TrisKem International

On the development of a method for the separation of Terbium from elevated amounts of Gadolinium using TK221 and TK211/2 Resins

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NOMRAD

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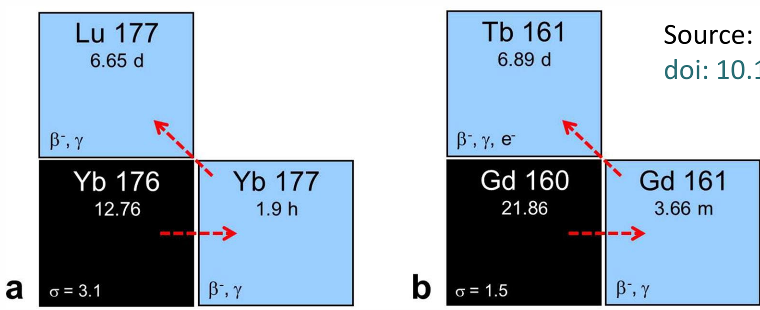
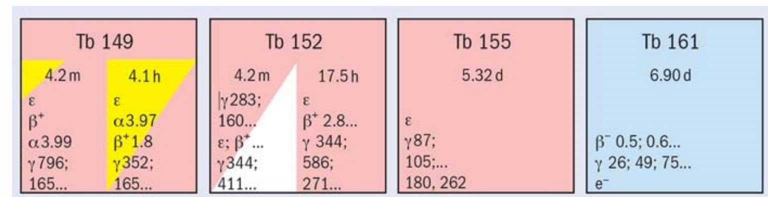
Tb-161

- nca Lu-177 very widely used but Tb-161 getting strong interest
  - Part of the ‘Swiss knife of nuclear medicine’ => Tb isotopes
- Similar n.c.a. 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/waste treatment) => typically ≥ 1g
- Tb very similar to Lu chemically and with respect to half-life et al.
- Additionally emits significant number of Auger-Meitner electrons
- Availability of Gd-160 problematic

TK212, TK211 and TK221 Resins

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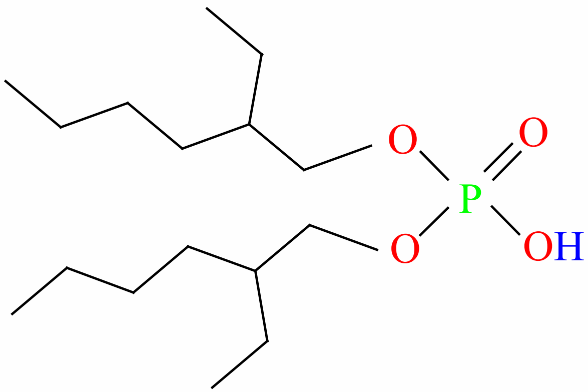
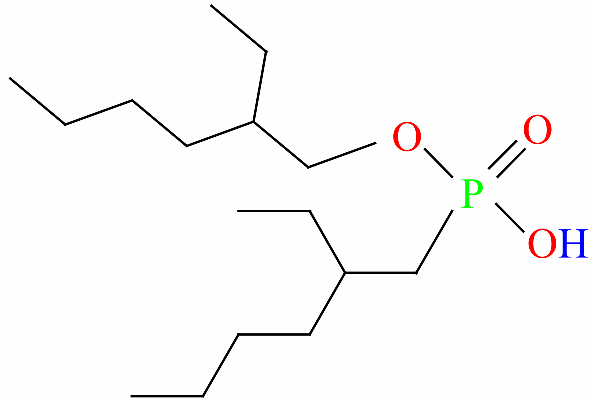
- Increasing demands for separation from larger Yb, Gd,… targets
- Resins exposed to high radiation throughout separation process
- Desire to re-use columns several times
  - Improvement of radiolysis stability
- Feedback from earlier project => stability against radiolysis can be improved via:
  - Use 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
- Note: more resins are more hydrophobic, require soaking in ≥20% EtOH for column packing

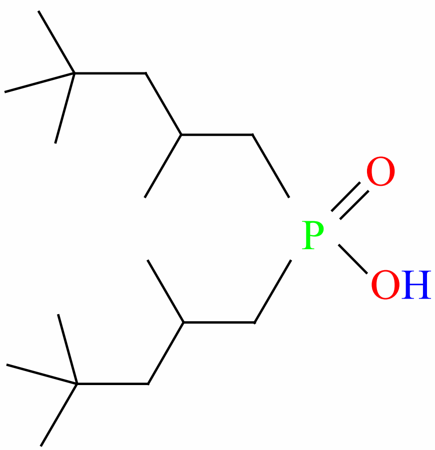
Lanthanide separation on TK211/2/3



HDEHP (LN)



HEH[EHP] (LN2)



H[TMPeP] (LN3)

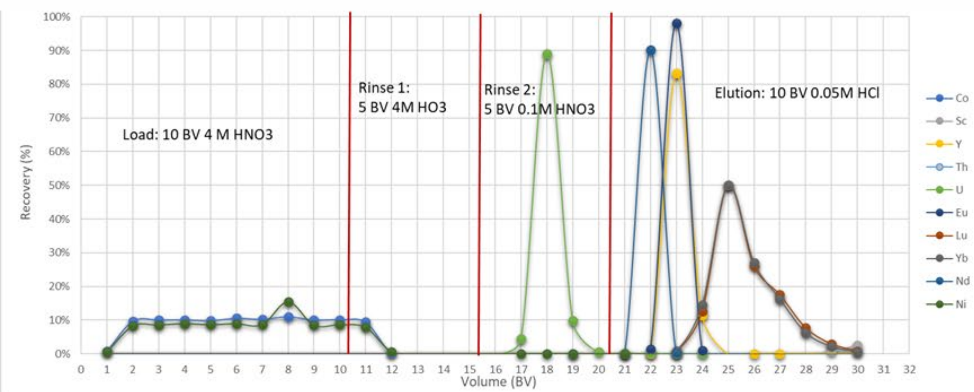
Cyanex 572

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

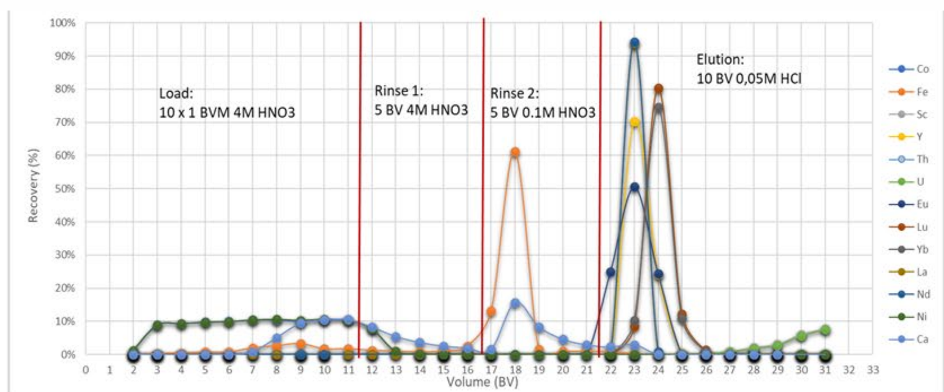
- Mixtures of different extractants
- Optimized for high radiation stability

TK221 Resin

- DGA well suited for ‘conversion’ and purification (Ca, Al, Fe,… removal)
  - Convert Lu from high nitric acid to dilute HCl => feedback, quicker Lu elution desired
- TK221 Resin
  - DGA / phosphine-oxide based => phosphine oxide should improve radiolysis stability
  - Better La and U, Th retention than DGA
  - Lu & Tb eluted in small volume in dilute HCl
  - Drawback, no (group) LN separation possible!
- TK221 also used for Tb recycling
  - Loading ‘Gd recycling fraction’ onto TK221
  - Elution in 0.05M HCl => suitable conditions for oxalate precipitation

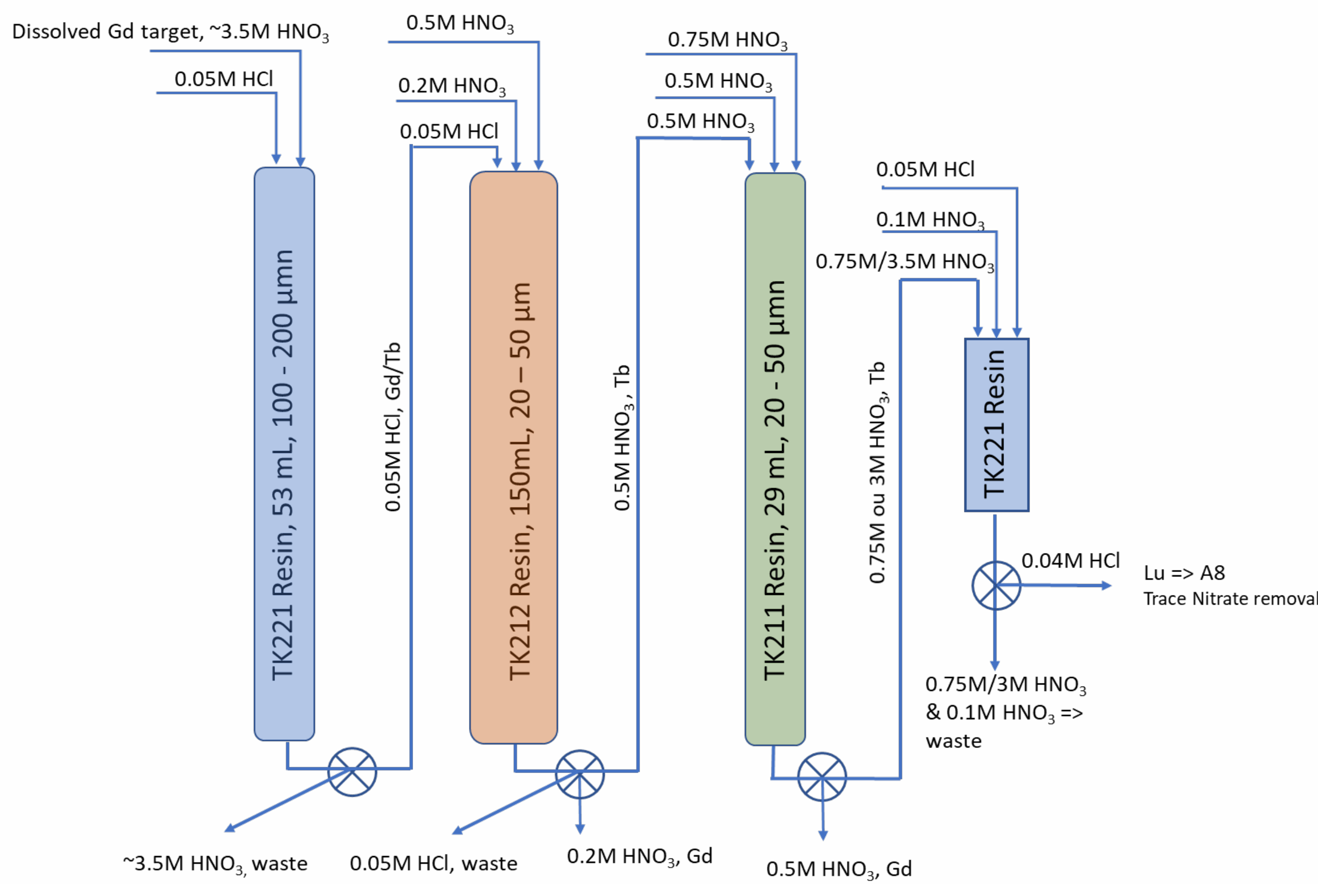


DGA Resin



TK221 Resin

Separation method



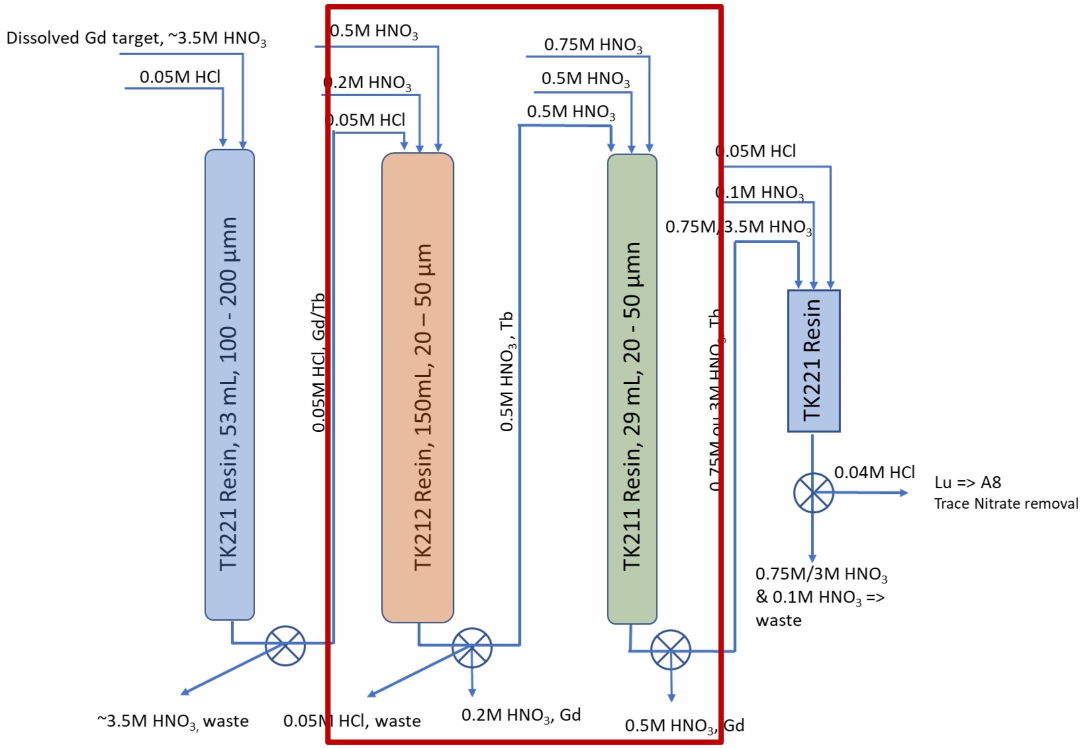
- TK221, TK212/1 based method
- First TK221 column size depending on amount of Gd
- For very large Gd amounts TK212 column might need to be ajdusted, too

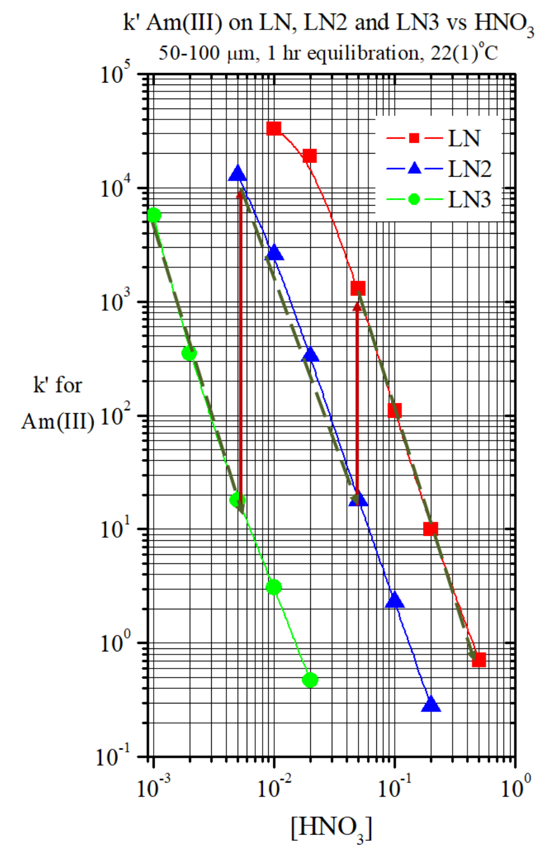
Experimental

- Work with pre-packed PP columns (PEEK also possible)
  - ¼’’28G connectors
- Focus on TK212/TK211
  - TK212: 30cm x 2.5cm column
    - For lower amounts of Gd (e.g. ≤ 100mg) smaller TK212 colums may be used
  - TK211: 30cm x 1.1cm column
  - First TK221 needs to be adapted to amount of Gd

- HPLC driven separations (10 – 15 mL/min)
- Cold testing by taking fractions of defined volume
  - Typically way more fractions than needed, helpful for understanding the chromatographic separation
- ICP-MS analysis of fractions

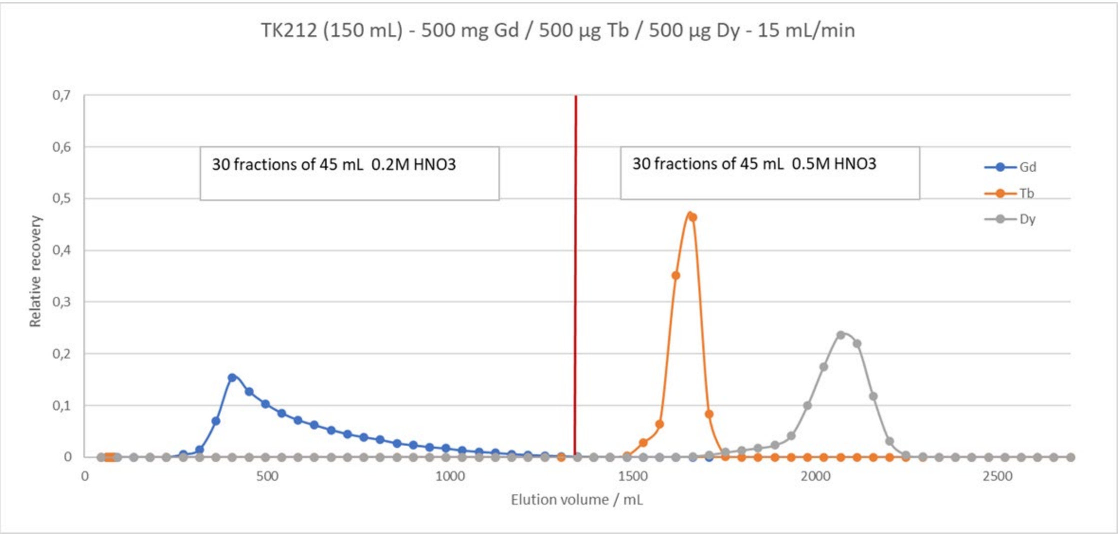
Sequential separation step





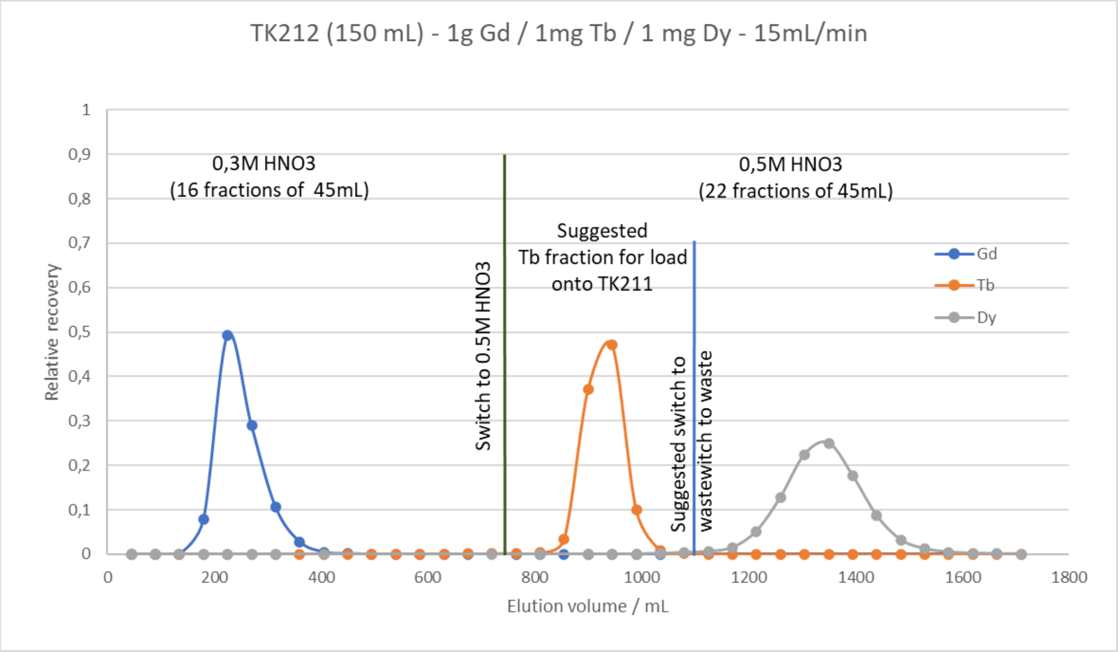
- Feedback: while conversion from high acid via TK221 or DGA works well, users frequently report losses of up to 2 - 5%
- Directly loading from TK212 onto TK211 avoids this conversion step and associated losses. Draw back => increased pressure drop

Initial work: 500mg and 1000mg Gd



- Initial test with 500 mg Gd
- Gd removal with 0.2M HNO_3
- Strong tailing
- Still very good separation

- Eliminating Gd with 0.3M HNO_3
- Larger amount of Gd (1g)
- Less tailing
- Clean separation



Increased amounts of Gd

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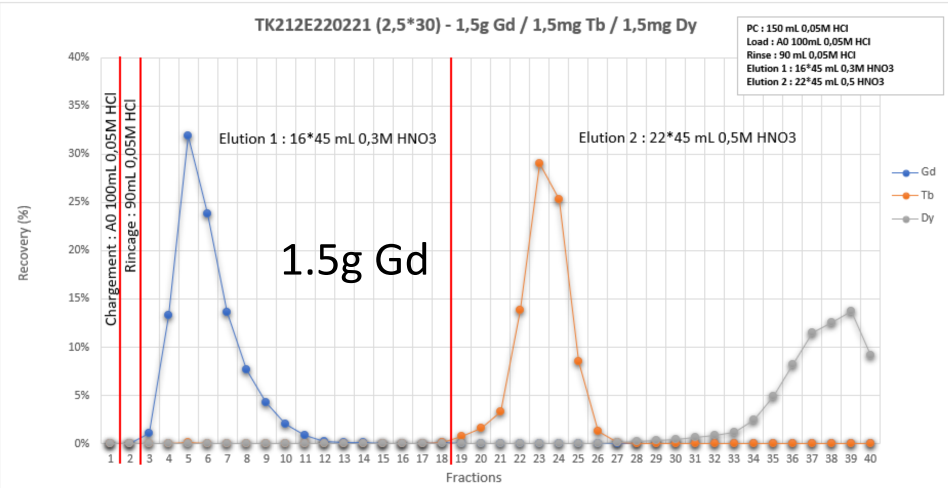
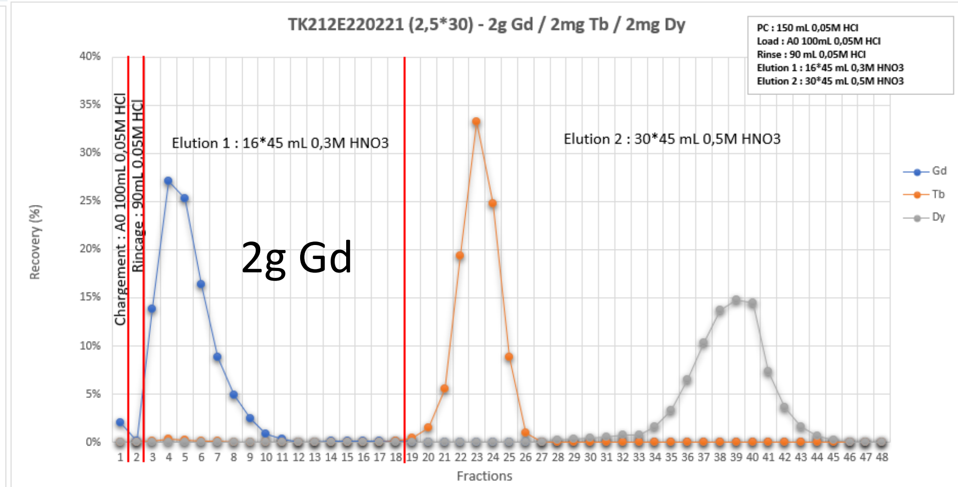
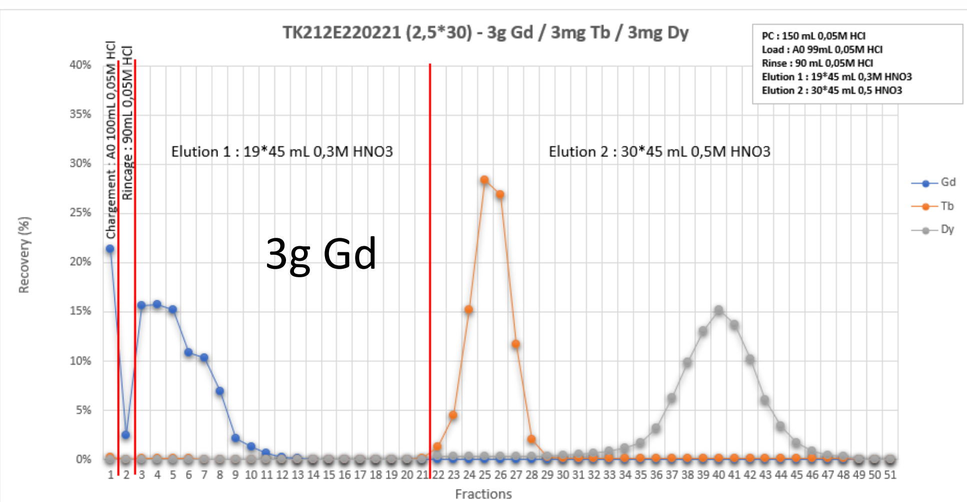
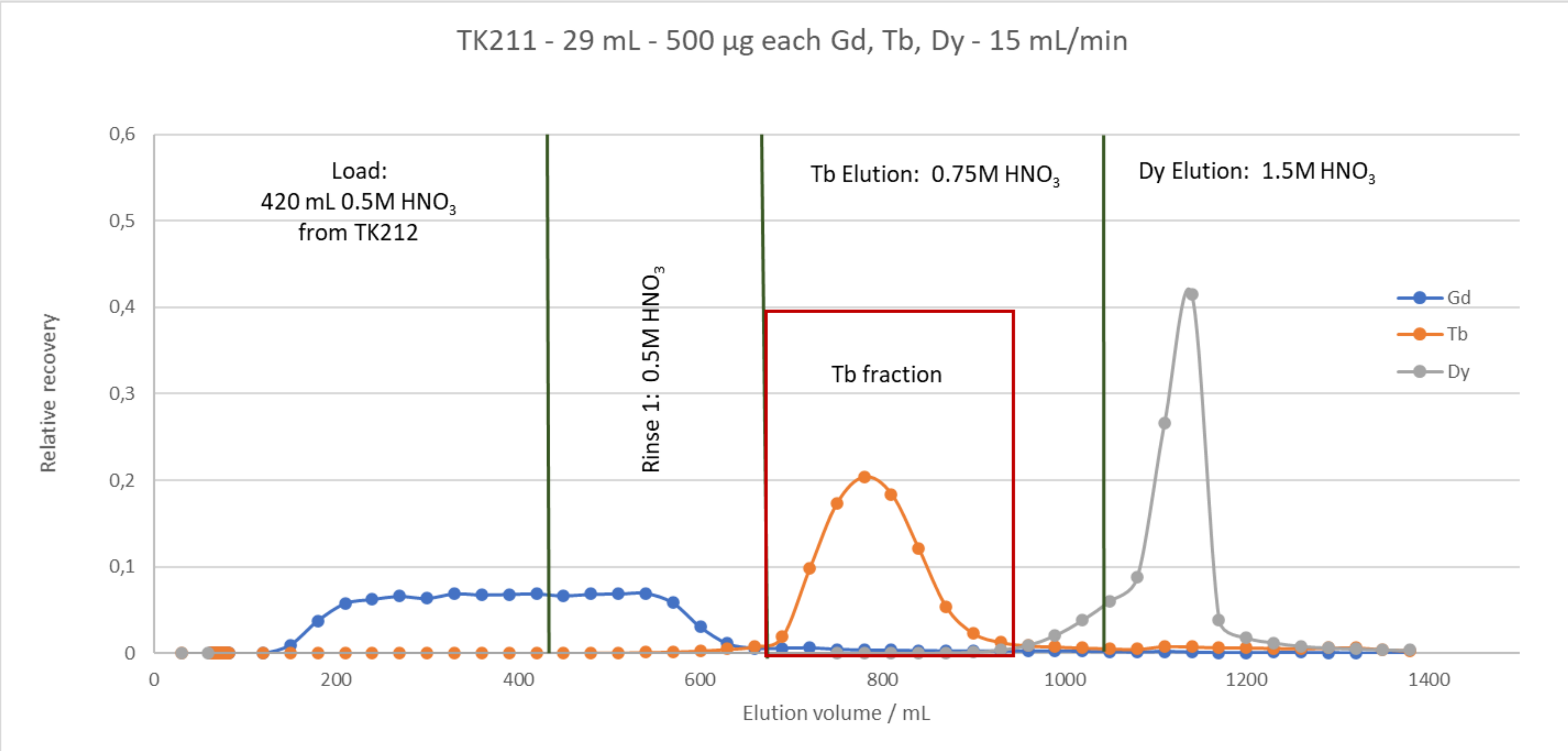






- On the same TK212 column
- More Gd => earlier elution
  - At 3g Gd start of breakthrough
  - More than 3g possible? Tb needs to remain retained…
- Little effect on Tb
- Small impact on Dy
- Tb / Dy sepration remains good.

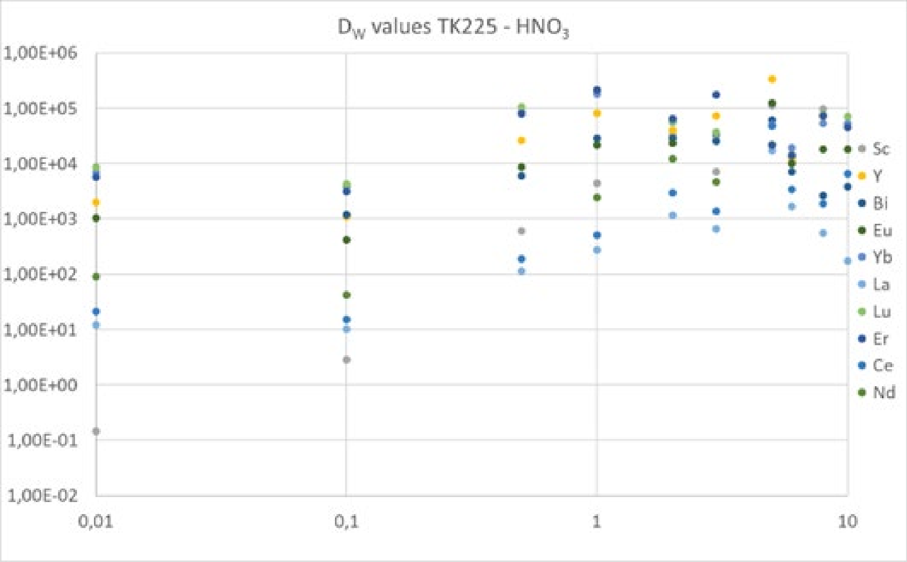
Tb polishining on TK211

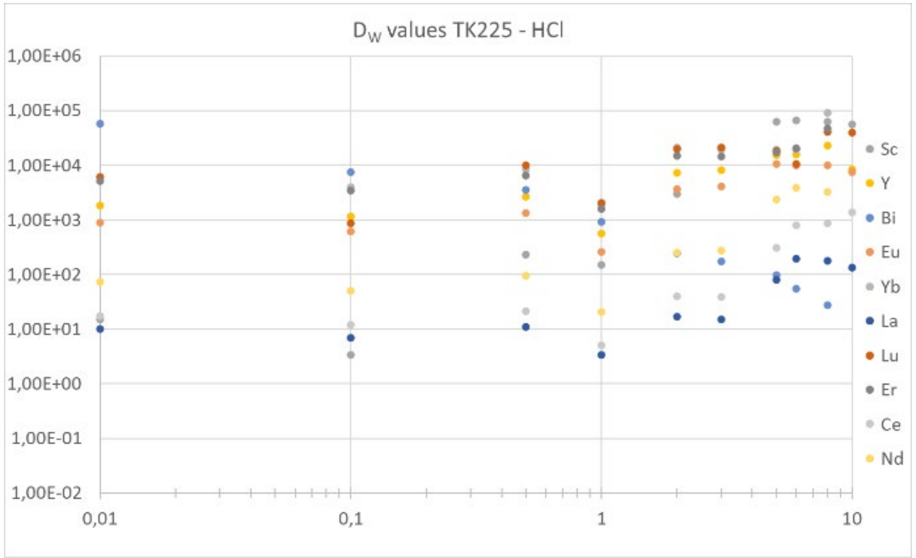


- Spiked solution to allow for obtaining a chromatogram
- Direct load of Tb fraction from TK212 onto TK211 (29 mL – 30cm x 1.1cm)
- Gd breakthrough during load & rinse with 0.5M HNO_3 (alternatively HCl)
- Feedback: Tb elution (Dy sufficiently well removed on TK212) in **>3M HNO_3**
- Conversion to dilute HCl via 2 mL TK221, A8 for nitrate removal

TK225 Resin

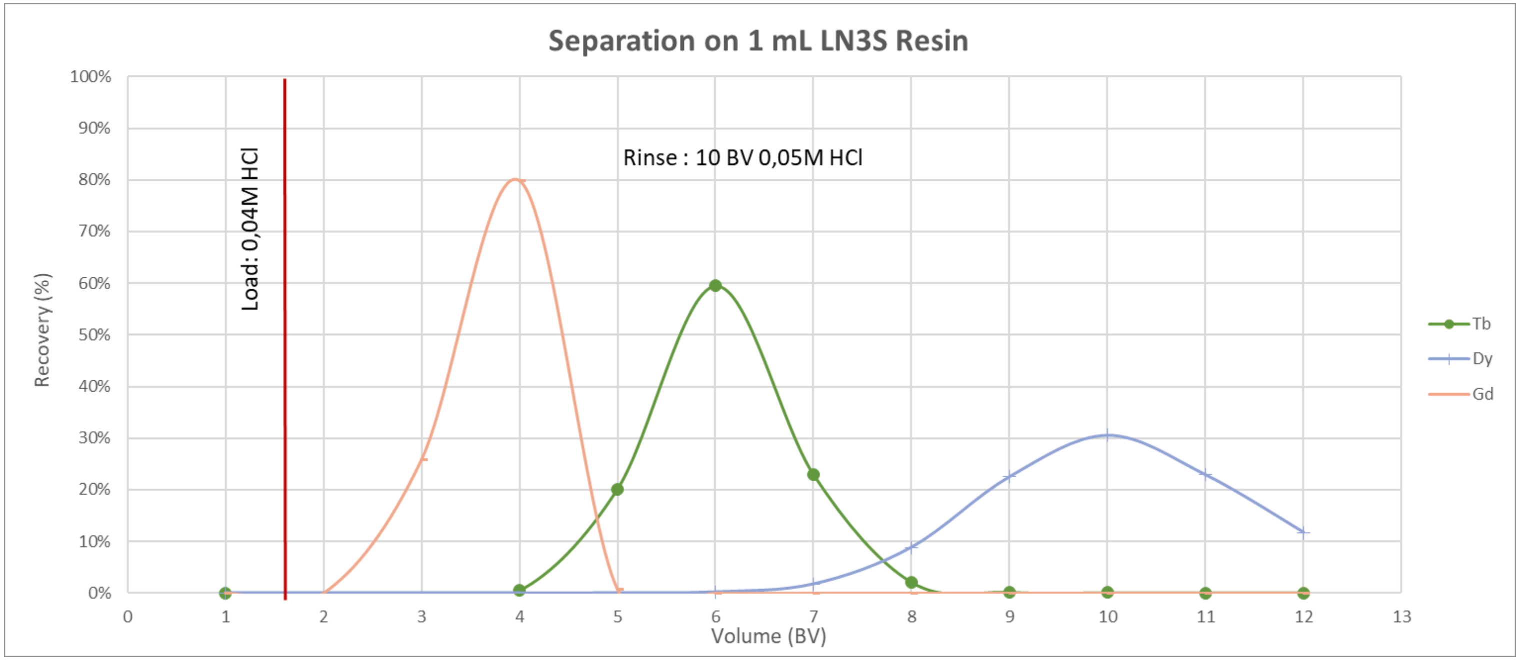
- TO-DGA plus ionic liquid
- High retention of light lanthanides at medium to high acid
- Heavy lanthanides also very well retained at low acid concentrations
- **Main application: Removal of radiolanthanides from effluents**





On-going: Tb/Dy separation

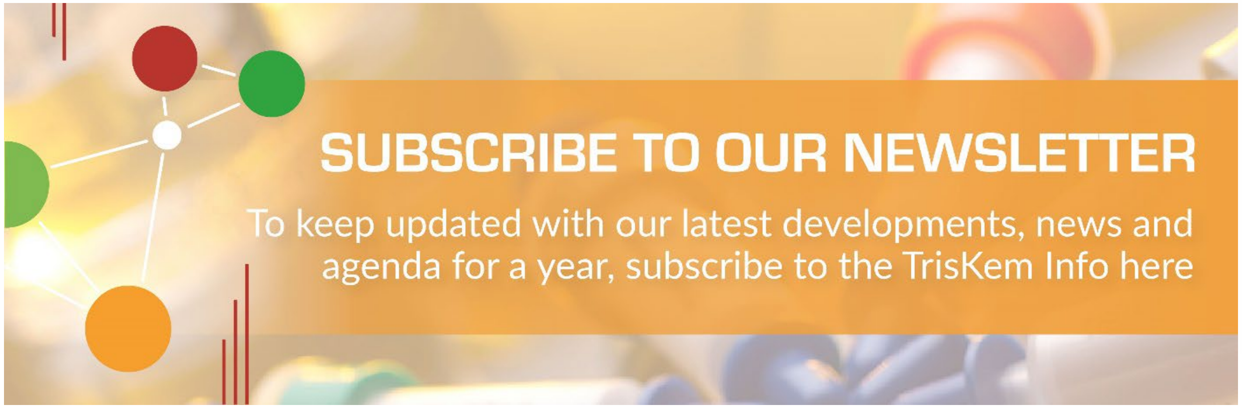
- Request:
  - Removal of Dy ingrown e.g. during transport
  - Aim: rapid removal, no significant change of volume and acidity of Tb
  - On-going work



On-going work and next steps

- Further up-scale
  - Same TK212 column (30cm x 2.5cm): 5g Gd,…
    - Gd will increasingly breakthrough during load
    - Pro:
      - Gd not fully retained during loading not problematic as long as Tb remains retained
      - May allow for treating very large targets
    - Contra:
      - Co-elution of potentially present impurities/no purification of the Gd (Eu…)
  - Use of 4 cm x 30cm TK212 for very large amounts of Gd
- Integrate Eu removal step into TK212 separation if needed
- Er/Tm separation (currently at 1g Er)
- Further Yb/Lu Upscale

Thank you for your attention!



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Tb separation from 10mg Gd

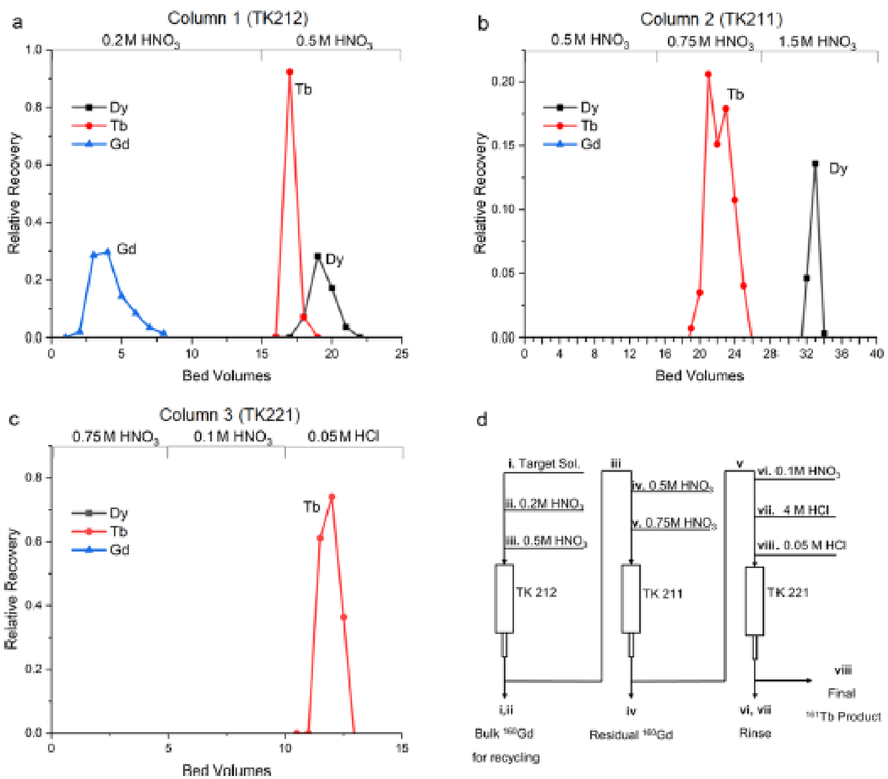

Fig. 3 Elution profile of Gd, Tb, and Dy (10 mg, 1 mg, and 1 mg respectively) TK212 (**a**), TK211(**b**) and TK221 (**c**). Tb containing fractions were combined for loading on the next column to simulate purfication run. Column bed volumes were 1 mL for each column during cold test but were later optimized for active runs. Overall process diagram (**d**) note steps i–v can be performed automactically, while steps vi–viii must be performed manually

McNeil *et al. EJNMMI Radiopharmacy and Chemistry* (2022) 7:31
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EJNMMI Radiopharmacy and Chemistry

RESEARCH ARTICLE Open Access

A simple and automated method for ^{161}Tb purification and ICP-MS analysis of ^{161}Tb

Scott W. McNeil[1], Michiel Van de Voorde[2], Chengcheng Zhang[3], Maarten Ooms[2], François Bénard[3], Valery Radchenko[1,4] and Hua Yang[1,5*]

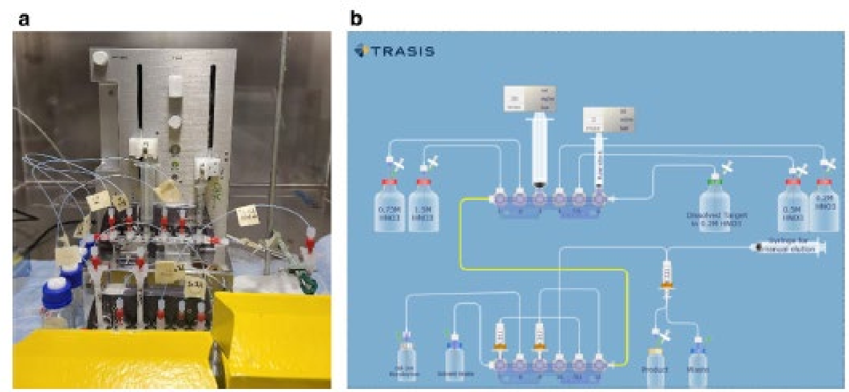
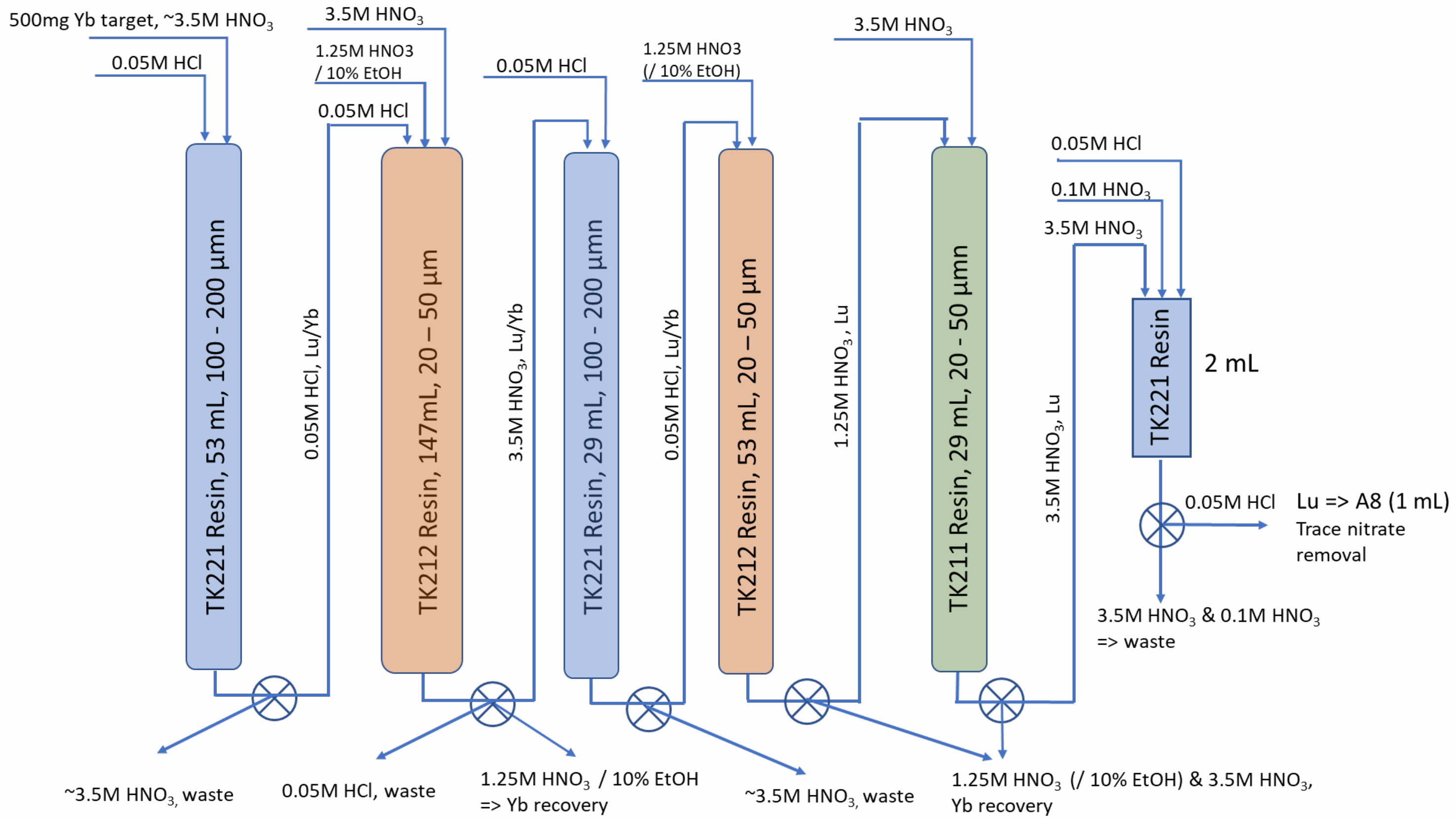


Fig. 4 TRASIS Mini AIO module and components set-up within hotcell (**a**), TRASIS layout diagram (**b**)

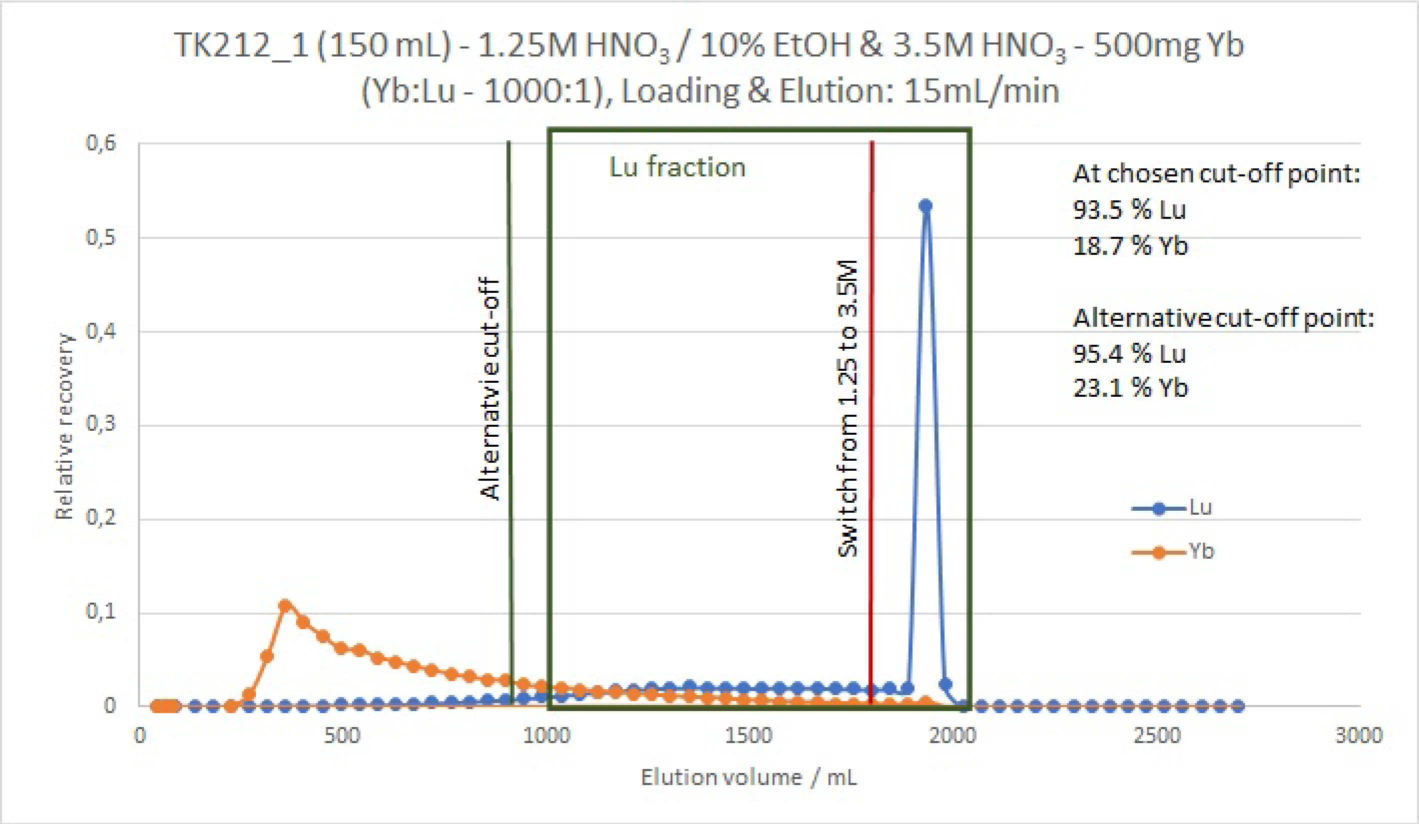
- Fully automized method (synthesizer) for Tb separation from 10mg Gd
- TK212, TK211 and TK221 based sytem

Simplified method for Lu separation from 500 mg Yb – TK211/2 & TK221



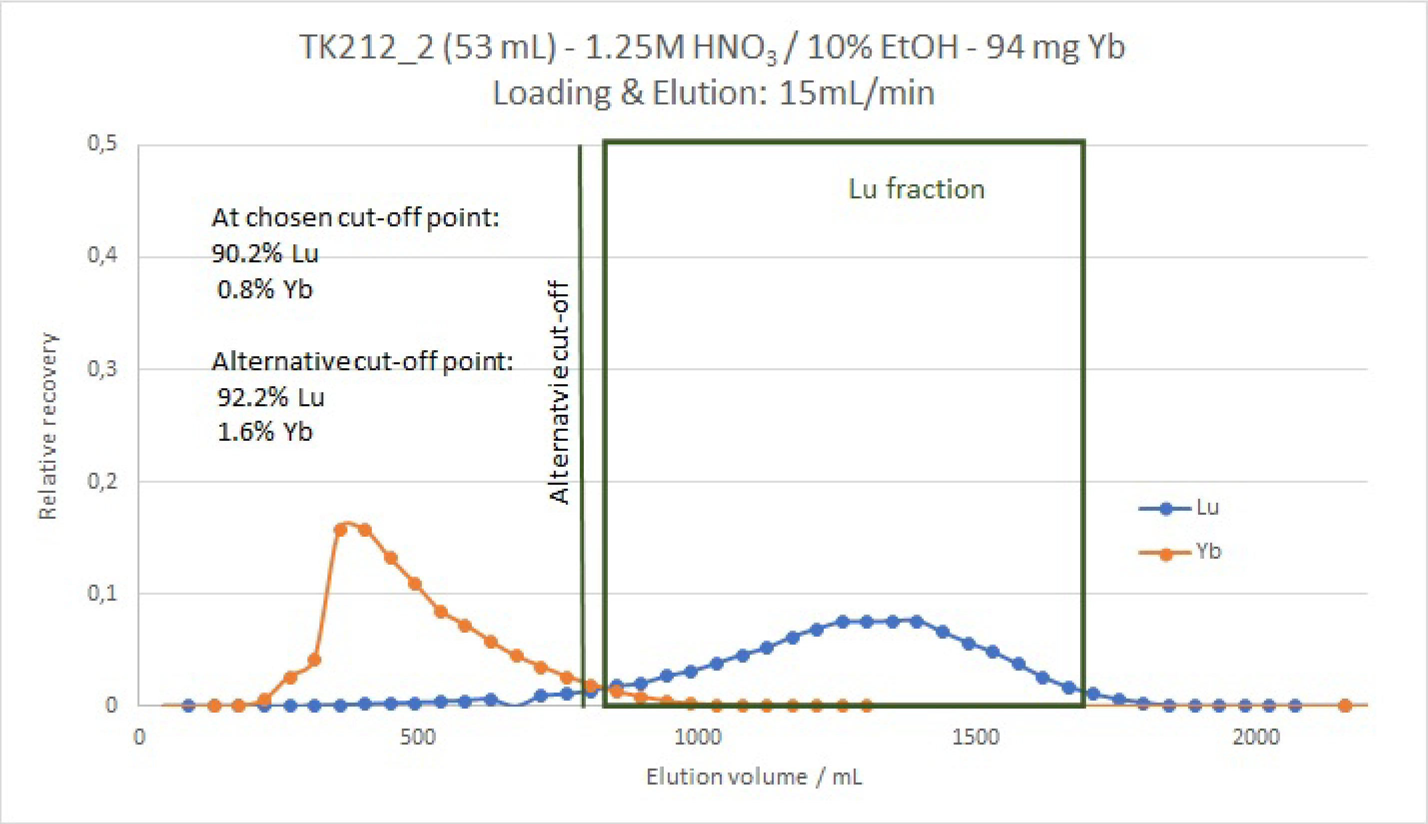
- Sequential separation step (direct load from TK212 onto TK211 for polish)
- Unfortunately complete sequential TK213=>TK212=>TK211 didn't work out
- Can be upscaled (larger columns,...)
- Further optimisation on-going

Lu separation form 500 mg Yb - **TK212**/TK221/TK212/TK211



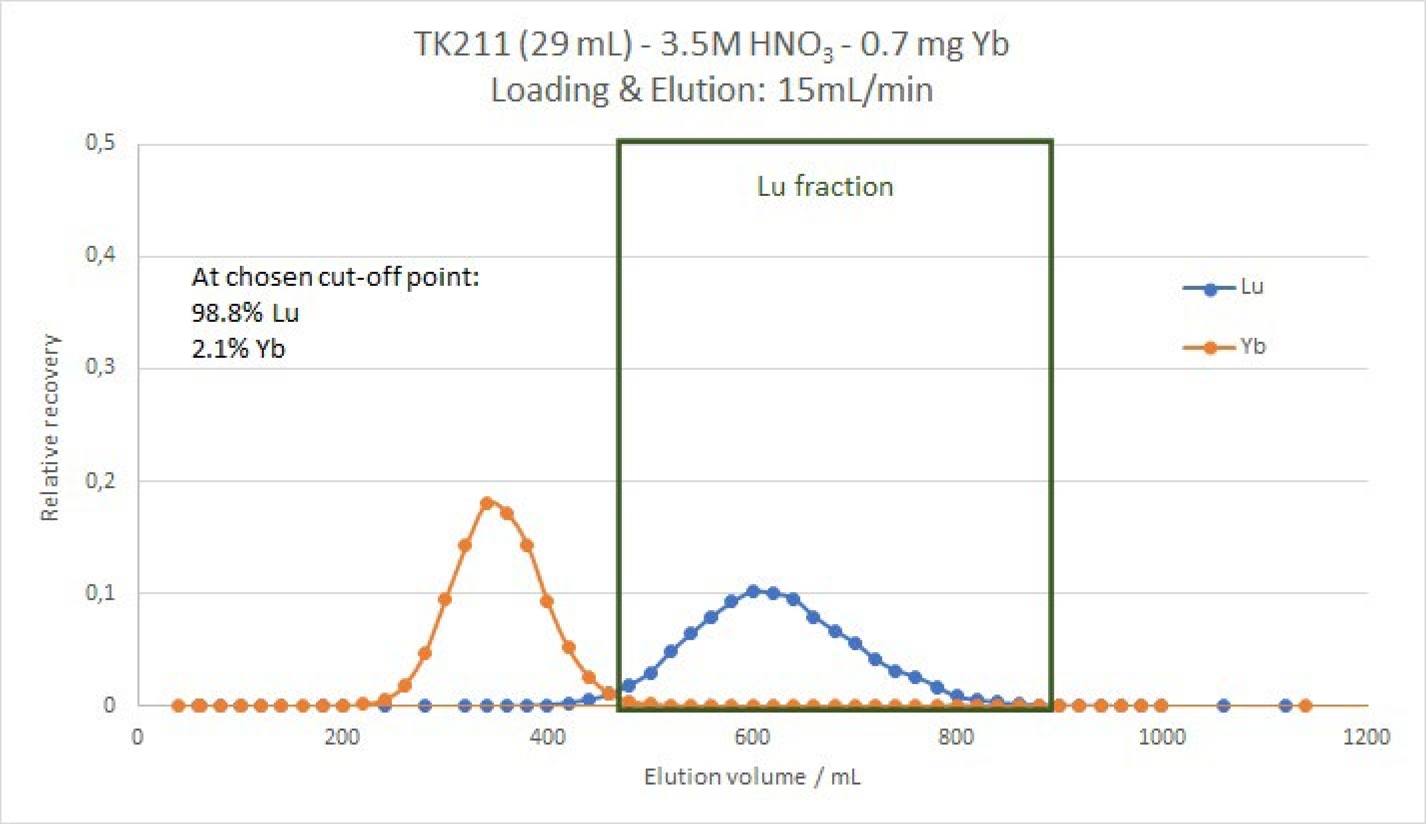
- Large tailing due to high Yb content => further optimisation on-going
- Improved separation through use of 1.25M HNO_3 / 10% EtOH (v/v)
- Higher Lu yield at similar residual Yb compared to LN2 based method
- Additional benefit from use of EtOH => improved radiolysis stability
- Online separation: switch at start of Lu fraction => ideally radiation detector driven

Lu separation form 500 mg Yb - TK212/TK221/**TK212**/TK211



- 2nd separation step on smaller TK212 (53 mL) after TK221 for conversion from high HNO_3 to dilute HCl on TK221
- Separation with e.g. 1.25M HNO_3 (with or without 10% EtOH)
- Direct loading of obtained Lu fraction onto TK211 Resin
  - Alternatively TK221/TK212 according to Horwitze et al.

Lu separation form 500 mg Yb - TK212/TK221/TK212/**TK211**



- Lu / Yb separation on TK211 (29 mL) => Lu fraction directly loaded onto TK211 from TK212
- Overall Lu recovery of process approx 85%
- Low remaining Yb
- Flow rates may be optimized (slower flow will improve separation but will take time)
- Final step: concentration/conversion to ≤ 0.05M HCl on TK221, nitrate removal via A8

Ongoing work – further upscale

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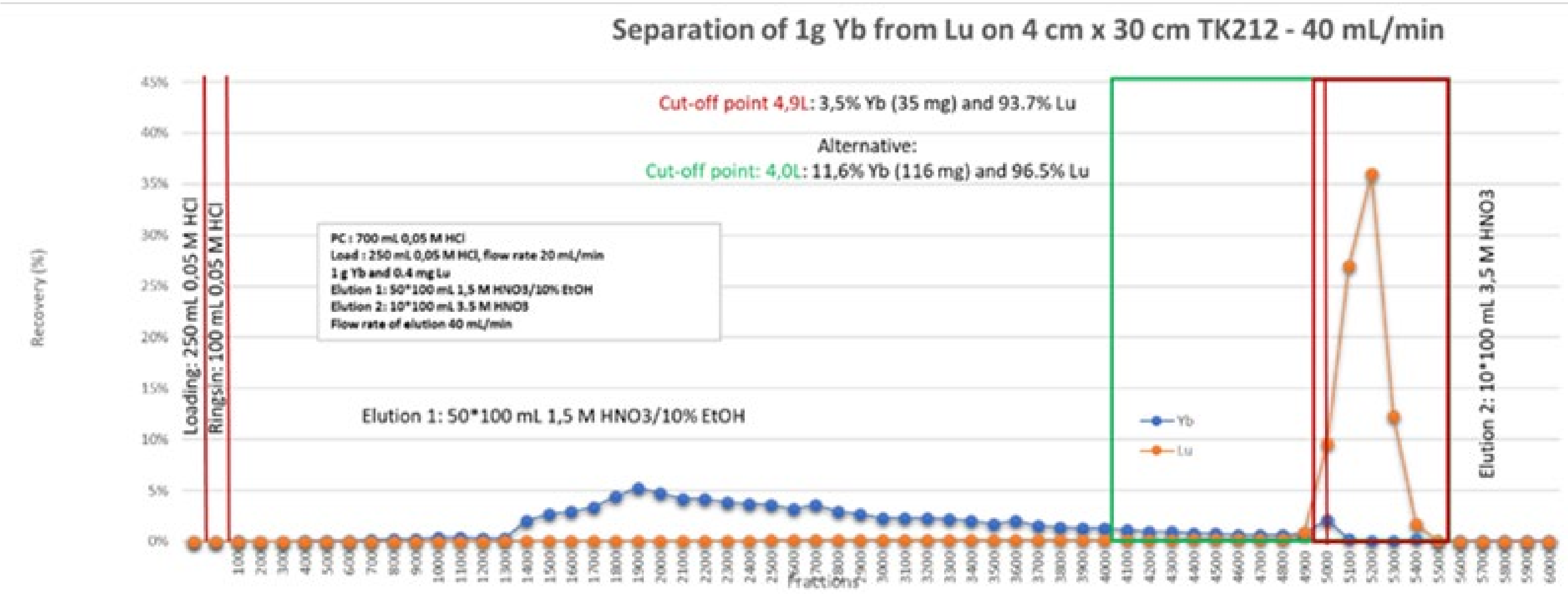

- 375 mL TK212 column
- 1g Yb
- 40 mL/min flow rate
- After separation <120mg Yb left => TK221/second TK212