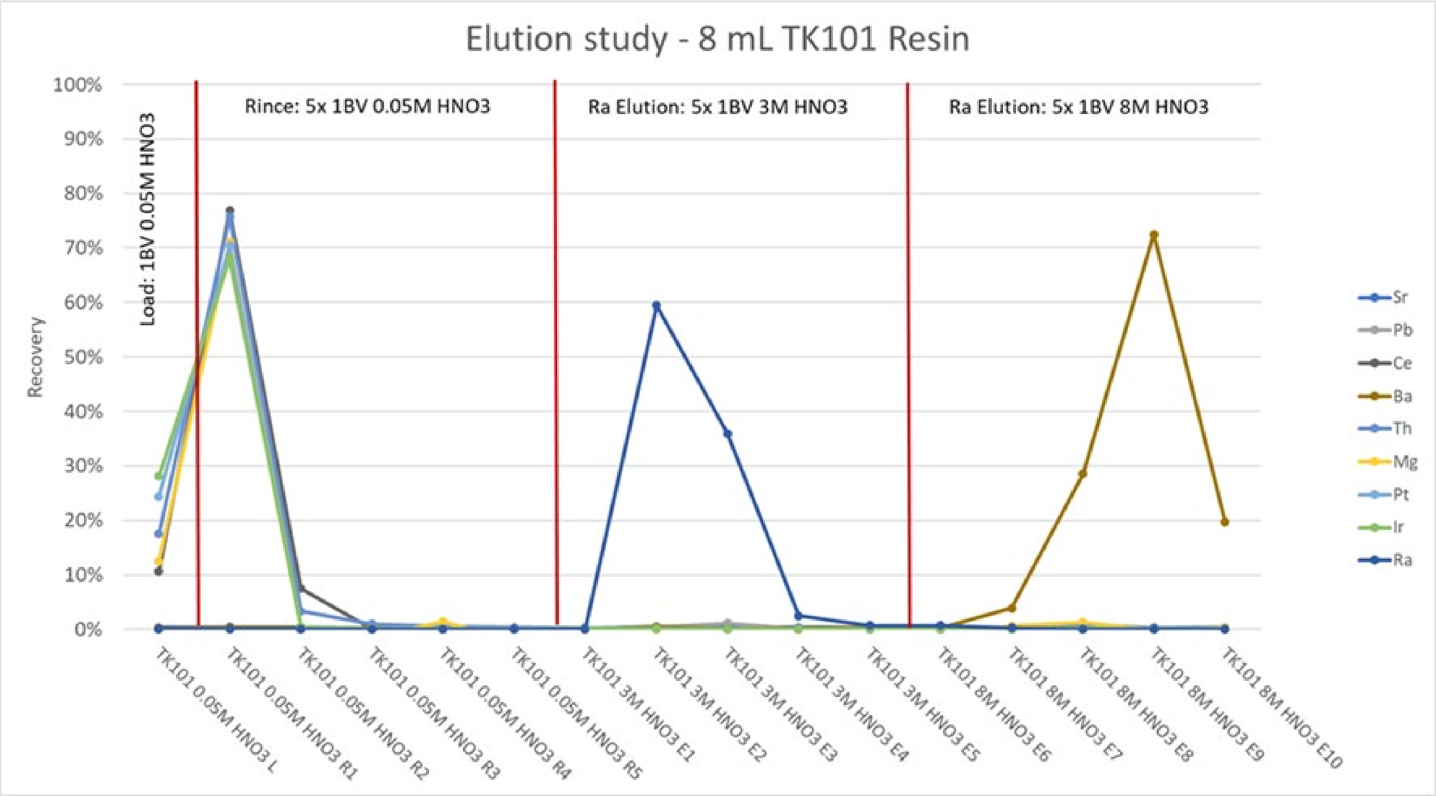




- No / extremely low selectivity for TM, Th/U, Ac
- Very strong Pb retention => elution in high HCl or citrate

Ra separation on TK101



- Good Ra separation when loading from dilute HNO_3/HCl
- When eluting Ra in 3M HNO_3, Ba, Pb, Sr remain retained
- No retention of U, Th, Pt, Ir,…
- Ra eluted in 3M HNO_3
- Tl and Ba eluted in 8M HNO_3

TK202 Resin

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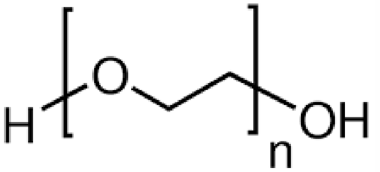
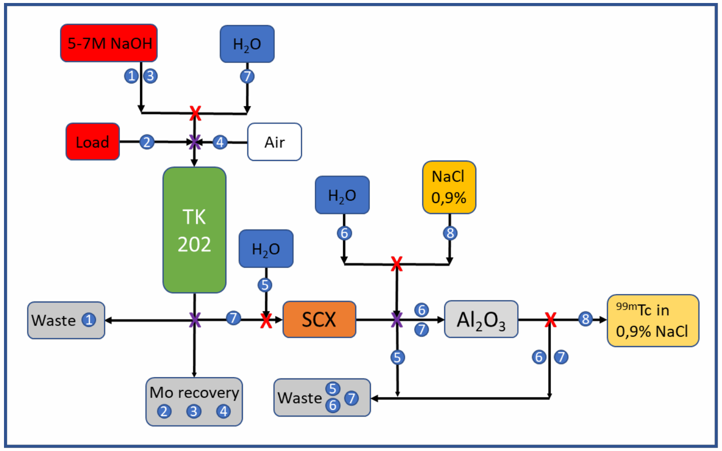
- Based on Polyethylene Glycol (PEG)
  - Less swelling/shrinking than crosslinked PEG
- Aqueous Biphasic System (ABS)
- Retention of chaotrophic anions like TcO_4^- in presence of kosmotrophic anions (SO_4^{2-}, CO_3^{2-}, OH^-, MoO_4^{2-},…)





① Pre-cond. TK202 – 5-7M NaOH ➔ alkaline waste
② Load Mo/Tc on TK202 ➔ Mo recovery
③ Rinse TK202 – 5-7M NaOH ➔ Mo recovery
④ Purge TK202 – Air ➔ Mo recovery
⑤ Pre-cond. SCX – HCl then H_2O ➔ Aq. waste
⑥ Pre-cond. Al_2O_3 – H_2O ➔ Aq. waste
⑦ Elute Tc from TK202 on SCX and load on Al_2O_3 – H_2O
⑧ Elute Tc from Al_2O_3 – NaCl 0,9% ➔ Tc recovery

TK202 : 35-75 or 75-150µm
X : 3-ways valve
X : 4-ways valve
SCX : Strong Cation Exchange
Al_2O_3 : Acidic Alumina

Developed with ReO_4^- as TcO_4^- surrogate

Re recovered on saline solution from alkaline

Separation with 2g Mo ➔ From 20mL to 2mL
Separation with 200g Mo ➔ From 3L to 20mL

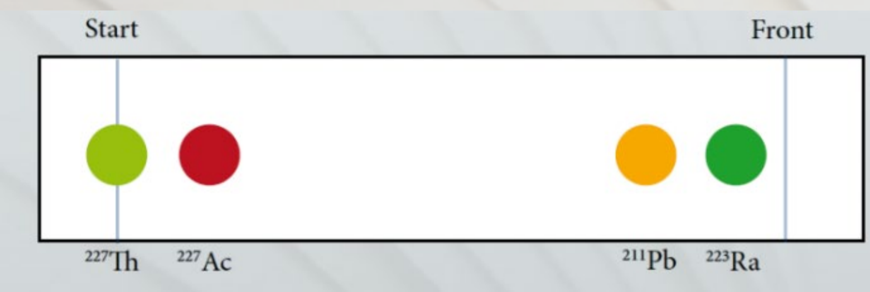
- Separation of Tc-99m from Mo
  - Tc-99m from Mo via cyclotron
  - Tc-99m from Mo via reactor
  - TK202 plus C8 and AlOxA
- **Separation of Re from W (and Ta) possible, too**

Similar to Zeisler et al.

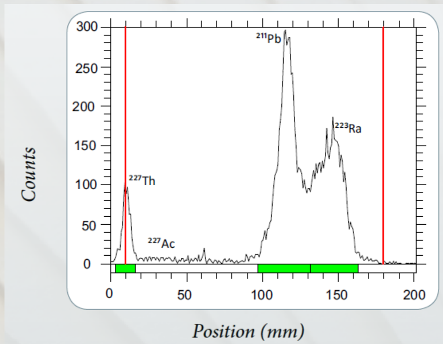
DGA Sheets

- TO-DGA (normal DGA) and TEH-DGA (branched DGA) impregnated TLC paper
  - Developed at CVUT (Kozempel et al.)
- QC of radionuclides and generator eluents

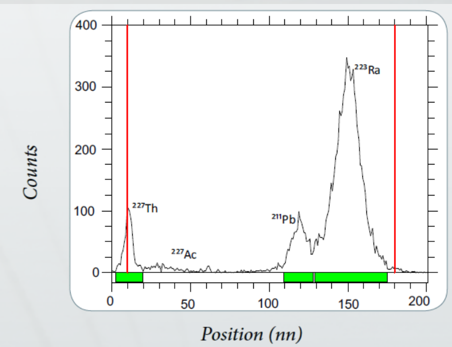
(p.ex. Ra-223, Ac-225/Bi-213, Pb-212, Ge-68/Ga-68 …)
  - TLC scanner or radiometer/LSC or HPGe after cutting
- Run under acidic conditions => radionuclidic purity



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 ?

CU Sheets

- 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, Whatman took 25 – 30 min.
- CU extractant impregnated iTLC paper showed superior resolution

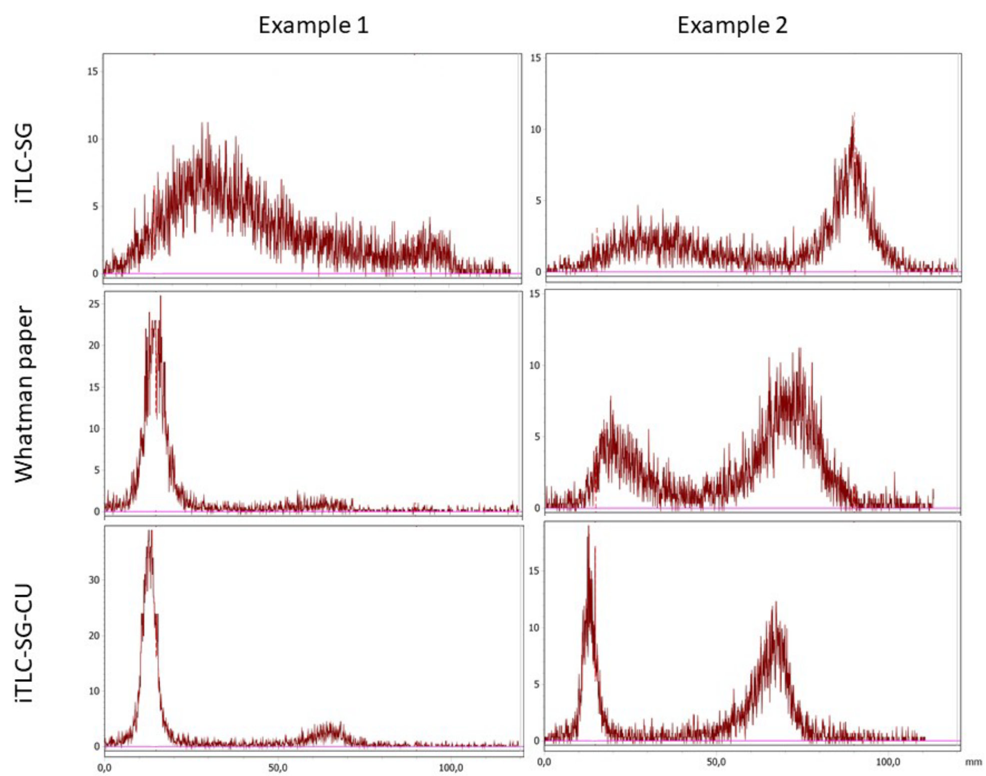


Figure 1. TLC scans of [^{61}Cu]Cu-NOTA-octreotide spotted on: top, iTLC-SG; middle, Whatman paper; bottom extractant-impregnated iTLC-SG. Example 1 notes elevated levels of unlabelled ^{61}Cu, while example 2 notes comparable levels of labelled to unlabelled ^{61}Cu.

- Other systems under development/testing (TK101, ZR,…)

Some other on-going projects

- Further upscale of radiolanthanide separations
- Zr-89 separation and elution in dilute HCl
- Scandium separation
  - TK200, TK221, TK222
- At separation
  - TK400, Rn-211/At-211 generator,…
- Other radiometals
  - Auger (Sb, Pd, Hg,…), Mn, V, In,…
- SE Resin
- Improvement of radiolysis stability
- Fate' of RN in the environment
  - Separation methods
  - Mainly longer lived RN (=> therapy)
    - Ac-225/7, Lu-177(m), radioiodine,…
  - Quantification
- In-field preconcentration
  - Impregnated membranes
  - Cartridges

Some other on-going projects

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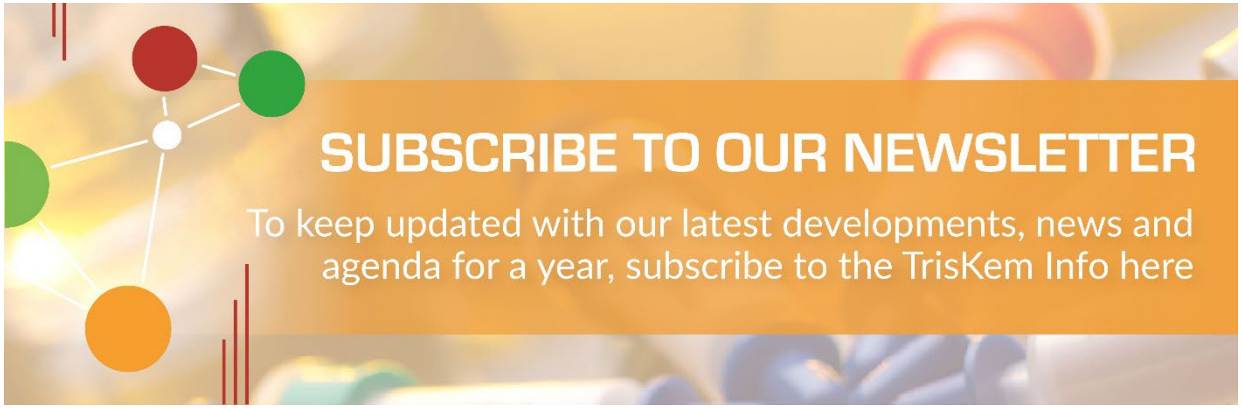
- Rapid tests
  - ➢ Range of impregnated PSm resins
    - Similar to TK-TcScint
  - ➢ Range of 'Test sticks'
    - Suitable impregnated support
    - JCU => rapide isotope ratio analysis by MS (metallomics)
    - NPL
      - – LSC measurement
      - – Decommissioning/screening
- Separation of DTM
  - SE Resin
  - Zr-93, Fe, Mo, Nb,…
- Passive sampling (DGT)
  - – TK100 discs for Sr, Pb, Zn
    - E.g. Wagner et al.: Labile Pb and Sr in soil samples via DGT
  - – CL resin for iodine, CA for Ra,…
- Decontamination
  - – AMP-PAN => Cs
  - – CeO_2-PAN => Ge
  - – …
- Microfluidics
- Other 'geometries' & 'Non-resin' separation materials

Thank you for your attention!



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