Overview and new Developments RadPharm

RadWorkshop 2024

Steffen Happel

09/09/2024

TRISKEM
Expertise in Separation Chemistry

Overview

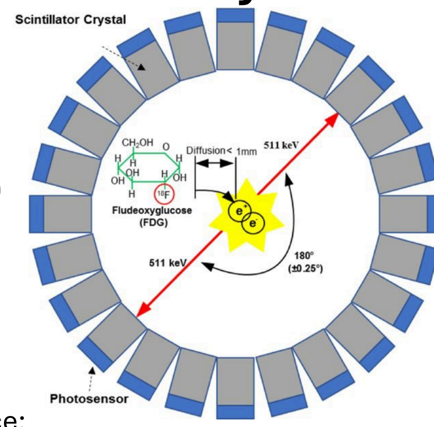
- Nuclear Medicine / RadPharm
- Research interests

  ‘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
- Radiolanthanides
  - Tb-161 from Gd targets
- Ac-225
- Ra-226
- Tc-99m from Mo
- Quality Control – Sheets
- Other on-going R&D

Nuclear Medicine / Radiopharmacy

Use of radioactivity for imaging and treatment

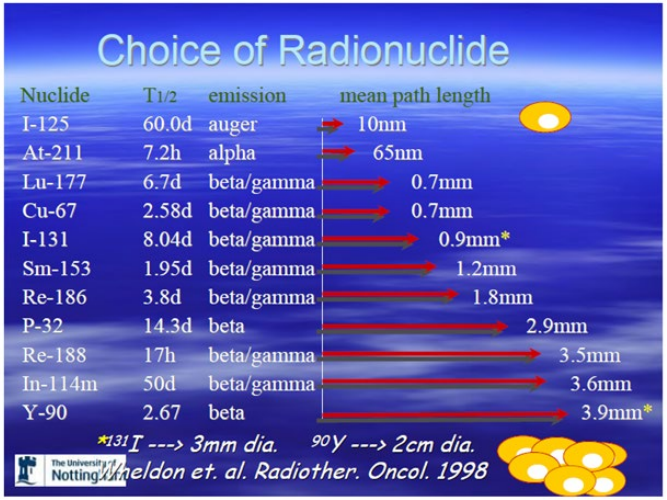
- Internalisation of radionuclides and distribution in the body
- Accumulation e.g. in cancer cells
  - Imaging: PET (e.g. ^{18}F-FDG) and SPECT (e.g. Tc-99m)
  - Treatment: I-131 for Thyroid cancer
- Iodine => first theranostic system (Saul Hertz)



Source:
Jiang et al. 2019 doi: 10.3390/s19225019

Renewed interest in use for therapy

- Bayer acquires Algeta => Ra-223 (Xofigo)
- Novartis (AAA and Endocyte) => Lu-177
- Generally use of alpha or beta emitter
  - Less frequent: Auger-Meitner emitters


Choice of Radionuclide

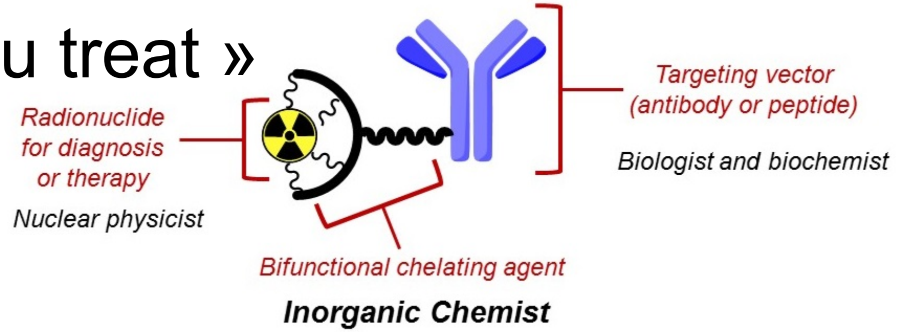
Nuclide	T1/2	emission	mean path length
I-125	60.0d	auger	10nm
At-211	7.2h	alpha	65nm
Lu-177	6.7d	beta/gamma	0.7mm
Cu-67	2.58d	beta/gamma	0.7mm
I-131	8.04d	beta/gamma	0.9mm*
Sm-153	1.95d	beta/gamma	1.2mm
Re-186	3.8d	beta/gamma	1.8mm
P-32	14.3d	beta	2.9mm
Re-188	17h	beta/gamma	3.5mm
In-114m	50d	beta/gamma	3.6mm
Y-90	2.67	beta	3.9mm*

*131I ---> 3mm dia. 90Y ---> 2cm dia.

Wheldon et. al. Radiother. Oncol. 1998

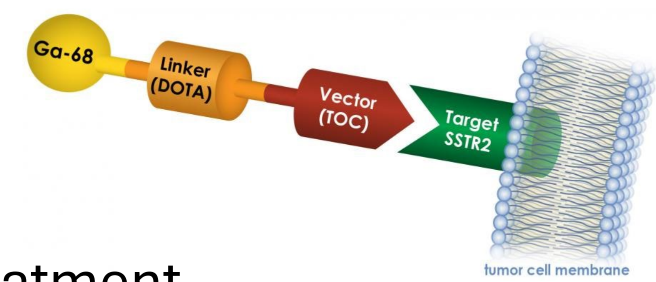
Thera(g)nostics

« Treat what you see and see what you treat »

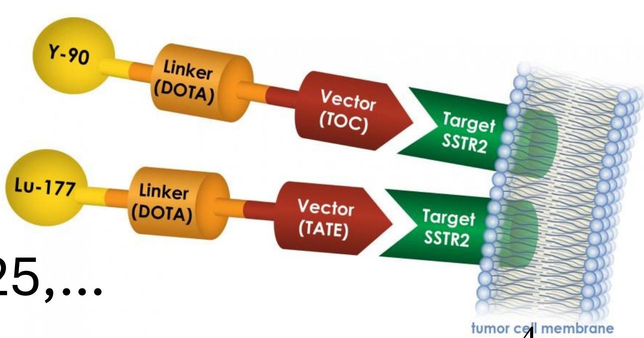


Source: https://wilson.chem.cornell.edu/research/

- Step towards personalized medicine
- Injection of targeted radiotracer
  - Labelling with positron or gamma emitter for imaging
    - Size / position of tumor, tracer distribution in body
    - Ideally allows dose calculation/adjustment
    - Decision whether treatment is suitable upfront
  - Labelling with alpha, beta (or Auger) emitter for treatment



- Theranostic pair for imaging and treatment
  - 'Real' theranostic pair: Cu-64/7, Sc-44/7, Tb, Pb,…
  - Other theranostic pairs: Ga-68/Lu-177, Ga-68/Ac-225,…
    - Sufficiently similar chemistry



Souce: https://uihc.org/health-topics/what-theranostics

Most promising systems: PSMA & FAPI

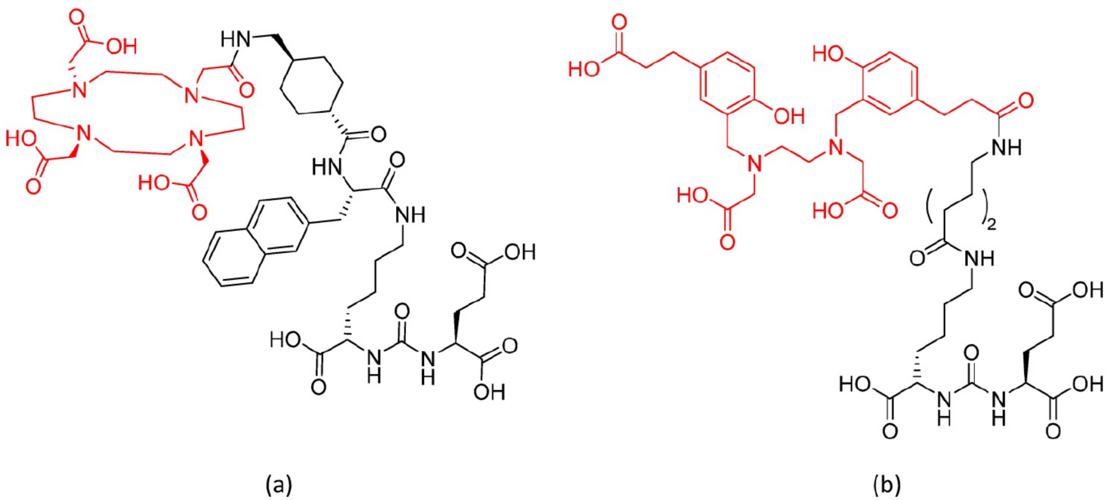
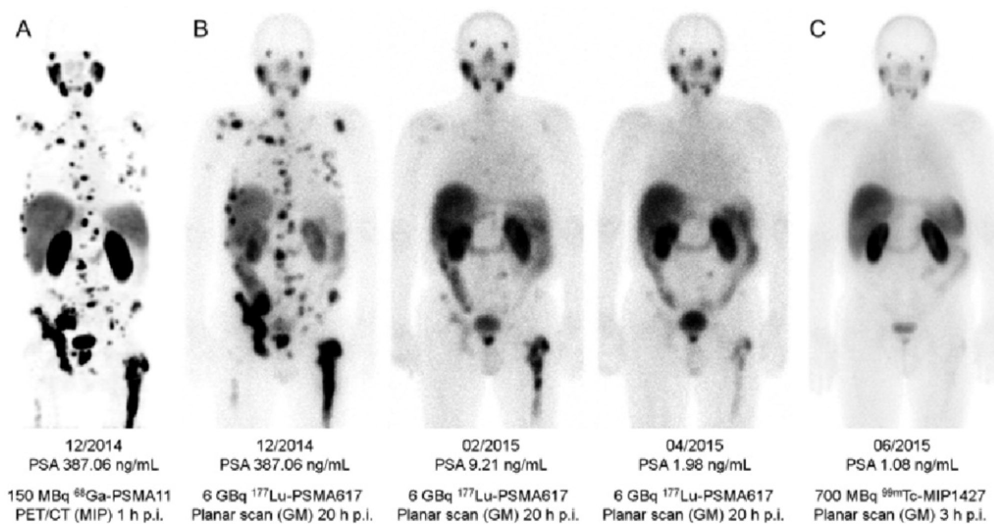


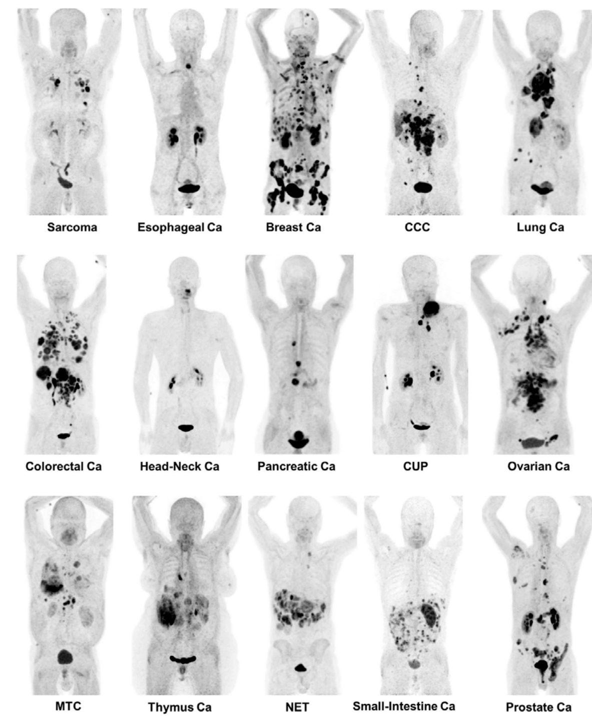
Figure 1. Structures of (a) PSMA-617 and (b) PSMA-11.

Source: Eppard et al. 2017 doi: 10.7150/thno.20586

- PSMA: Treatment of metastatic castration resistant prostate cancer
- PSMA-617, PSMA-11,...
- Ga-68 and Lu-177 or Ac-225
- i.e. Vision study (Novartis)
- Large interest in FAPI
    - Detection of 28 different cancers



Source: Yadav et al. 2018 doi:10.1007/s00259-016-3481-7



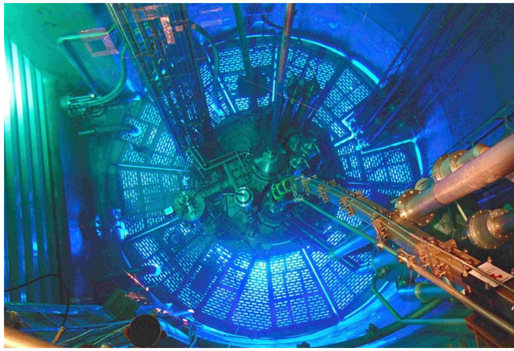
SNMMI image of the year 2019

Kratochwil et al. doi: 0.2967/jnumed.119.227967

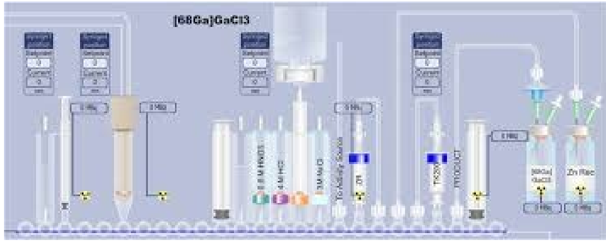
Radionuclide production

- ‘Legacy materials’
  - “Th”/Pb-212, Th-229/Ac-225
- Cyclotron
  - Irradiation of targets e.g. with protons (i.e. $^{68}Zn(p,n)^{68}Ga$)

- Reactors (or other neutron sources)
  - Fission (e.g. Mo-99)
  - « Neutron reactions »
  - ‘Carrier added’ Lu-177 => Lu-176 (n, γ) Lu-177
  - ‘Non-carrier added’ Lu-177 => Yb-176 (n, γ) Yb-177 → Lu-177 + β^-

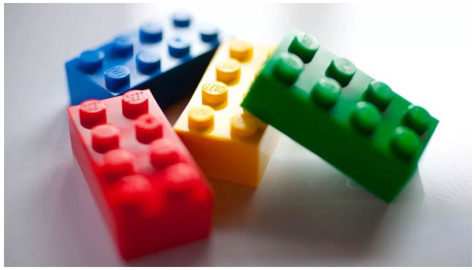


- Common challenges:
  - Large excess of matrix (target material)
  - Very high decontamination factors required
  - Especially cyclotron produced radionuclides:
    - often quite short half-life of product
  - Very high radioactivity levels => increased radiation stability



Research interests - Radiopharmacy

- Radionuclide production/purification
  - Resin and method development 'cold'
    - Cooperation with cyclotrons & reactors (NL, RN producers,...)
    - Equipment provider (targetry, synthesizer,...)
  - Separation of radionuclides from irradiated targets
    - Diagnostics: Zr-89, Cu-64, Ga-68, Ge-68, Ti-44/5, Tc-99m, Sc-43/4...
    - Therapy: alpha emitters, Lu-177, Tb-161, Cu-67, Sn-117m, Sc-47...
  - 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



Research interests - Radiopharmacy

- Quality control
  - Cartridge based methods (e.g. Sr-90 in Y-90,...)
    - Use of “TK-ELScint cartridges”?
  - **“Sheets”**
    - p.ex. DGA sheets (functionalized TLC for Ra-223, Ga-68, Pb-212,.... => CVUT Prague), CU Sheets,...
- Decontamination of effluents/waste (Ge-68, lanthanides, radioiodine,...)
- ‘Recycling’/valorization of long-lived RNs (Ge-68,...) and target materials
- Radiolysis stability (polymer, radical scavengers,...)
- **Determination of radionuclides (mainly used in therapy, generally Lu-177 and Ac-225) in environmental and bioassay samples**

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)

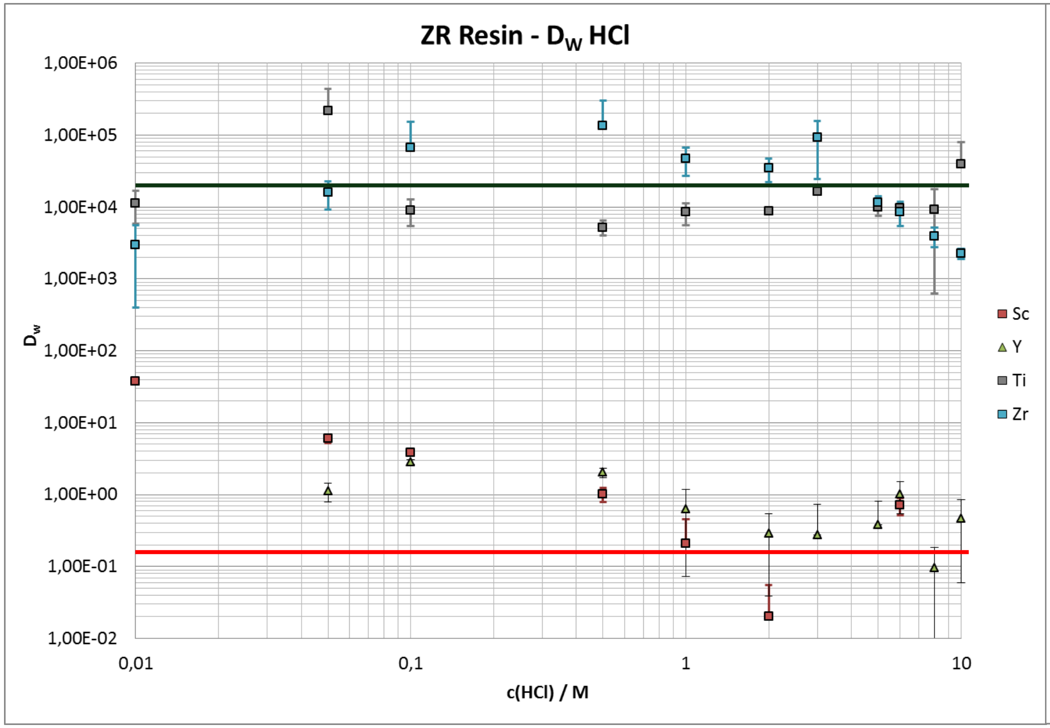
Zr-89 production via (p,n) reaction from ^{nat}Y targets

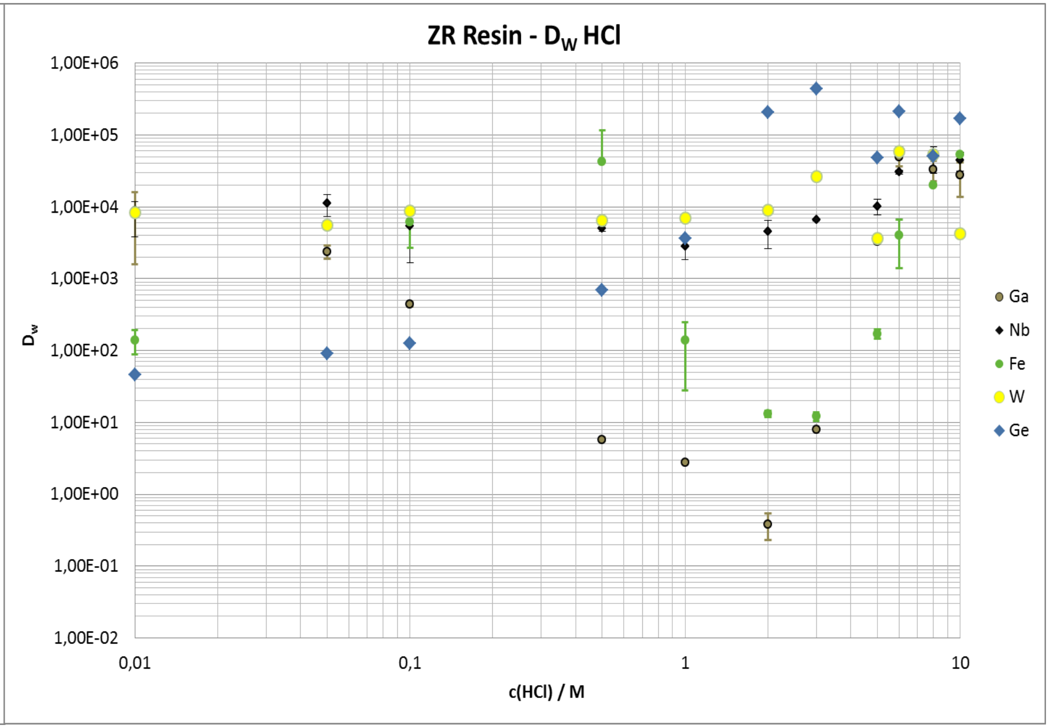
- High Zr/Y selectivity necessary
- Alternative e.g. TBP Resin (=> Graves et al.)

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

On-going work => improvement of radiolysis stability

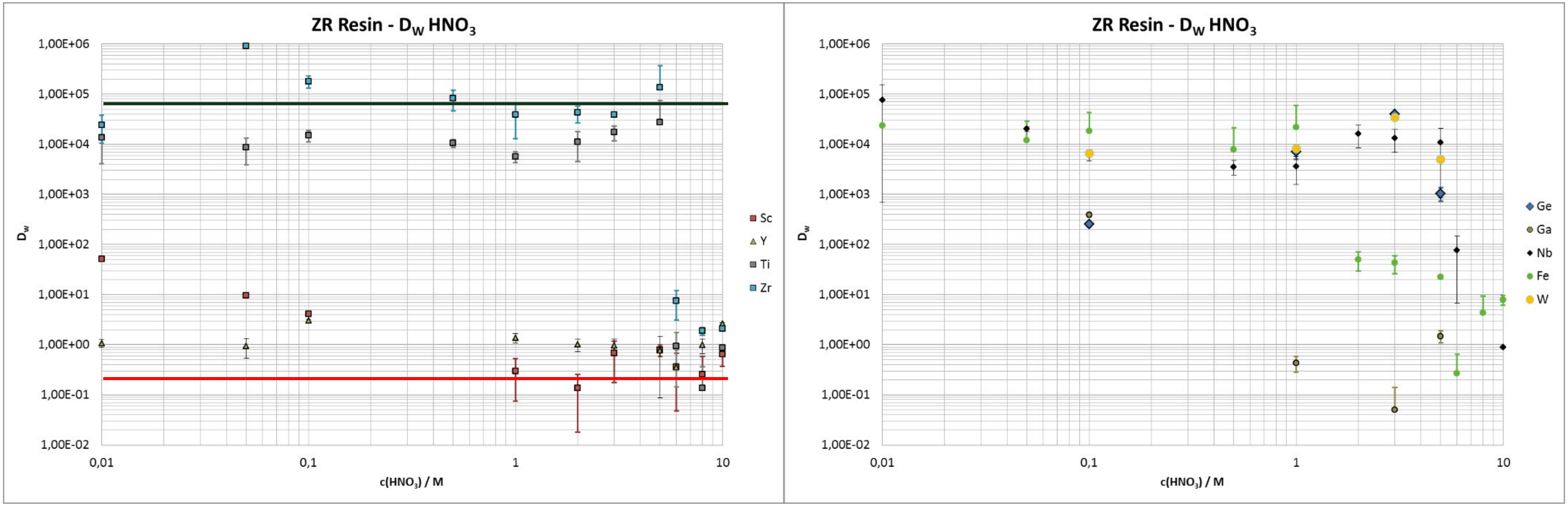
ZR Resin – HCl





- 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

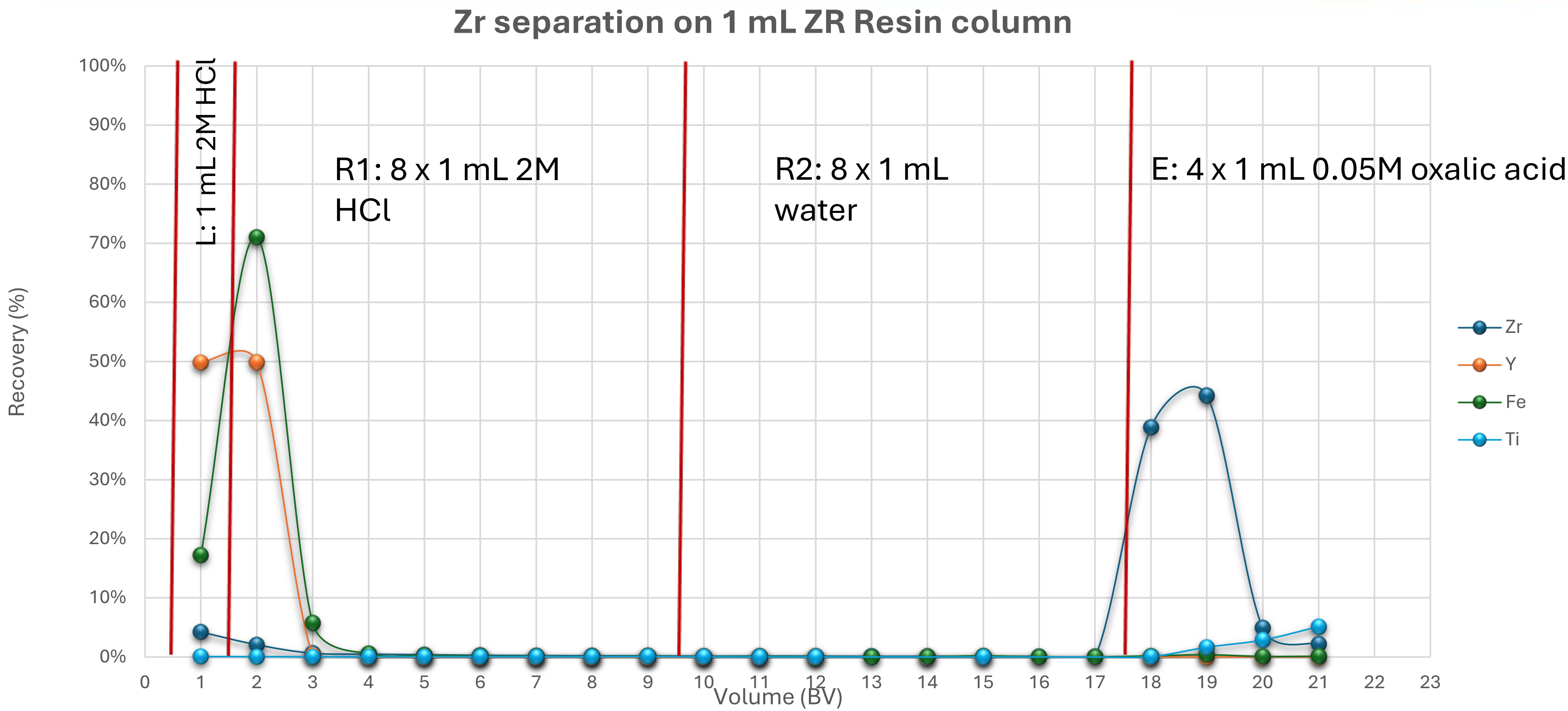


- High selectivity for Zr, Ti, Nb, W over wide HNO_3 concentration range
  - Loss of selectivity at 6M HNO_3

  => 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



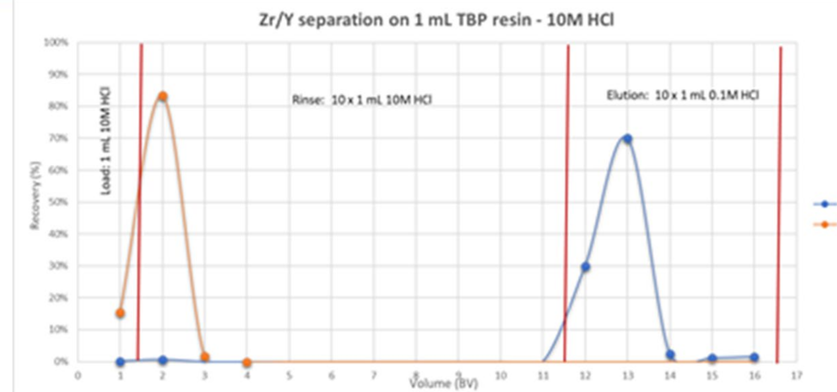
- Load from 2 – 6M HCl
- Rinsing described by Holland may be used
- No activation with acetonitrile
- Quantitative Zr elution in 1.5 - 2 mL ≥ 0.05M oxalic acid
- Clean Fe removal
- Use in commercial systems
  - Taddeo, Pinctada,…

Zr-89 separation on TBP Resin

- Frequent request: Zr elution without oxalate
- Method published by Graves et al.
  - 400mg Y foils irradiated at 14 MeV (50 µA)
  - Separation on 220 mg TBP Resin
  - Load from 9.6M HCl, rinse with 20 mL 9.6M HCl
  - Zr elution with 1 mL 0.1M HCl
- Zr yield: 89 ± 3%, Y decontamination: 1.5 x 10^5
- Zr elution should also be possible with citrate, phosphate, oxalate…
- (Fe and) Nb removal not ideal

- Improvement => use of TK400 Resin

- Implemented sucesfully by Lyashchenko et al.
- Two TK400 cartridges for high Fe removal



ELSEVIER
Nuclear Medicine and Biology
Volumes 64–65, September–October 2018, Pages 1-7

Evaluation of a chloride-based ^{89}Zr isolation strategy using a tributyl phosphate (TBP)-functionalized extraction resin

Stephen A. Graves [a], Christopher Kutyreff [b], Kendall E. Barrett [b], Reinier Hernandez [c], Paul A. Ellison [b], Steffen Happel [d], Eduardo Aluicio-Sarduy [b], Todd E. Barnhart [b], Robert J. Nickles [b], Jonathan W. Engle [b]

Show more

https://doi.org/10.1016/j.nucmedbio.2018.06.003

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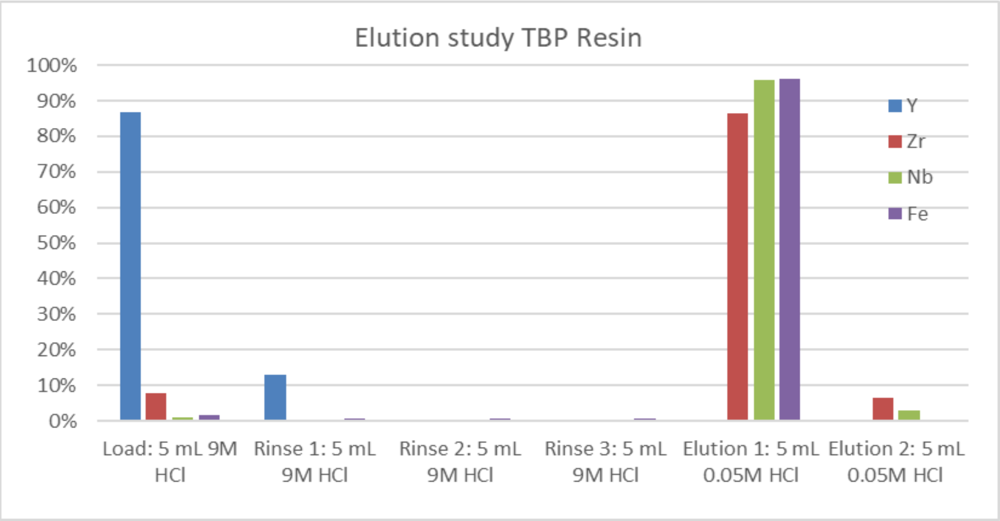
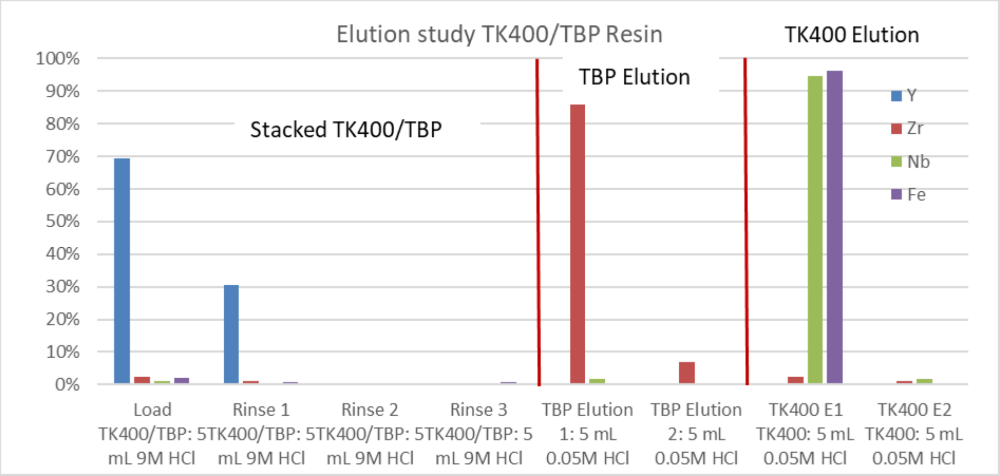
journal homepage: www.elsevier.com/locate/nucmedbio
ELSEVIER

[^{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

Use of TK400 for Fe/Nb removal

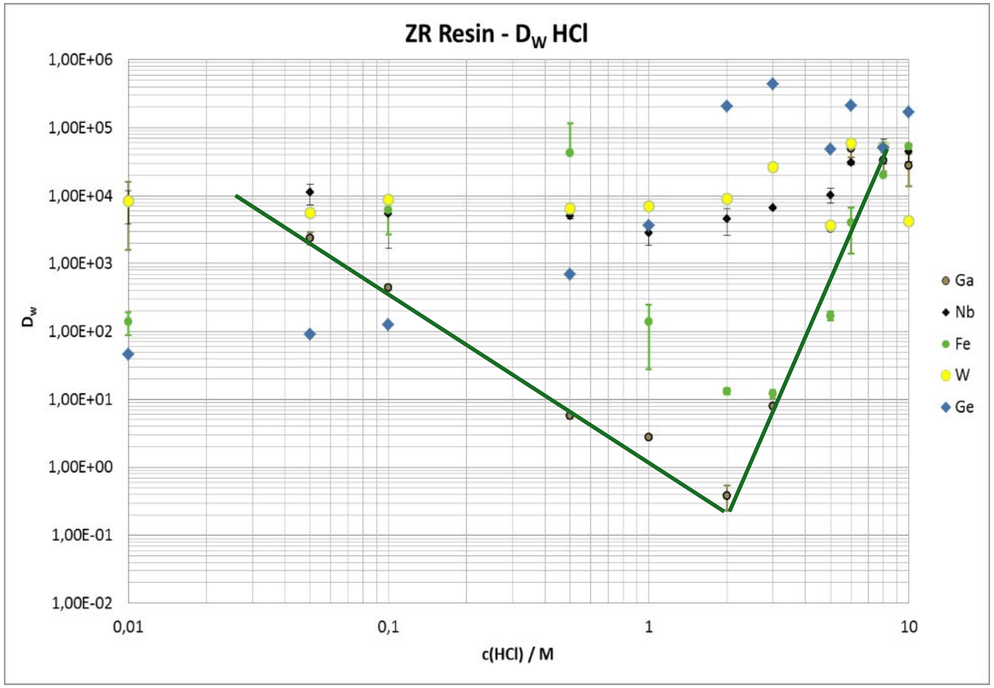


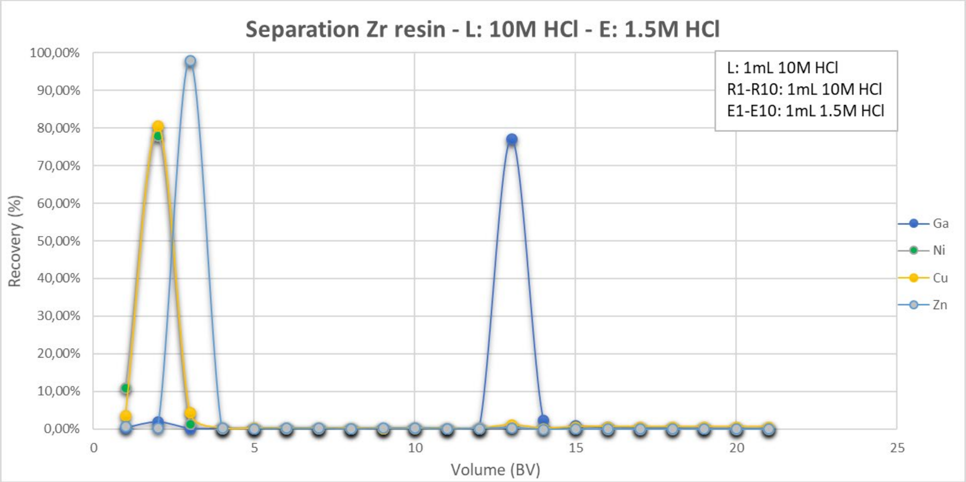


- On TBP only: Fe and Nb follow Zr
- Removal of Fe & Nb upfront possible using TK400 Resin
- Test with stacked 2 mL TK400/TBP cartridges
  - Load and Rinse at 10M HCl with TK400 stacked above TBP
  - Splitting of cartridges and separate elution with dilute Hcl
    - TBP => ZR only
    - TK400 = > Fe & 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

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*]

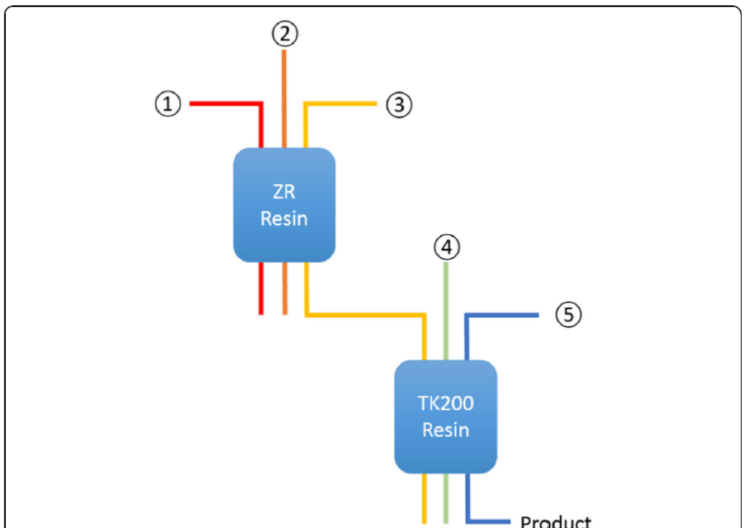


Fig. 4 Two-column approach for ^{68}Ga chemical separation

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 kinetics than ZR Resin

W. Tieu et al. use of single TK400 cartridge for solid Zn targets

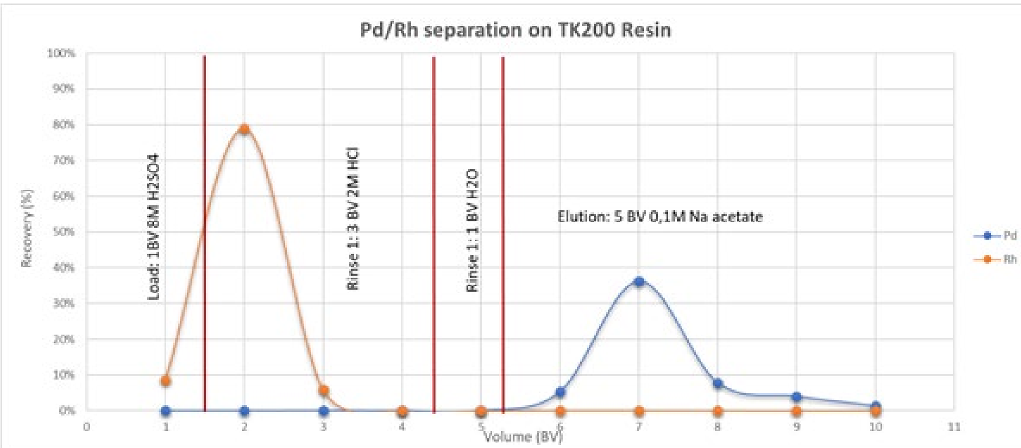
Svedjehed et al. use of TK400/A8/TK200 for solid Zn targets

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

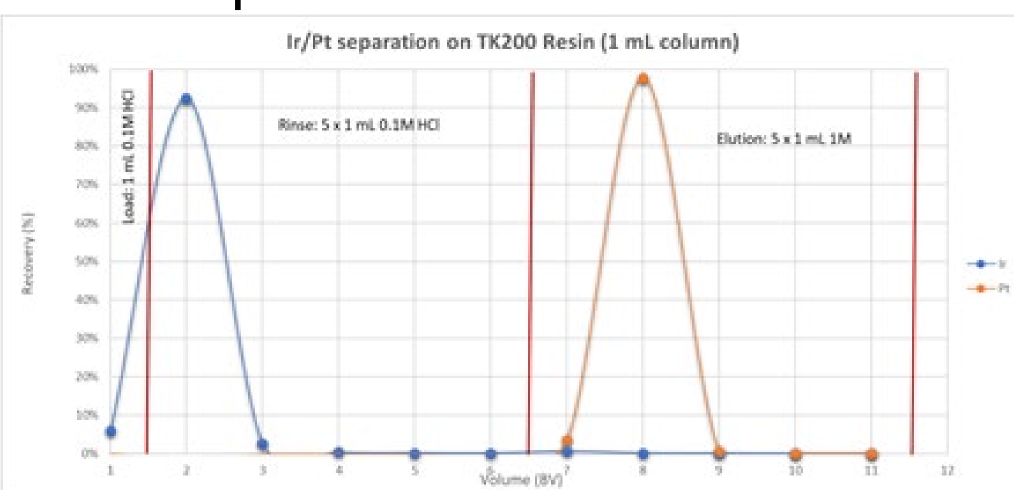
Ongoing work on TK200

- Pd separation from Rh



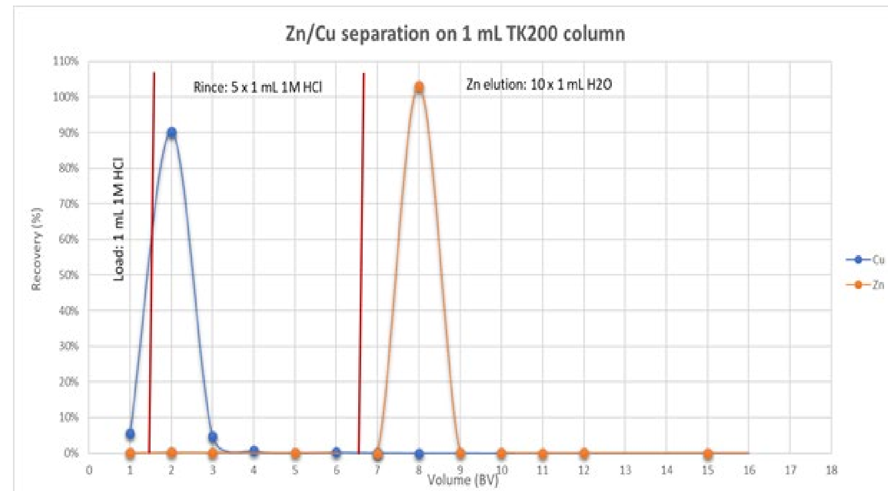
- Pd/Rh separation. Elution study, ICP-MS measurement

- Pt separation from Ir

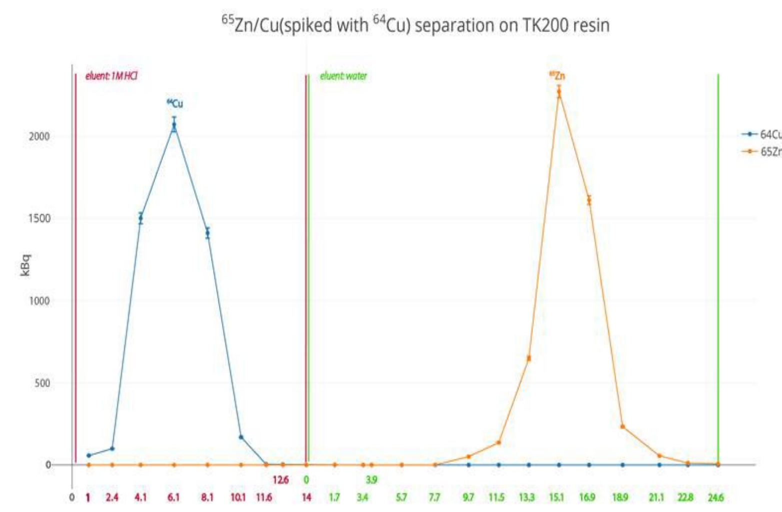


- Pt/Ir separation. Elution study, ICP-MS measurement

- Zn separation from Cu

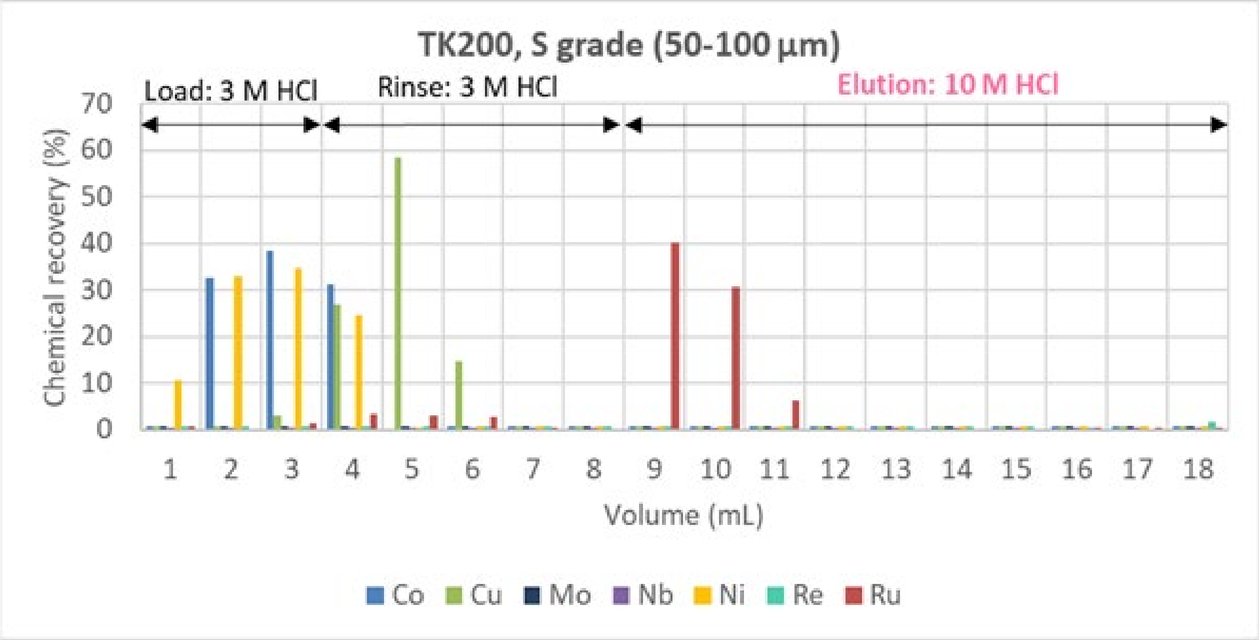


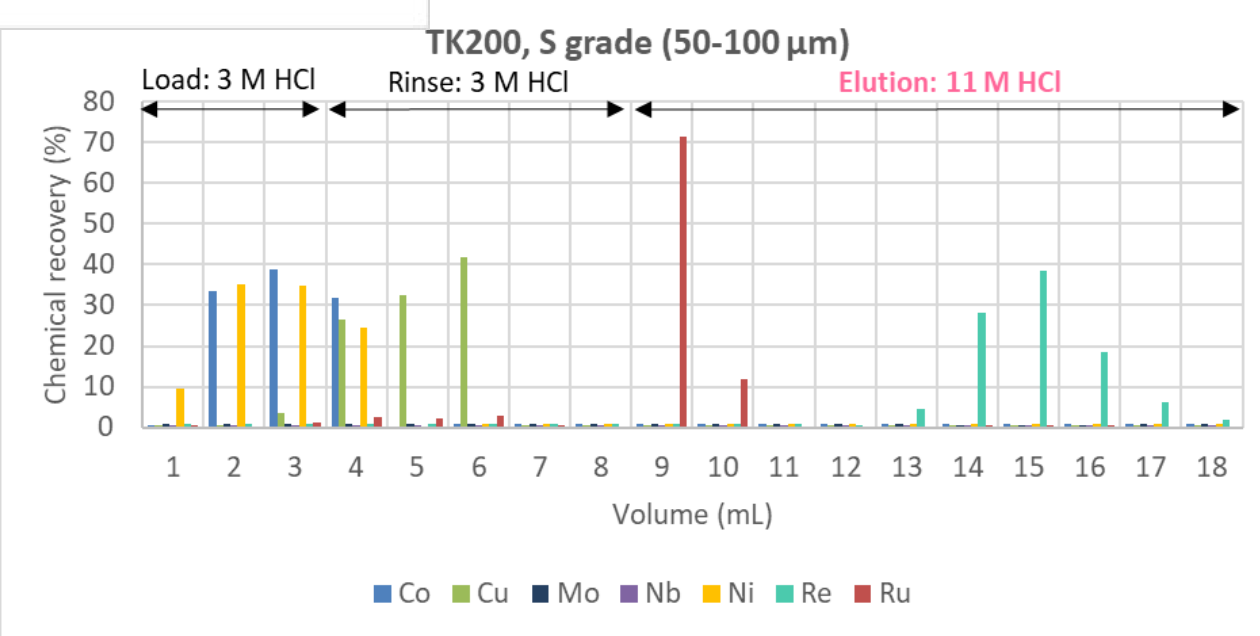
- Zn/Cu separation. Elution study, ICP-MS measurement



- Zn-65 separation. Data kindly by Fedor Zhuravlev, DTU

Ru separation on TK200





Ag/Pd separation

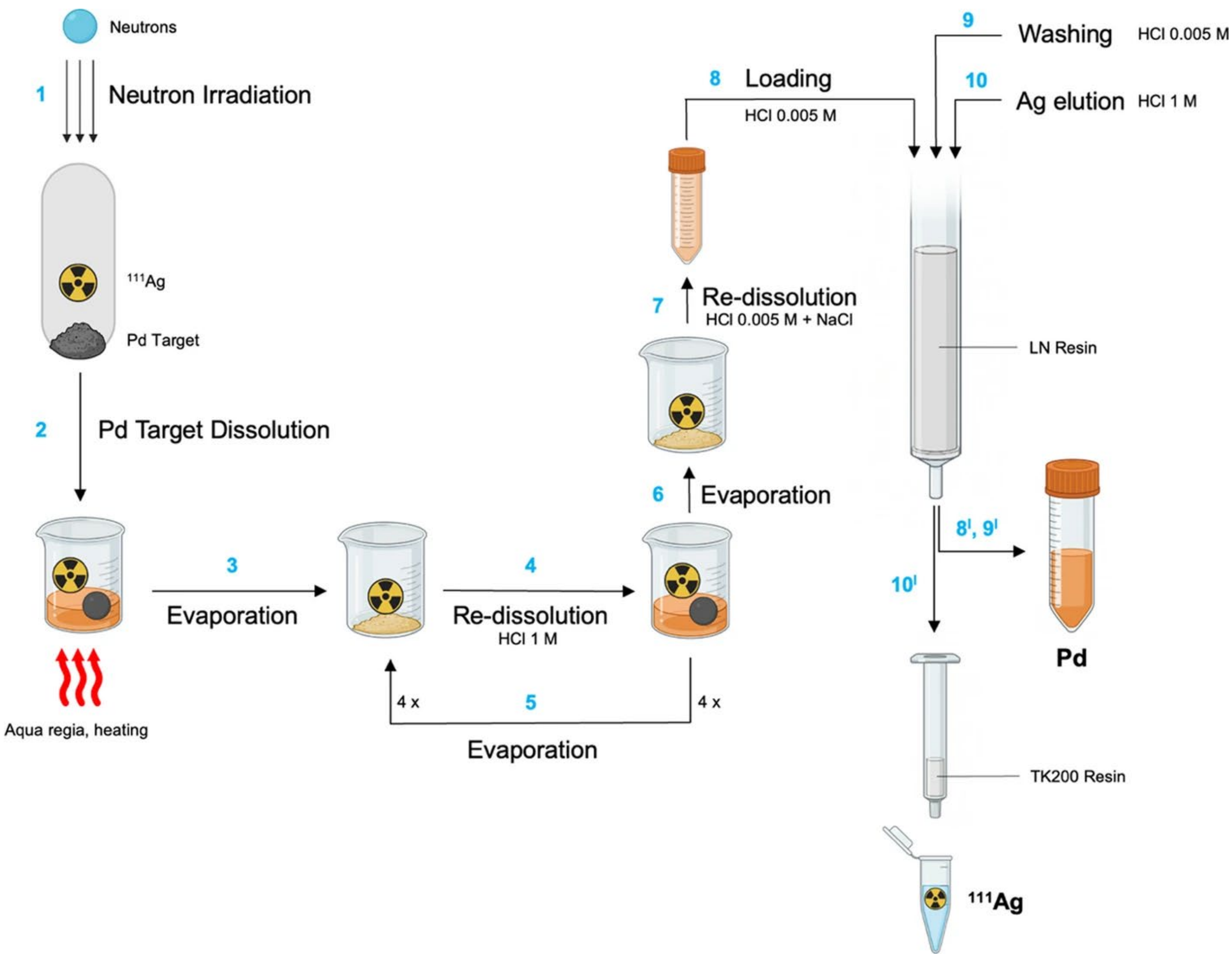
Tosato et al.
EJNMMI Radiopharmacy and Chemistry (2023) 8:43
https://doi.org/10.1186/s41181-023-00232-0

EJNMMI Radiopharmacy and Chemistry

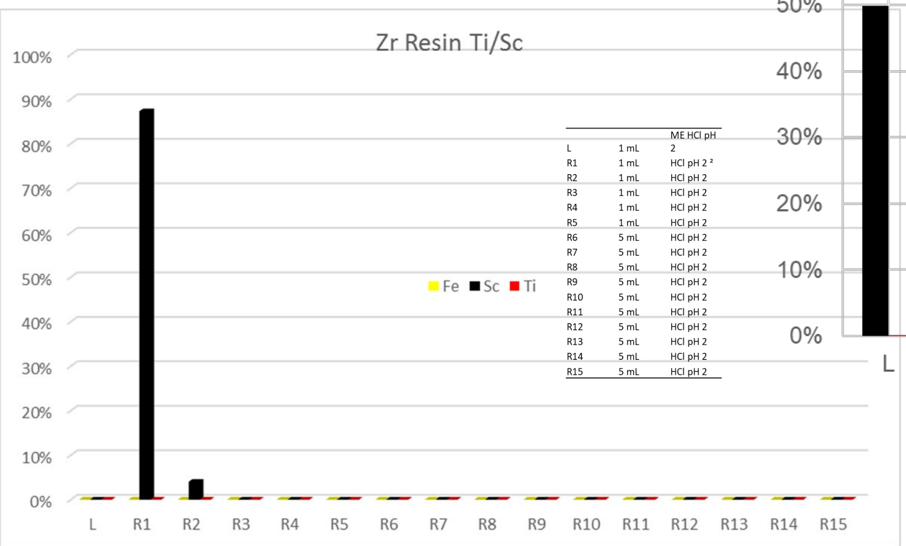
RESEARCH ARTICLE Open Access

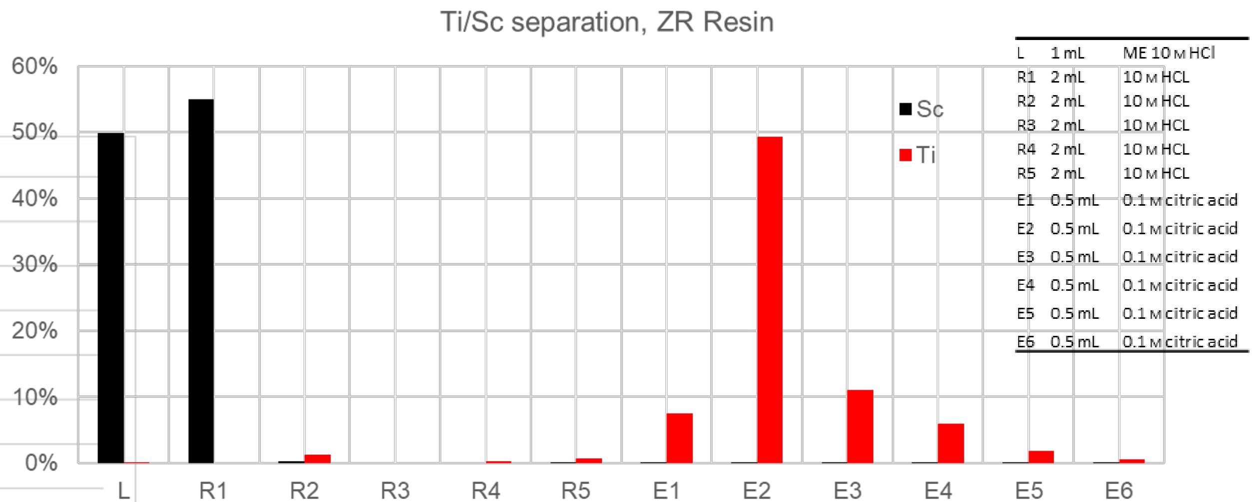
Chromatographic separation of silver-111 from neutron-irradiated palladium target: toward direct labeling of radiotracers

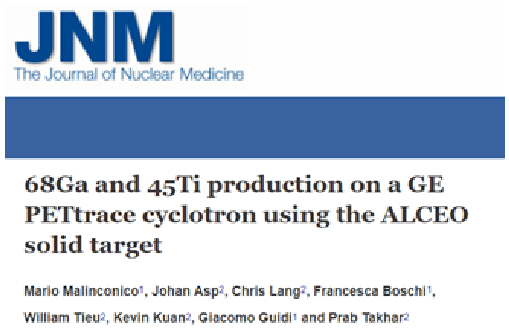
Marianna Tosato[1,2], Andrea Gandini[3], Steffen Happel[4], Marine Bas[4], Antonietta Donzella[5,6], Aldo Zenoni[5,6], Andrea Salvini[3], Alberto Andrighetto[7], Valerio Di Marco[2] and Mattia Asti[1*]



Ti-Sc Separation (Ti-44/5)






JNM
The Journal of Nuclear Medicine

68Ga and 45Ti production on a GE PETtrace cyclotron using the ALCEO solid target

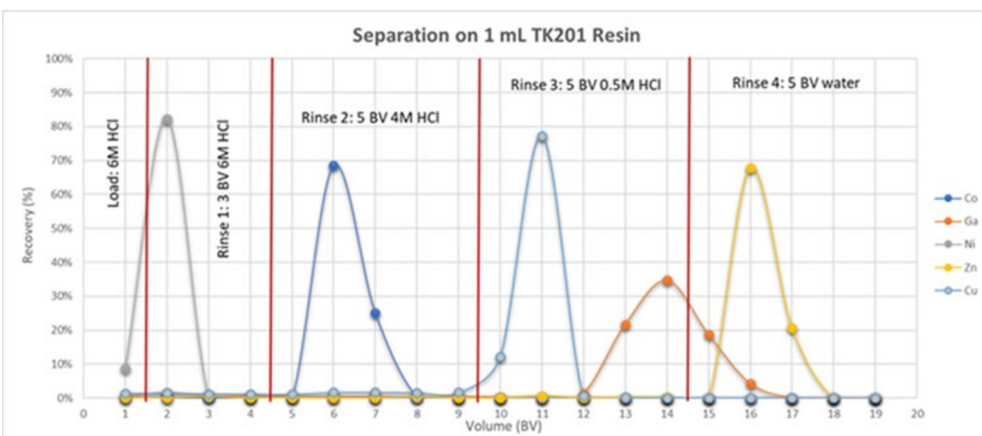
Mario Malinconico[1], Johan Asp[2], Chris Lang[2], Francesca Boschi[1], William Tieu[2], Kevin Kuan[2], Giacomo Guidi[1] and Prab Takhar[2]

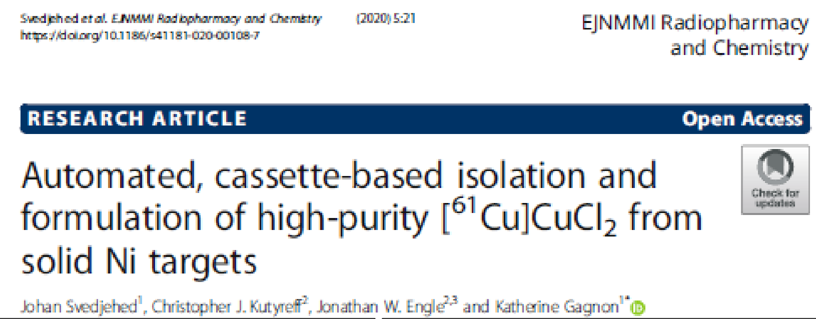
- Ti retained from (high) HCl, Sc not retained
- Ti also retained in dilute acid, Sc not => Ti generator?
- Ti elution with 0.1M citric, >0.2M oxalic acid, 0.1M H_2O_2
- K. Olguin: https://www.triskem-international.com/scripts/files/5fc95b3398a614.03970900/olguin_sfu_vugm20_production-and-purification-of-titanium-45-for-positron-emission-tomography.pdf
- Publication:
  - Malinconico et al.: J Nucl Med May 1, 2018 vol. 59 (supplement 1 664)

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



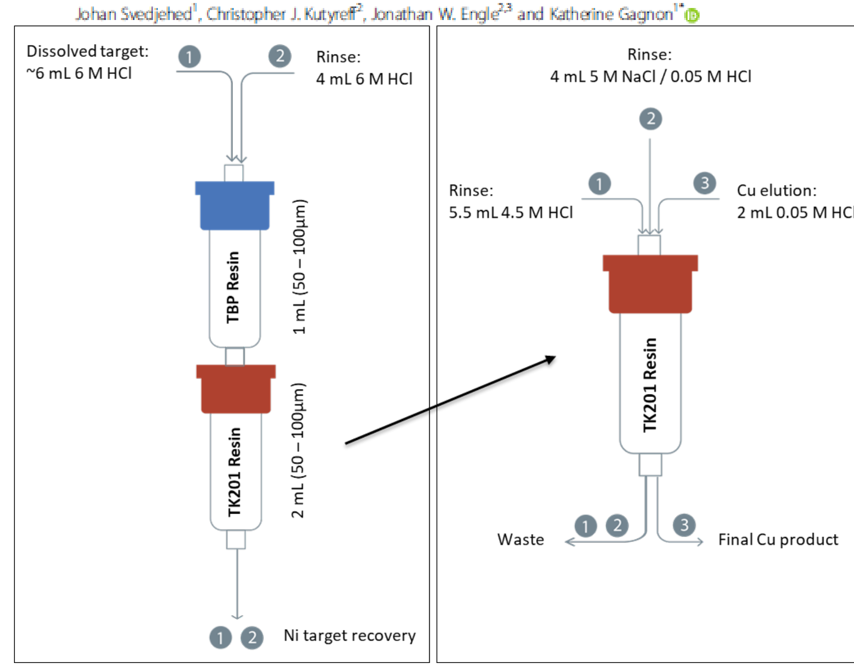

Svedjehed et al. EJNMMI Radiopharmacy and Chemistry (2020) 5:21
https://doi.org/10.1186/s41181-020-00108-7

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*]



- Gagnon et al. use of NaCl/HCl for better

  pH control of eluate

– Also be used for Zn separation

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

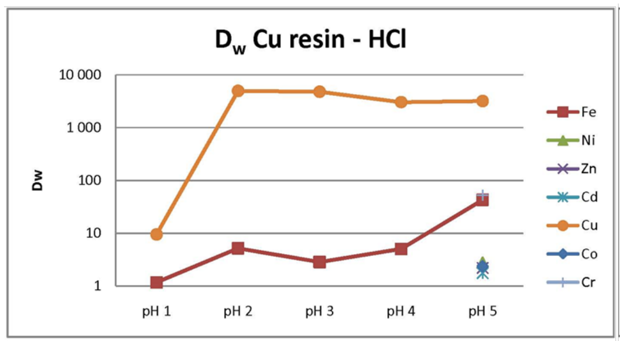
  => allows for Cu elution in 0.05M HCl

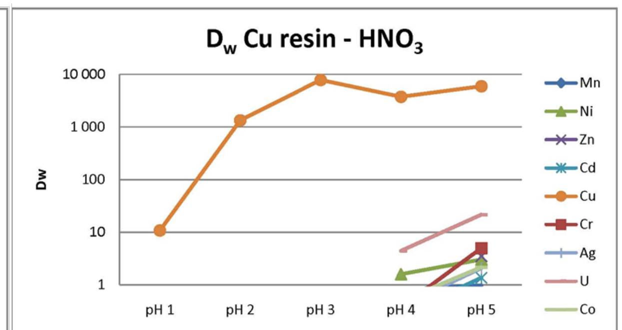
CU Resin

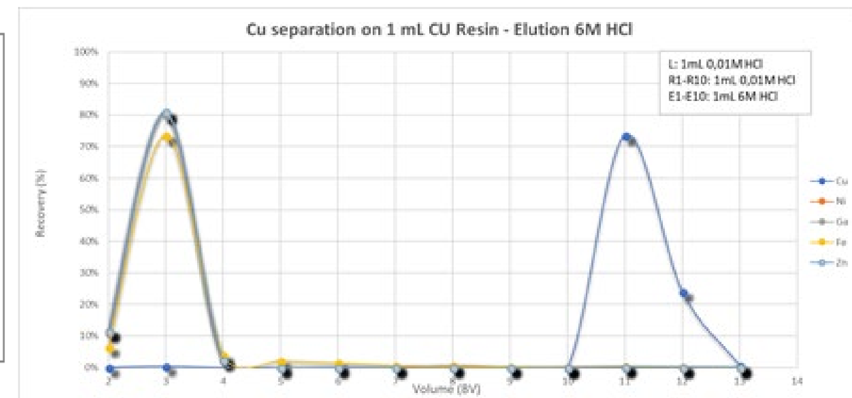
TK201 can not be used for Cu separation from Zn targets (e.g. Cu-67)

Use of oxime based CU Resin instead

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







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.

Cu-67 at BNL (DeGraffenreid et al.)

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

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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
- Original suggestion: AIX

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

Alternatives to AIX- use of TK201:

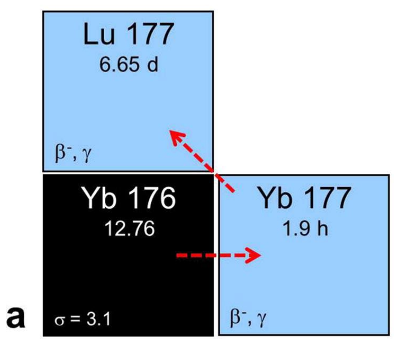
- Cu elution with 6M HCl directly onto TK201
- Cu elution from TK201 in dilute acid
- Optional: rinse with NaCl/HCl for better pH control

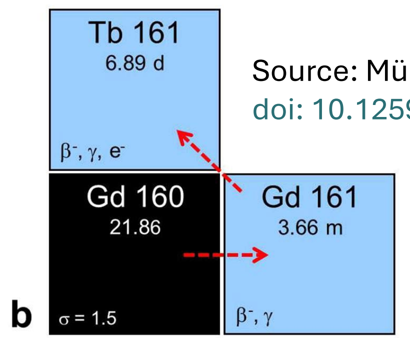
Lu-177/Tb-161

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

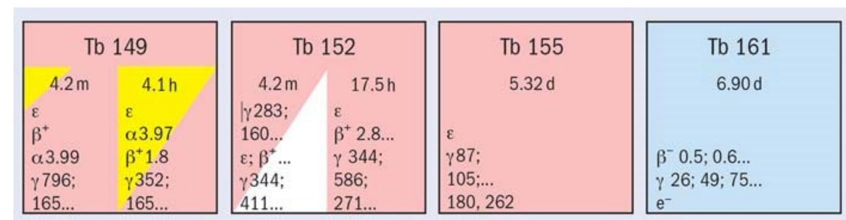
- Part of the 'Swiss knife of nuclear medicine' => Tb isotopes

Similar production for both





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



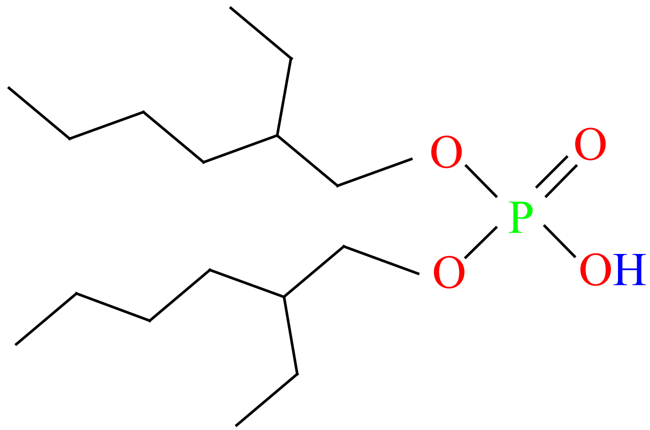
Terbium: a new 'Swiss army knife' for nuclear medicine
Source: https://cerncourier.com/a/terbium-a-new-swiss-army-knife-for-nuclear-medicine/

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

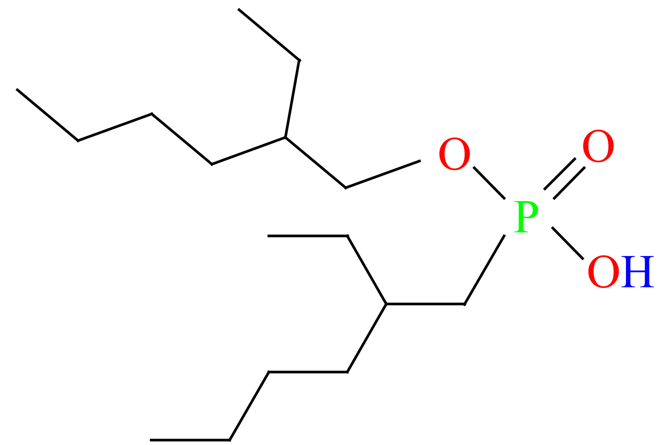
Prepacked PP columns available

- 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

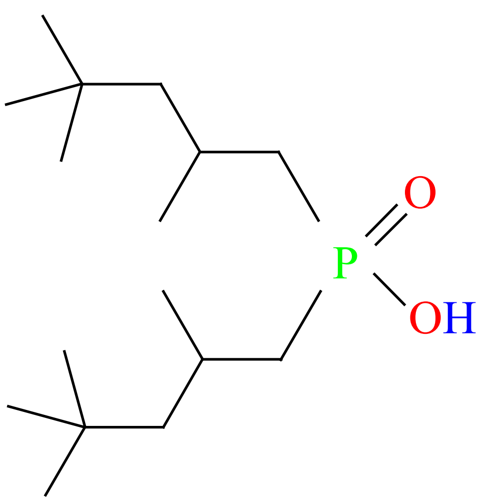
Lanthanide separation on TK211/2/3



HDEHP (LN)



HEH[EHP] (LN2)



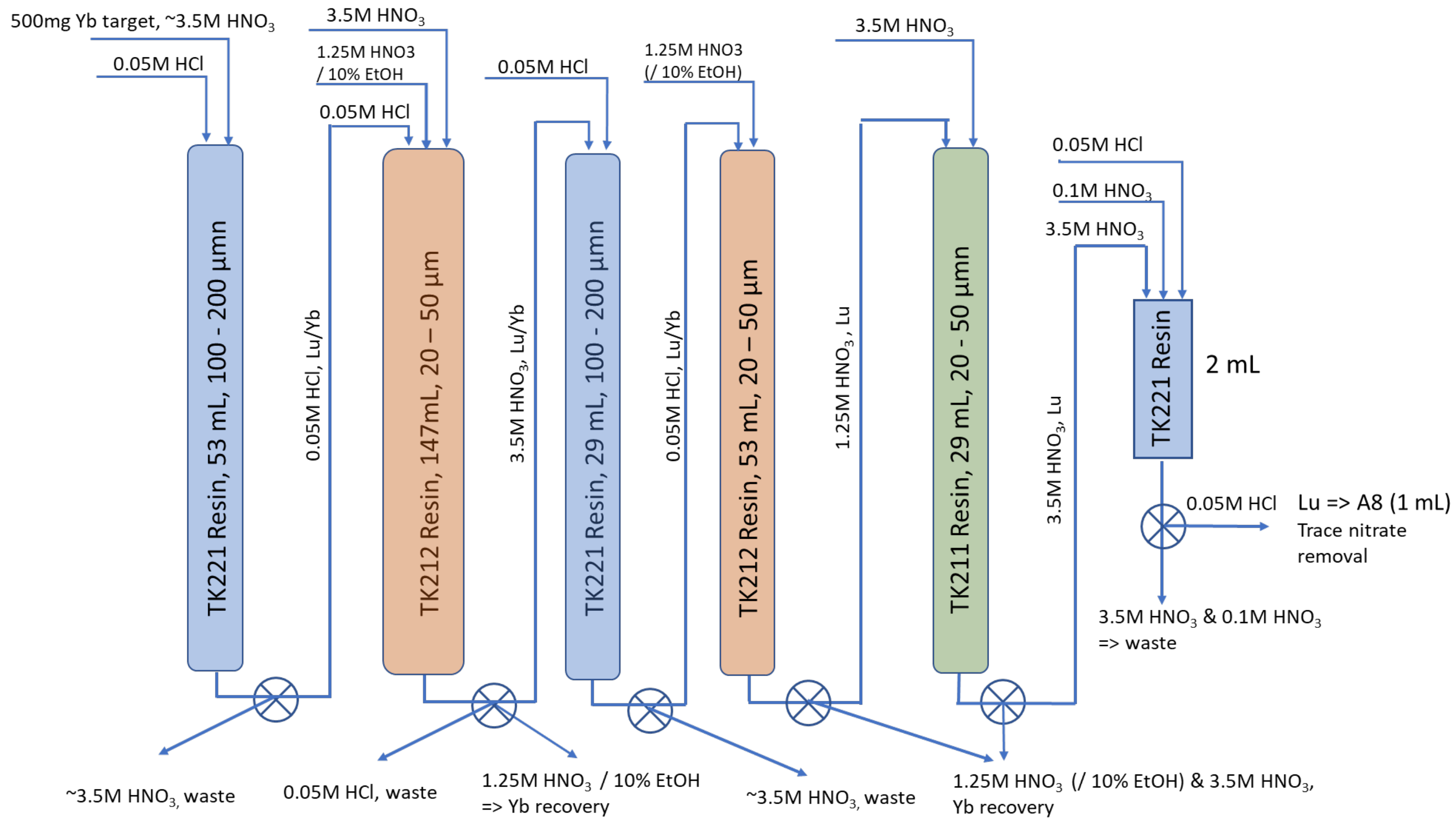
H[TMPeP] (LN3)

Cyanex 572

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

- Mixtures of different extractants
- Optimized for high radiation stability

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

Tb separation from 1000 mg Gd targets

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

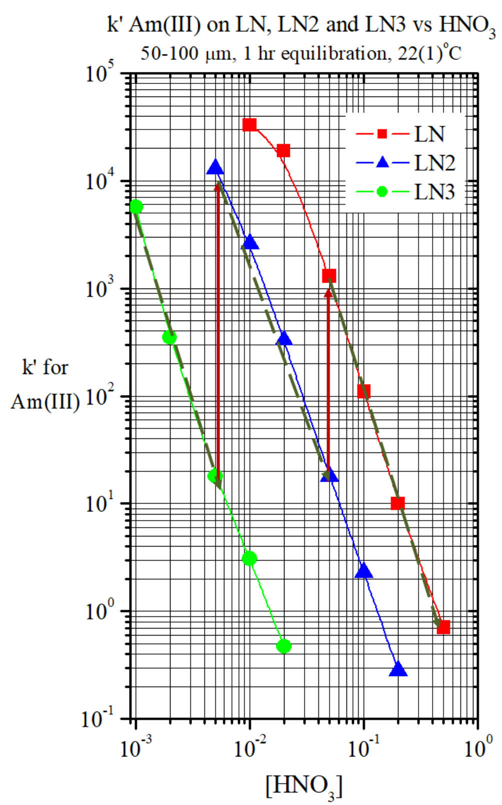
- For separation solution needs to be dilute acid

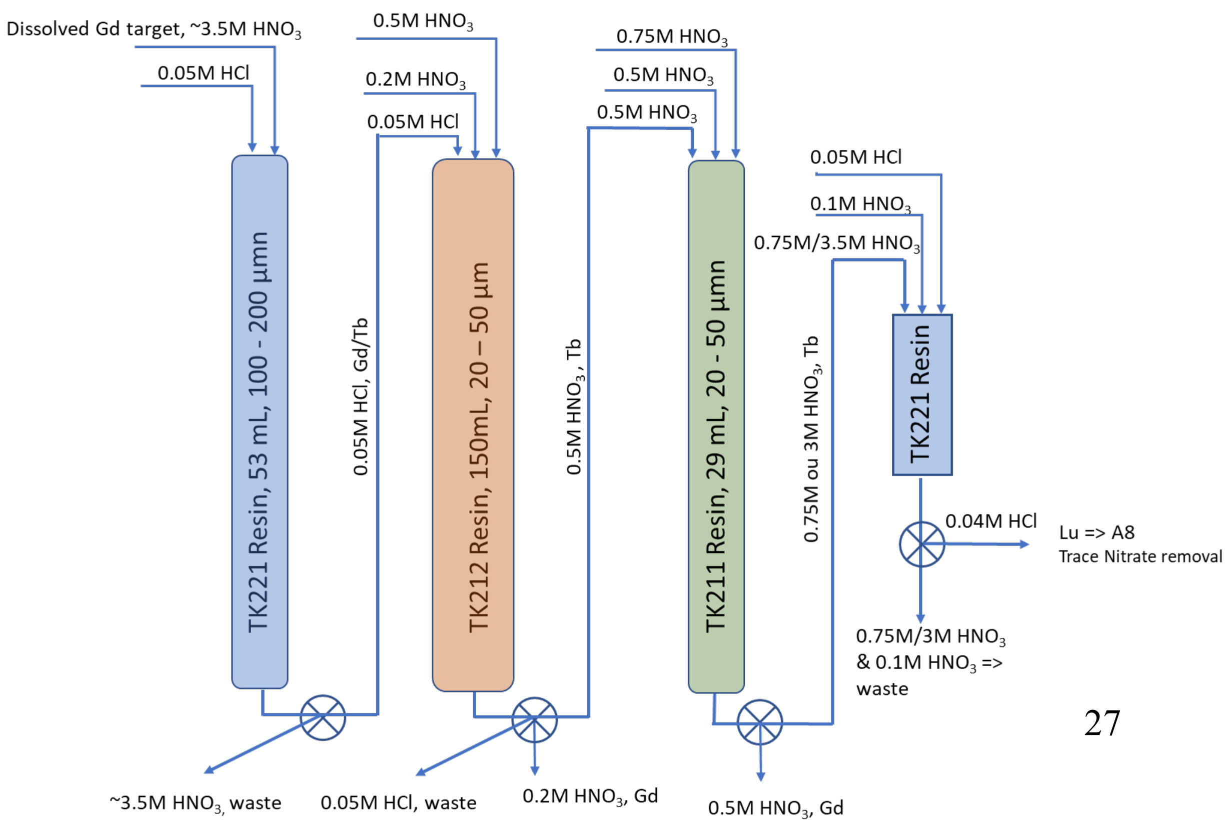
Conversion via TK221 Resin

Sequential separation on TK212/TK211

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

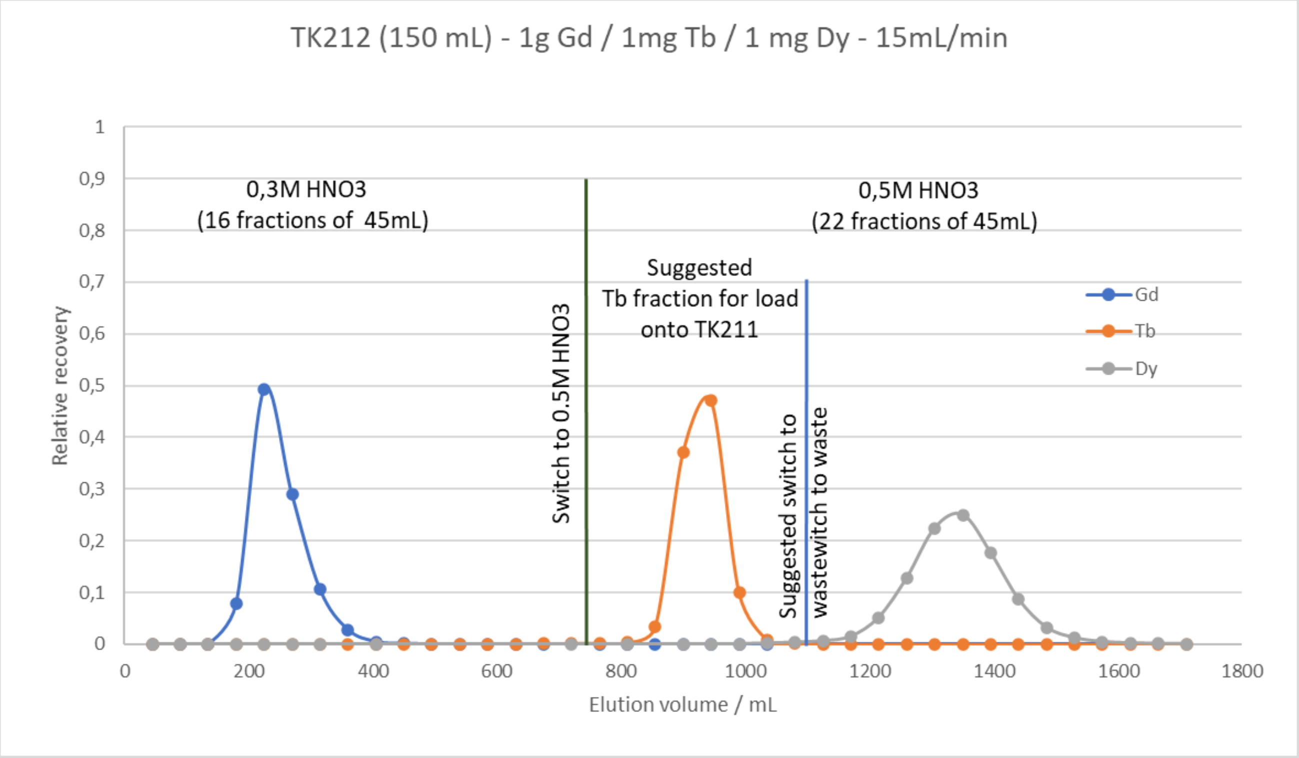
Mainly Tb-161, also Tb-155





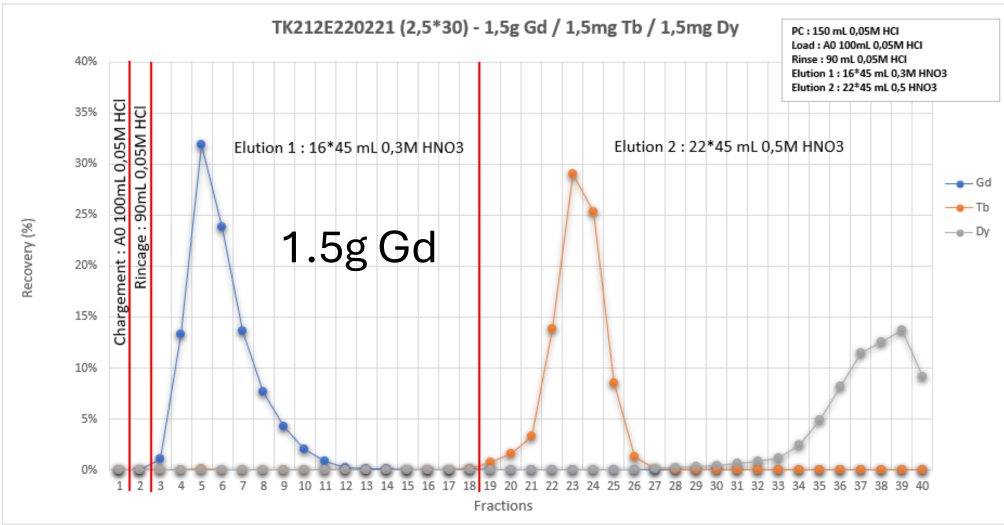
Tb separation from 1000 mg Gd targets

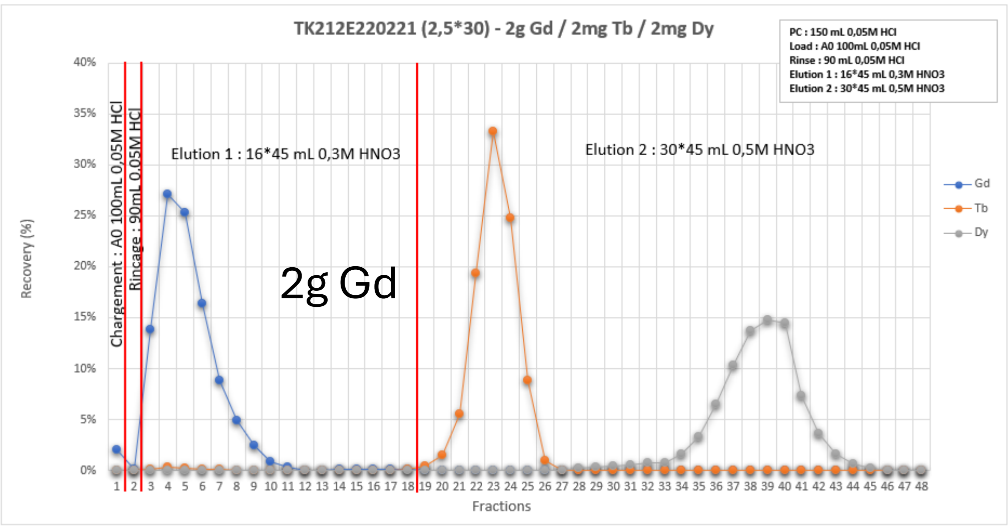
- Initial separation on TK212 – 150 mL column (30cm x 2.5cm)
- Allows for working with up to 2g of Gd
- Gd recovery => very expensive & difficult to find
- Tb separation from Gd and Dy – ideally using online detection
- Fine purification on TK211 (29 mL)

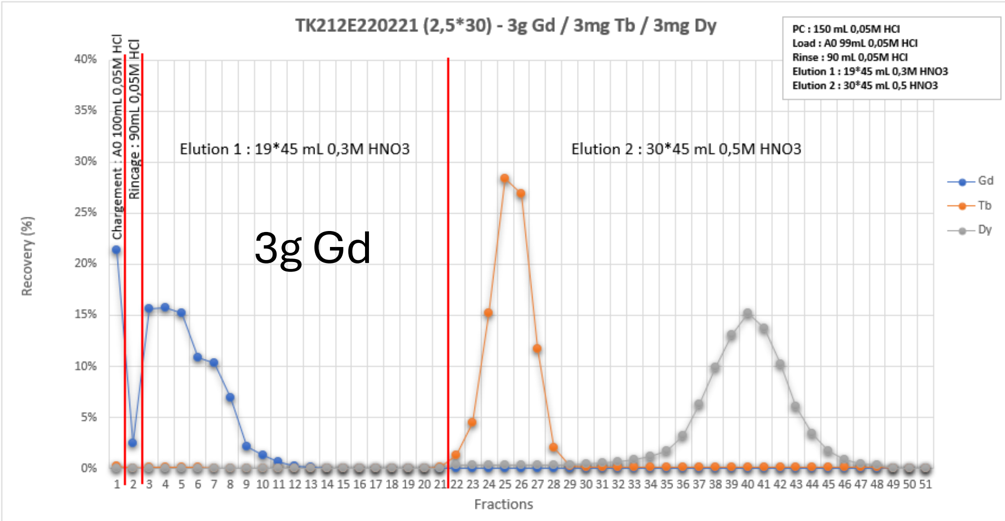


Tb separation from 1000 mg Gd on TK212 (147 mL column)

Increased amounts 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…

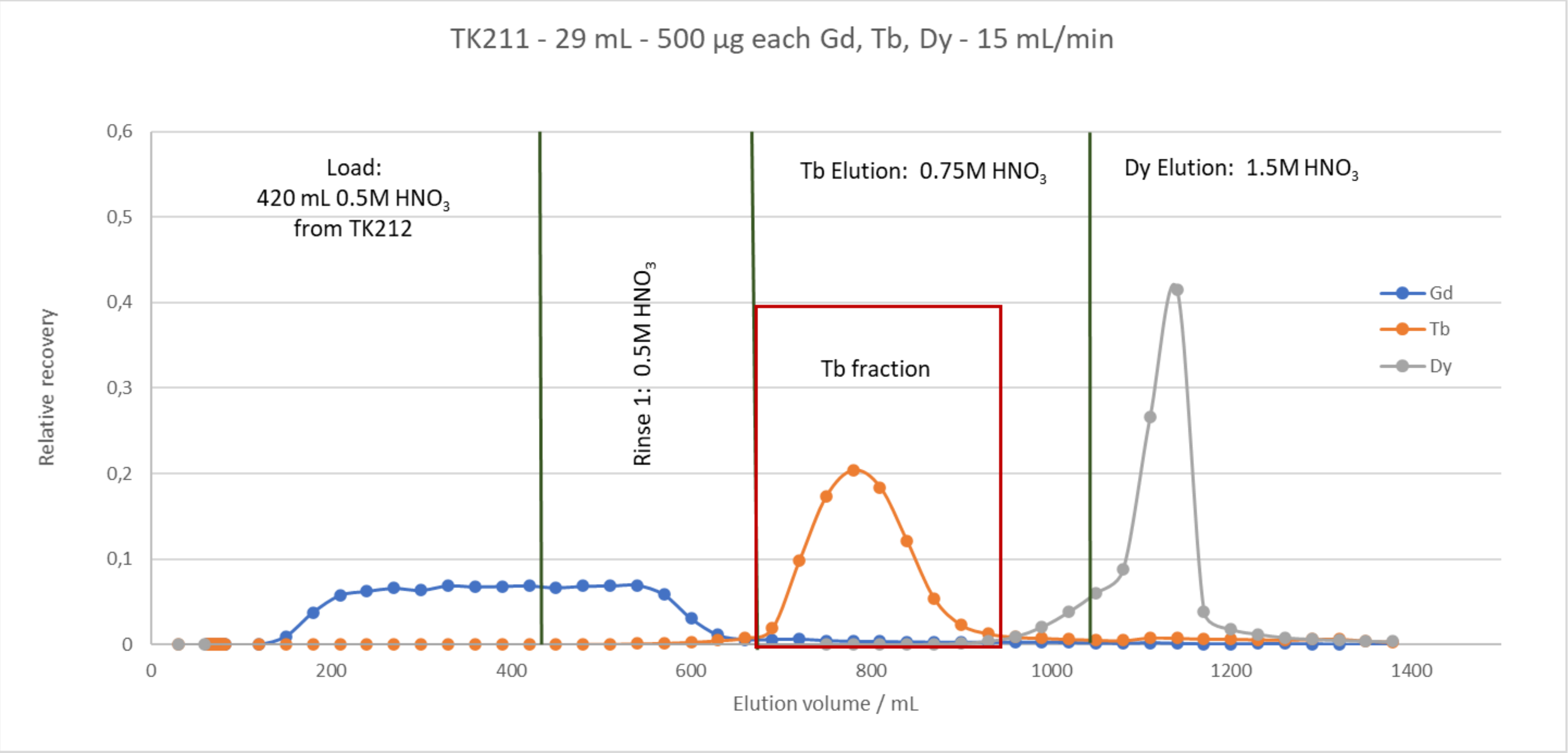
Little effect on Tb

Small impact on Dy

Tb / Dy sepration remains good.

=> Further improvement via EtO addition?

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

TK221 Resin

DGA well suited for ‘conversion’ and purification (Ca, Al, Fe,… removal)

- Convert Lu from high nitric acid to dilute HCl

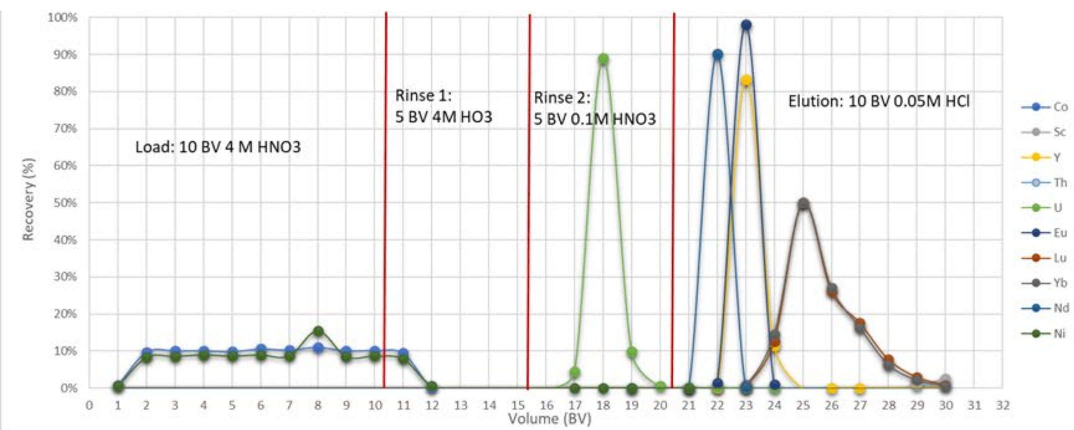
Elution of heavy lanthanides at as low volumes as possible

- small volume prefered => high activity concentration

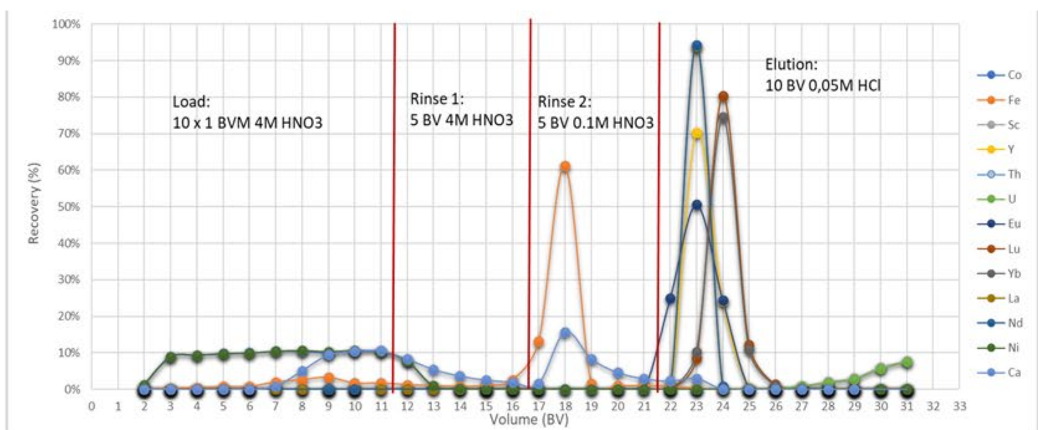
TK221 Resin

- DGA / phosphine-oxide,improved radiolysis stability (inert support, scavanger,…)
- Better La and U retention
- Lu & Tb eluted in small volume in dilute HCl => drawback, no group RE separation possible

DGA Resin



TK221 Resin



- **TK222 Resin => DGA, B/phosphine oxide**

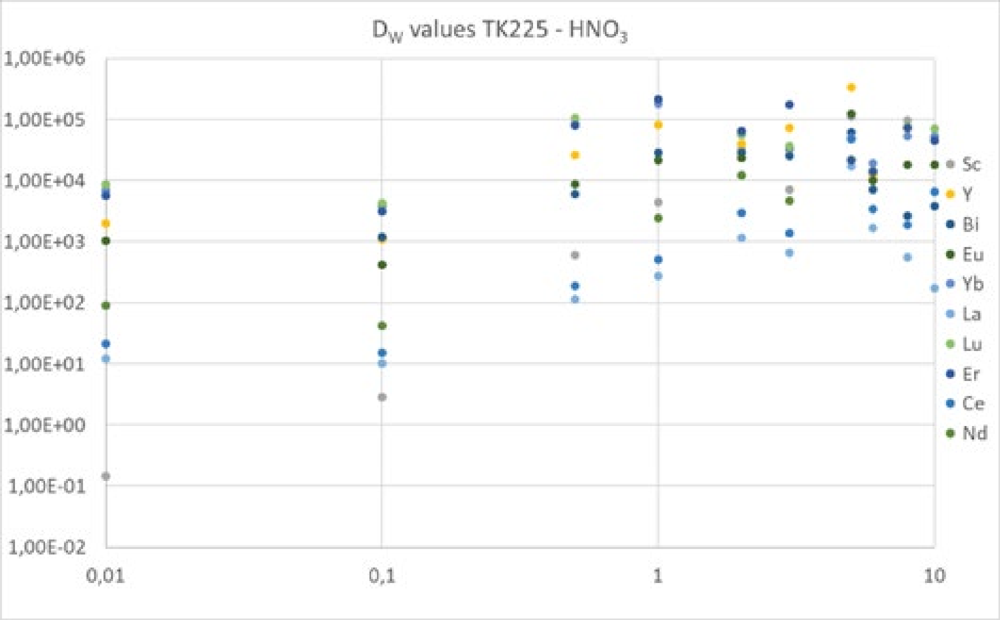
TK225 Resin

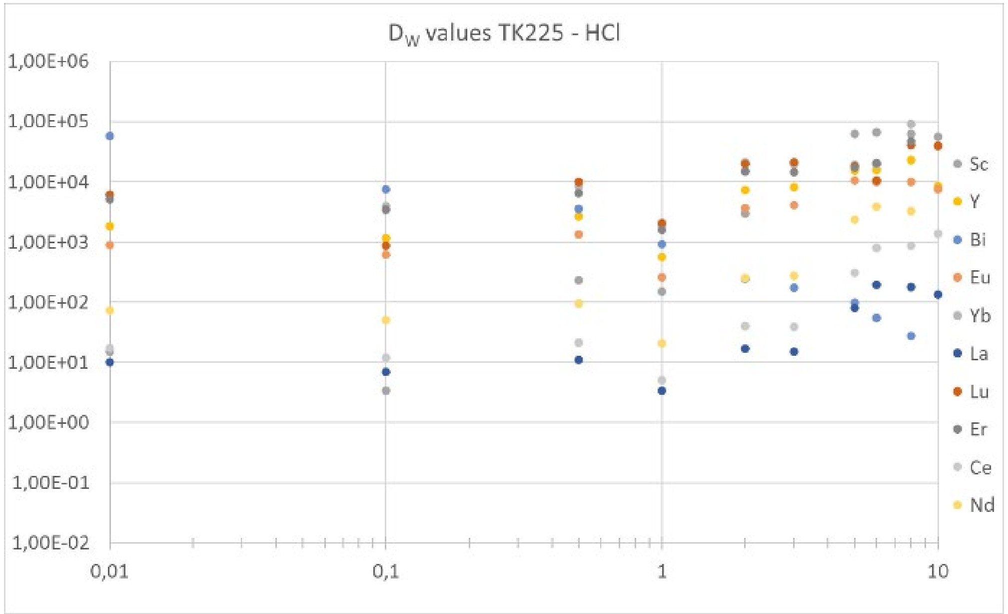
TO-DGA plus ionic liquid => originally failed experiment

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





Ac-225 separation

Ac-225 separation chemistry well established

- DGA (mainly B is used) allows for facile Ac/Ra and La/Ac separation
- Problem: availability of branched and normal DGA Resin
  - Eichrom/Northstar situation & Eichrom/TrisKem contract
  - Imperfect La/Ac separation
  - Radiolysis stability sufficient?

Ongoing beta testing:

- Use of TK221 (TO-DGA / phosphine oxide) or
- TK222 (TEH-DGA / phosphine oxide)
  - Focus on La/Ac separation
  - Ac elution
  - Resalting possible? Ac nitrate => Ac chloride
  - Improved radiolysis stability?

TK221/2 Resins – Ac Dw values

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

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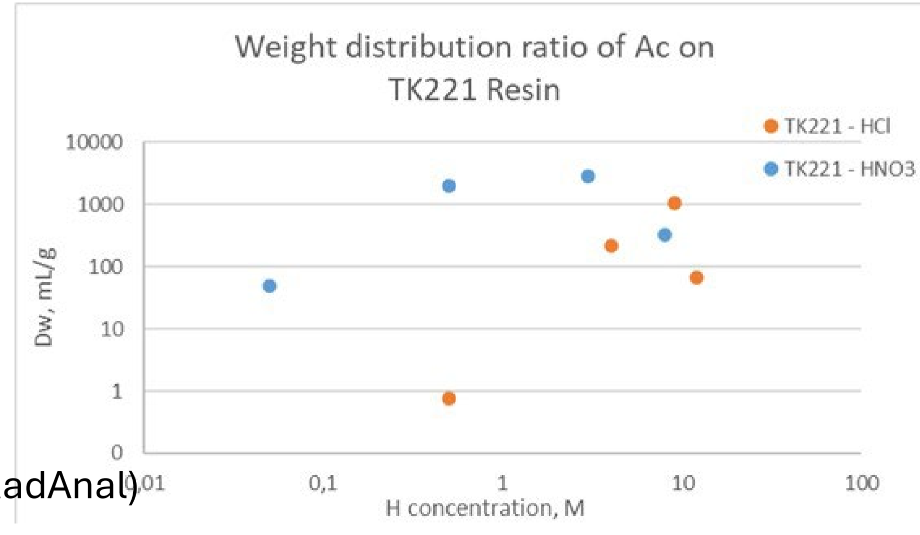


Data courtesy of N. Vajda (RadAnal)

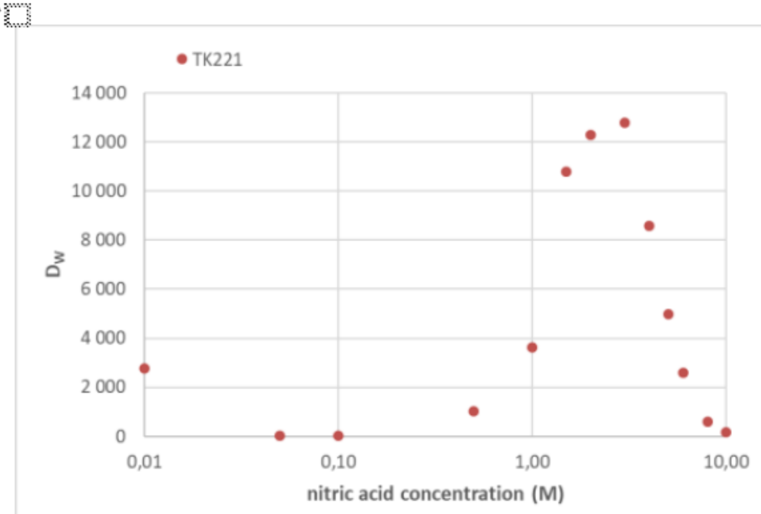


FIG. 1 The D_W values for ^{225}Ac between TK221 and nitric acid

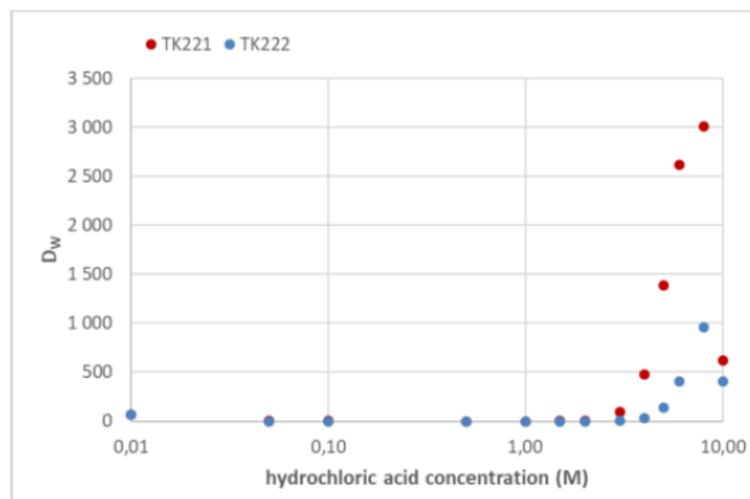


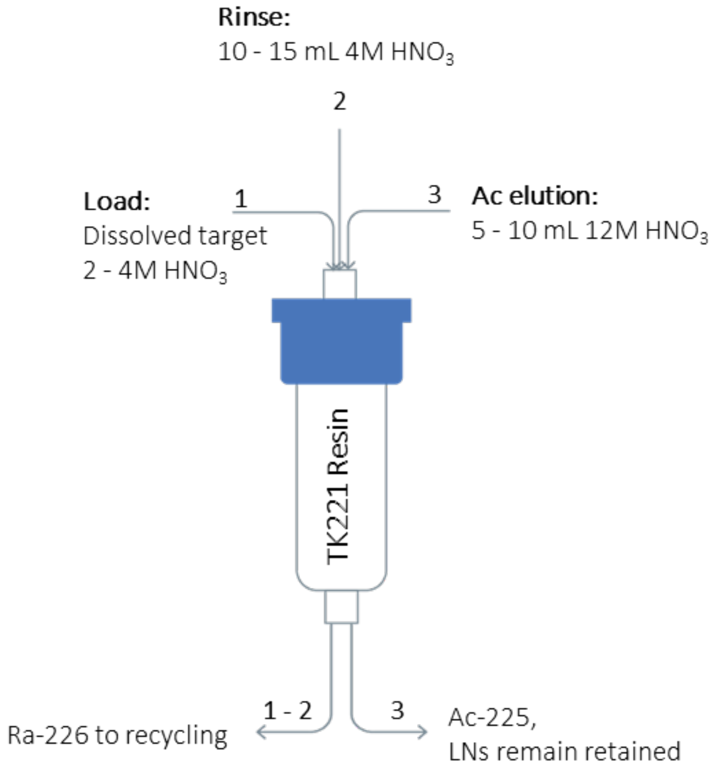
FIG. 2 The D_W values for ^{225}Ac between TK221 and TK222 and hydrochloric acid

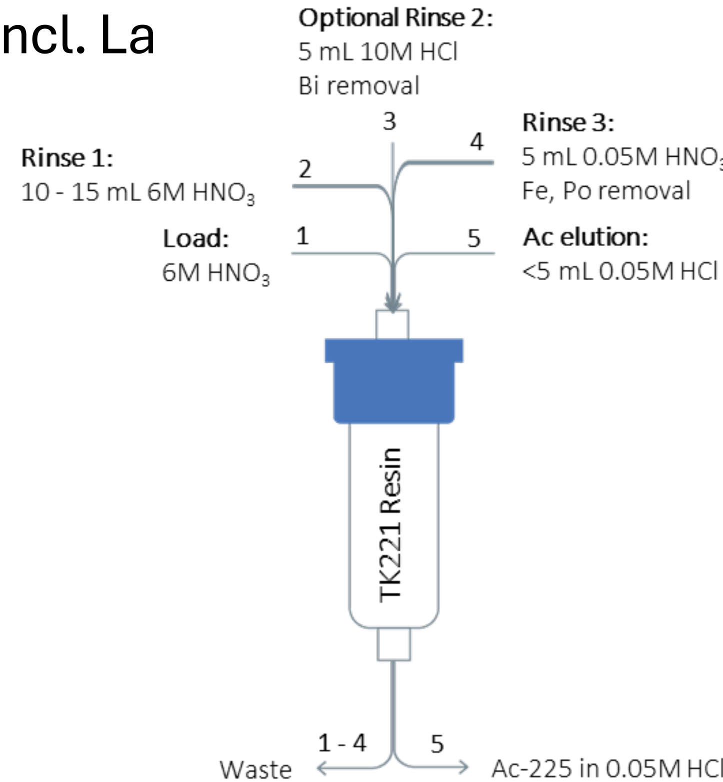
Data courtesy of O. Lebeda (UjV Rez)
Upcoming publication

Ac-225 separation

Two TK221 cartridges for removal of impurities incl. La

- In case La can be excluded step 2 only

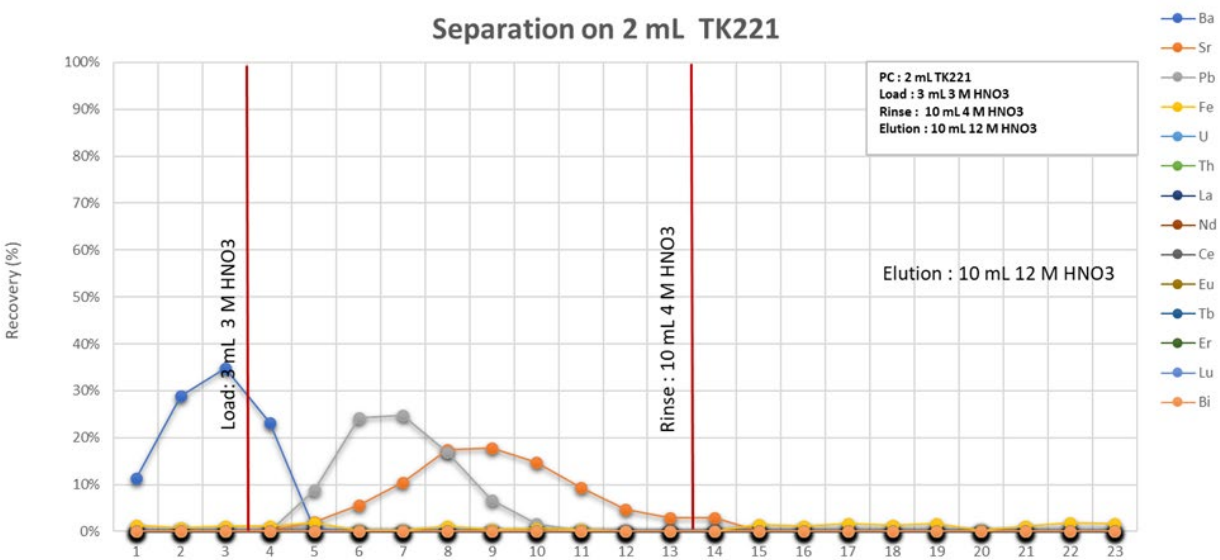


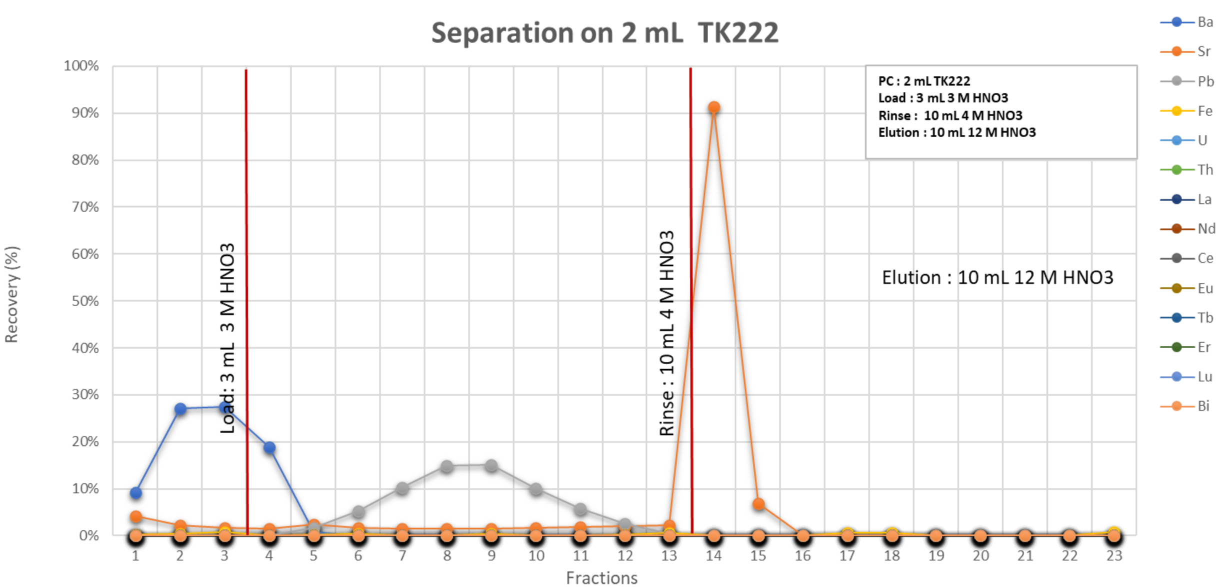


Step 1 TK221:
Target dissolved in 2 – 4M HNO_3
Ra, Ba, Pb, Sr,… removal with 4M HNO_3
Ac elution in 14M HNO_3 (LNs retained)

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

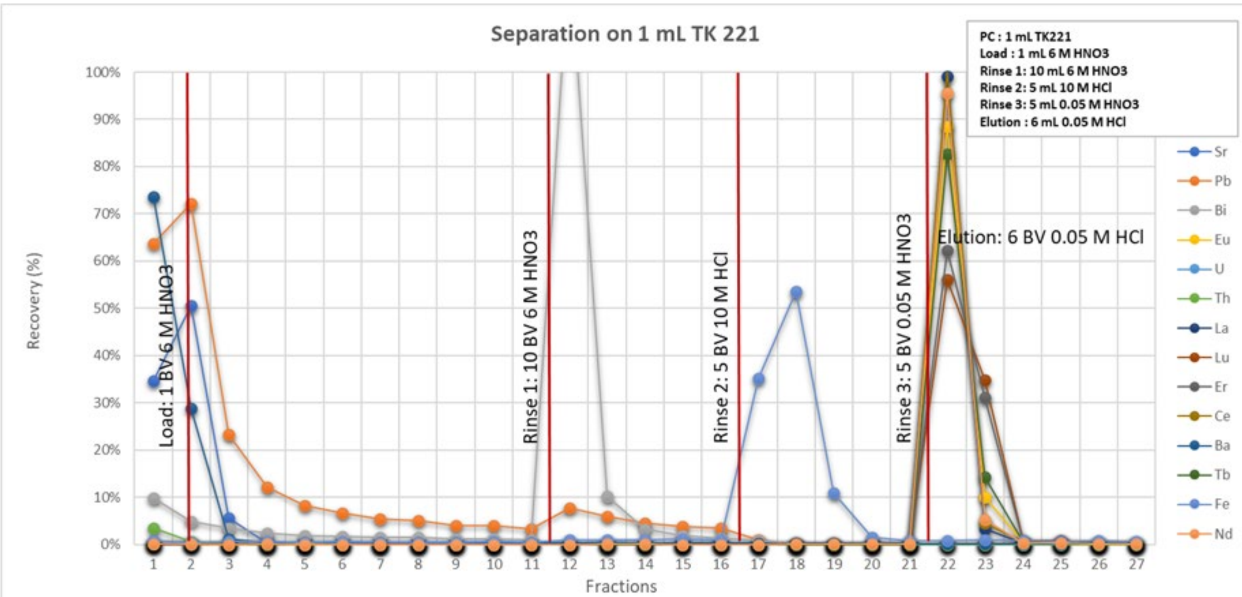
- Load from elevated HNO_3
- Ac elution in very high HNO_3
- LNs, U, Th retained
- Particular attention to Pb/Sr
  - Elution in 4M HNO_3

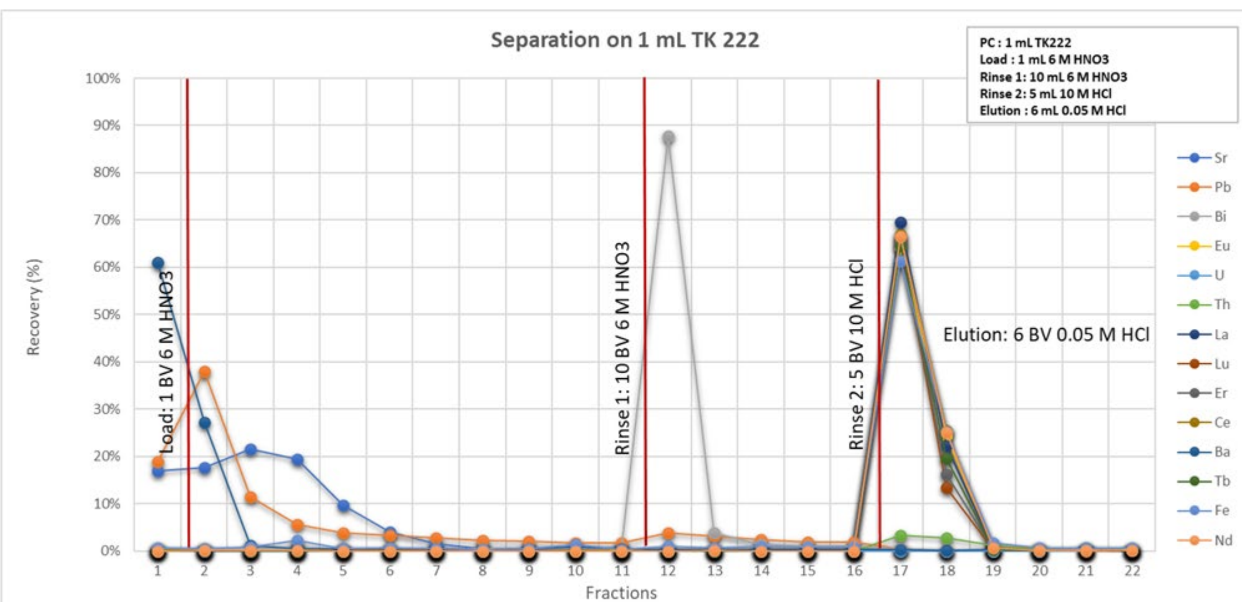
TK222

- 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

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)
  - Additional purification on TK101 possible (Ra, Ba, Pb, Sr)
- 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 elution from TK221 and TK222

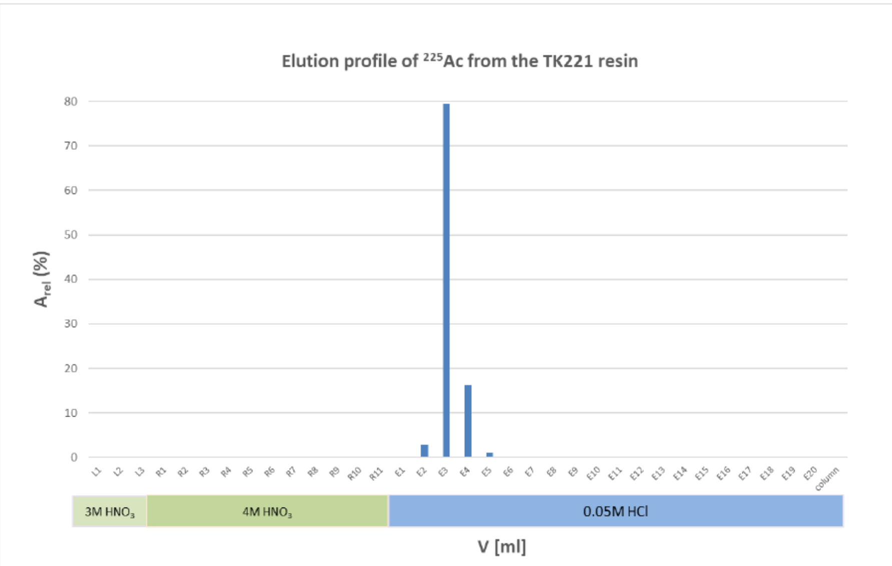


FIG. 3 Elution profile of ^{225}Ac loaded on the TK221 column in 3M nitric acid, rinsed with 4M nitric acid and eluted into 0.05M hydrochloric acid

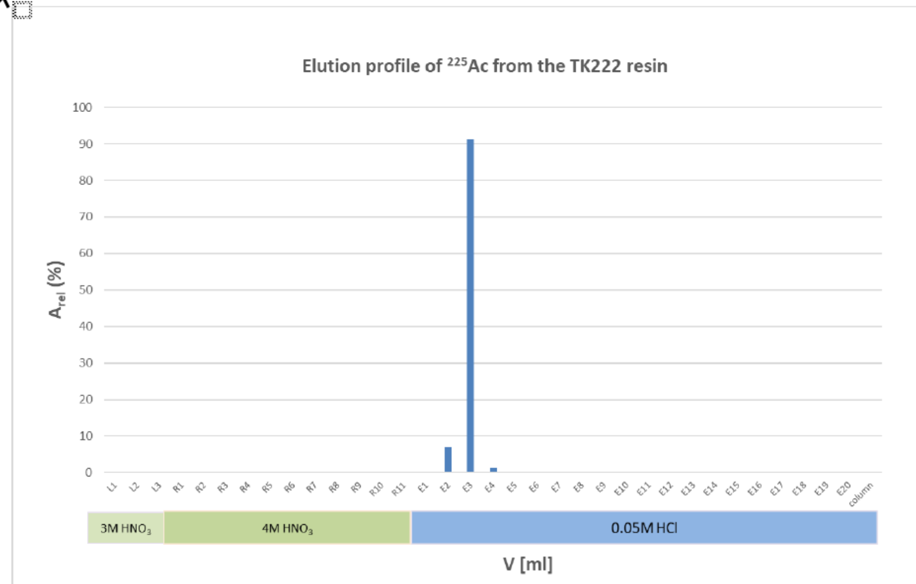


FIG. 4 Elution profile of ^{225}Ac loaded on the TK222 column in 3M nitric acid, rinsed with 4M nitric acid and eluted into 0.05M hydrochloric acid

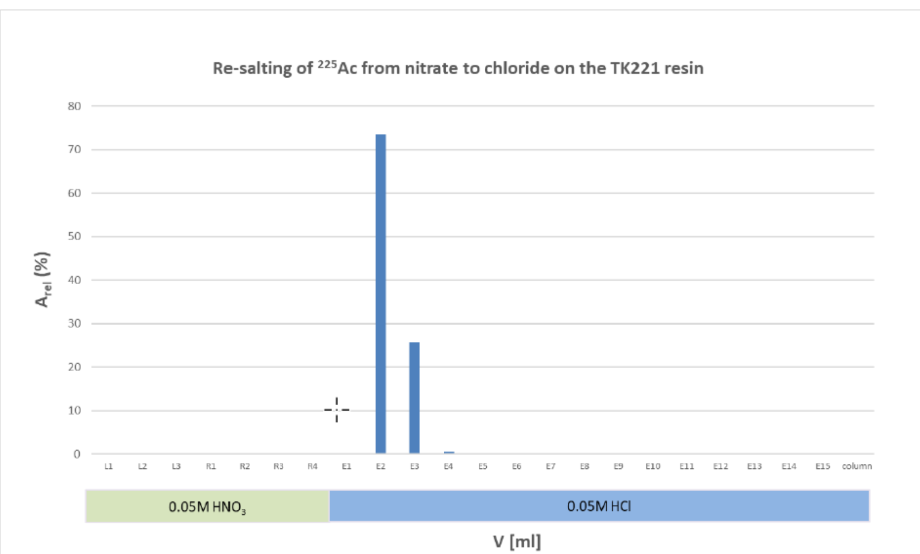


FIG. 5 Re-salting of ^{225}Ac loaded on the TK221 column in 0.05M nitric acid and eluted into 0.05M hydrochloric acid

- 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

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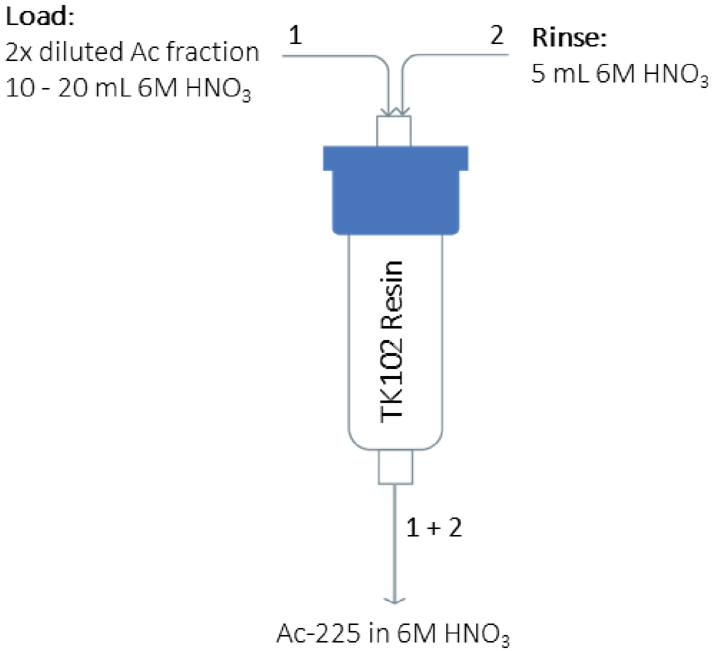
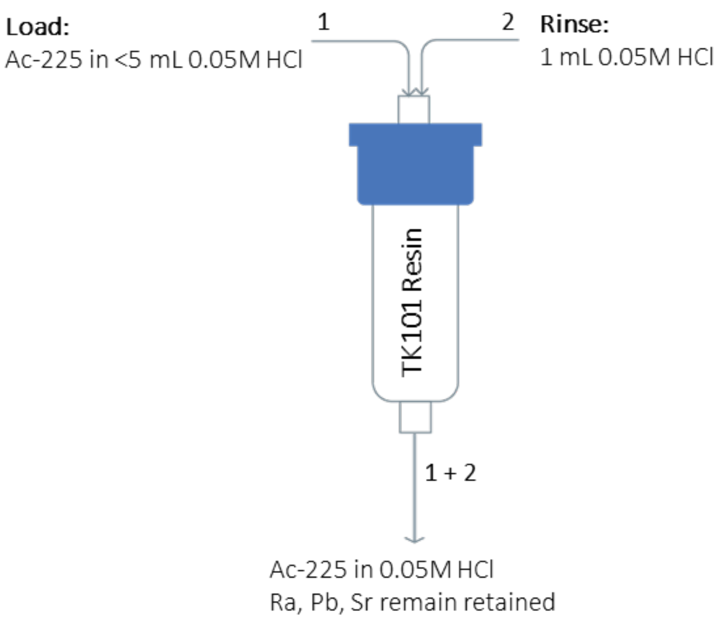
Ac-225 separation – Optional additional purification

Optional:
Pb removal on TK102



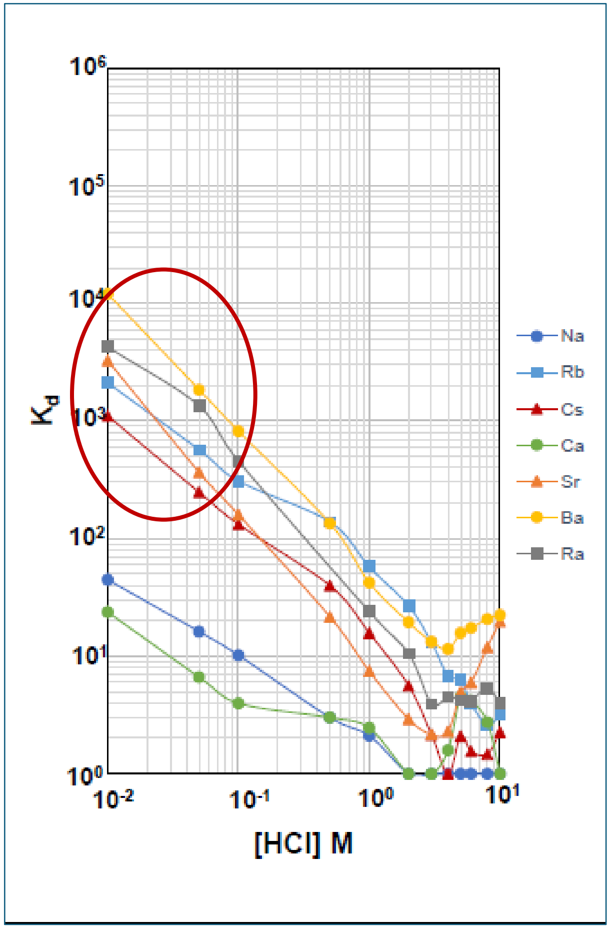
Optional:
Ra, Pb, Sr, Ba removal on TK101

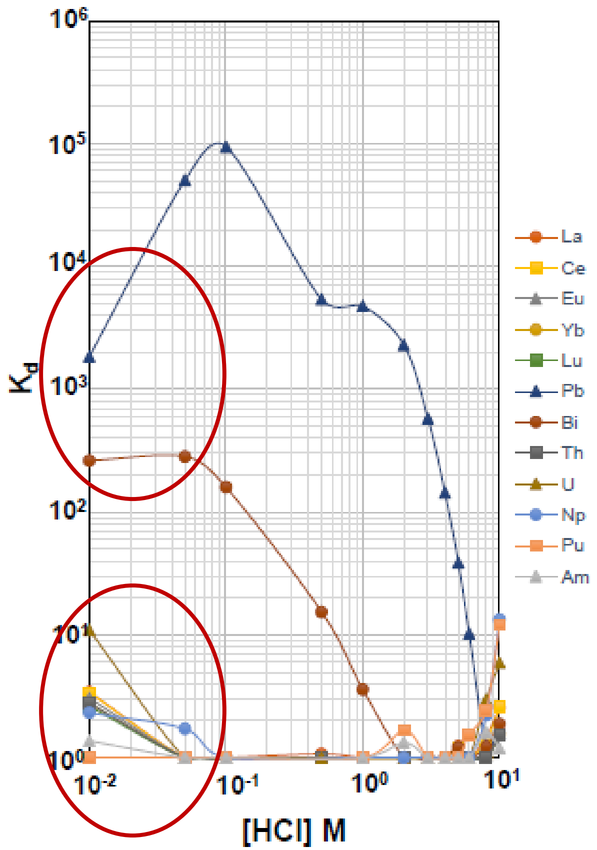


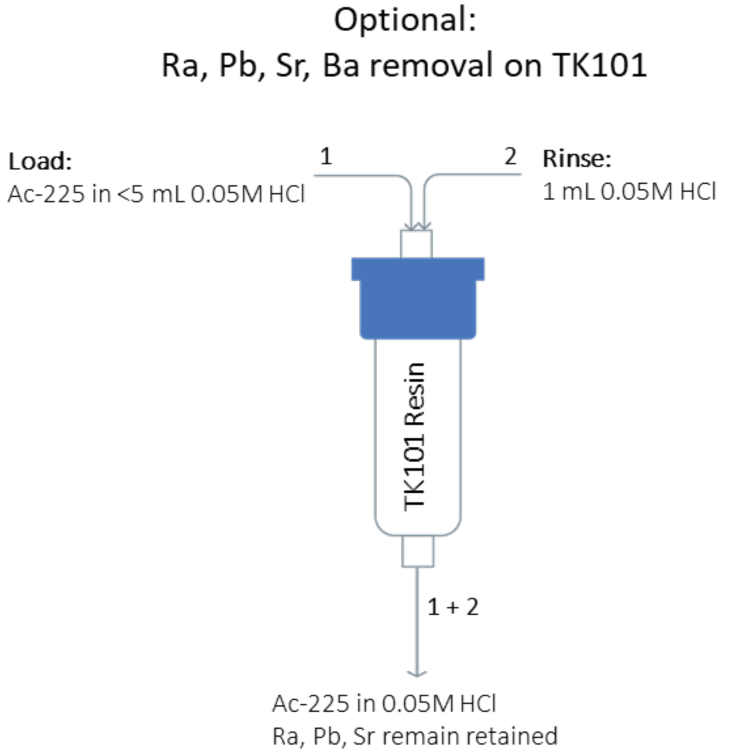
Optional Pb removal step (TK102)
Eluate of step 1 dilute by x2
Load through TK102
Pb and Sr retained, Ac passes through

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

Optional: TK101 purification step







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

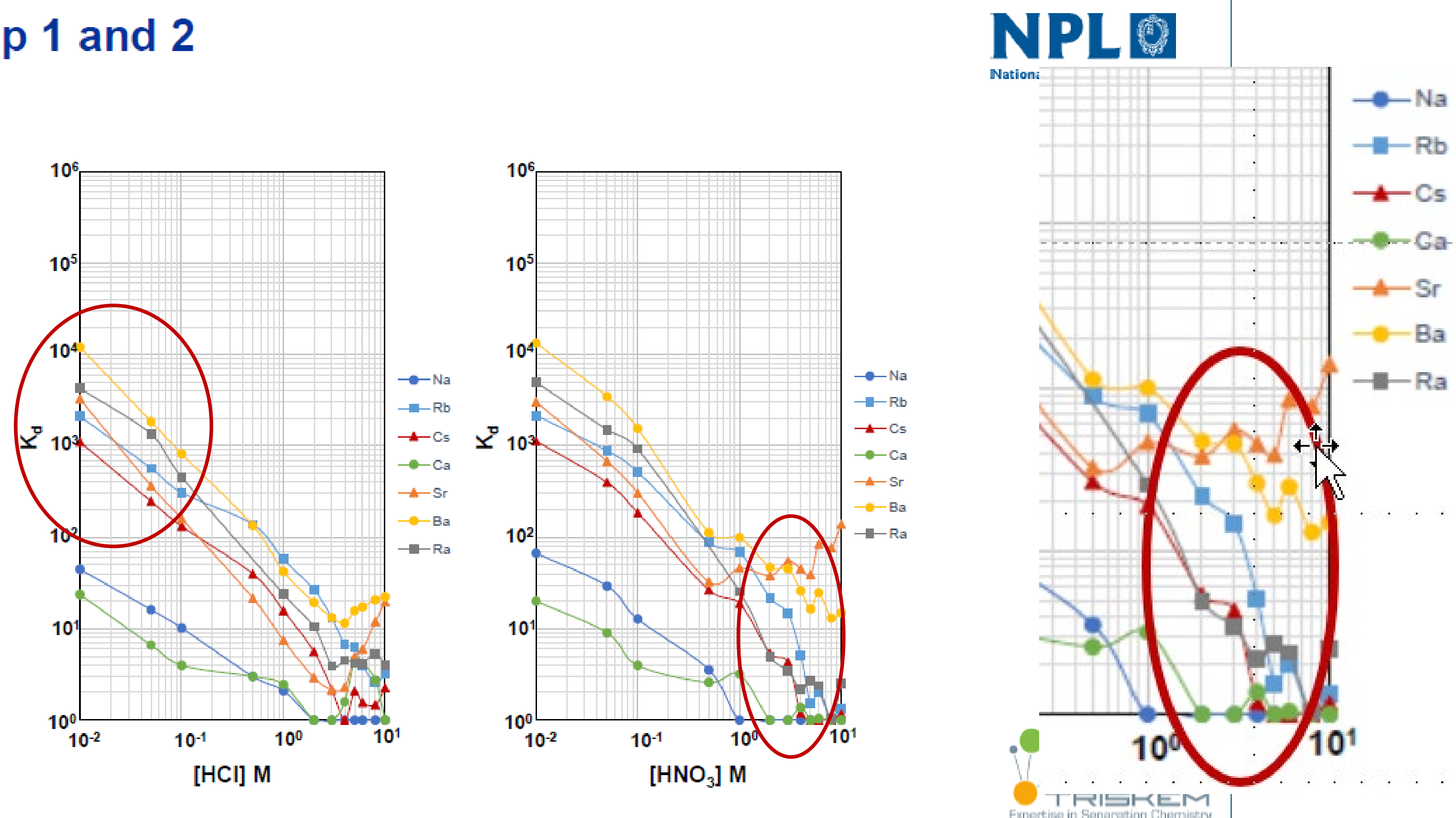
=> Load onto TK101 for purification

Alternatively: dissolution in EDTA solution

=> TK101 allows for Ra extraction from EDTA at pH 4

TK101 - Radium

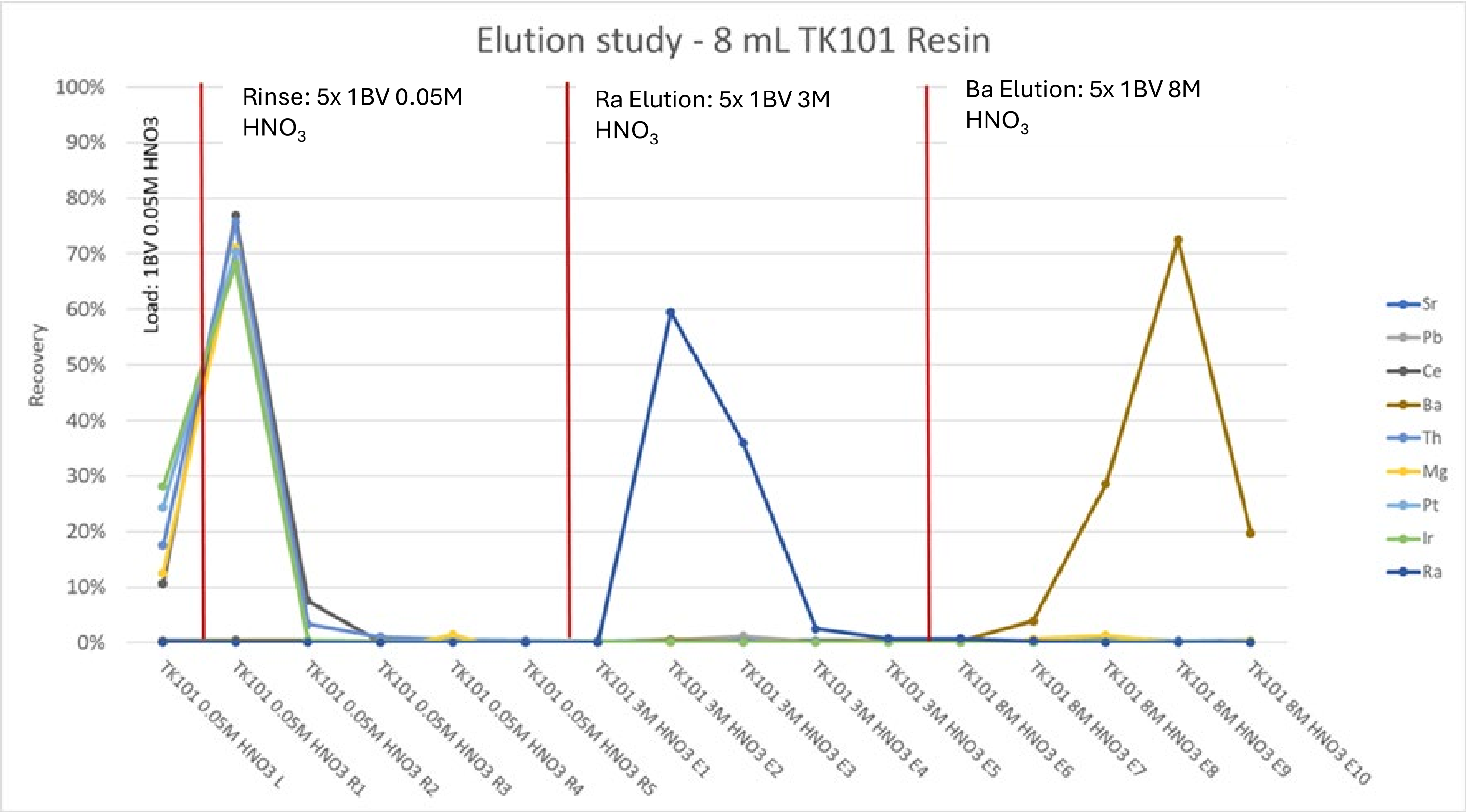
TK101 Group 1 and 2



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

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,...

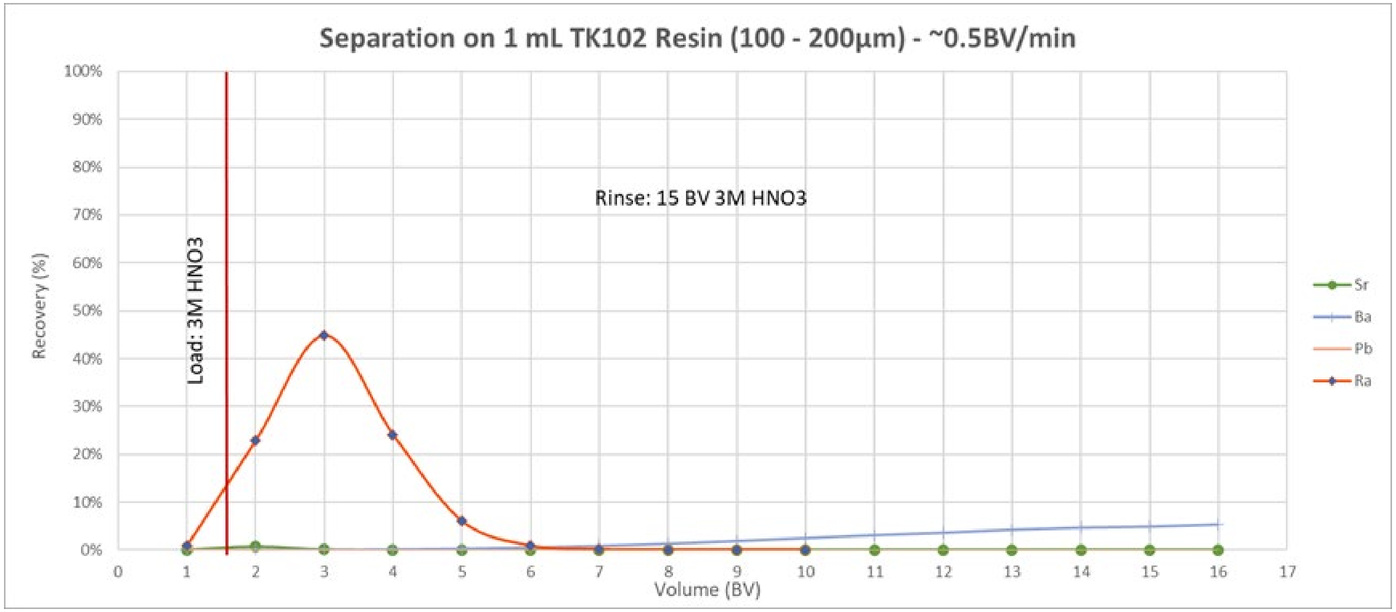
Bi partially retained from 0.05M HNO_3/HCl

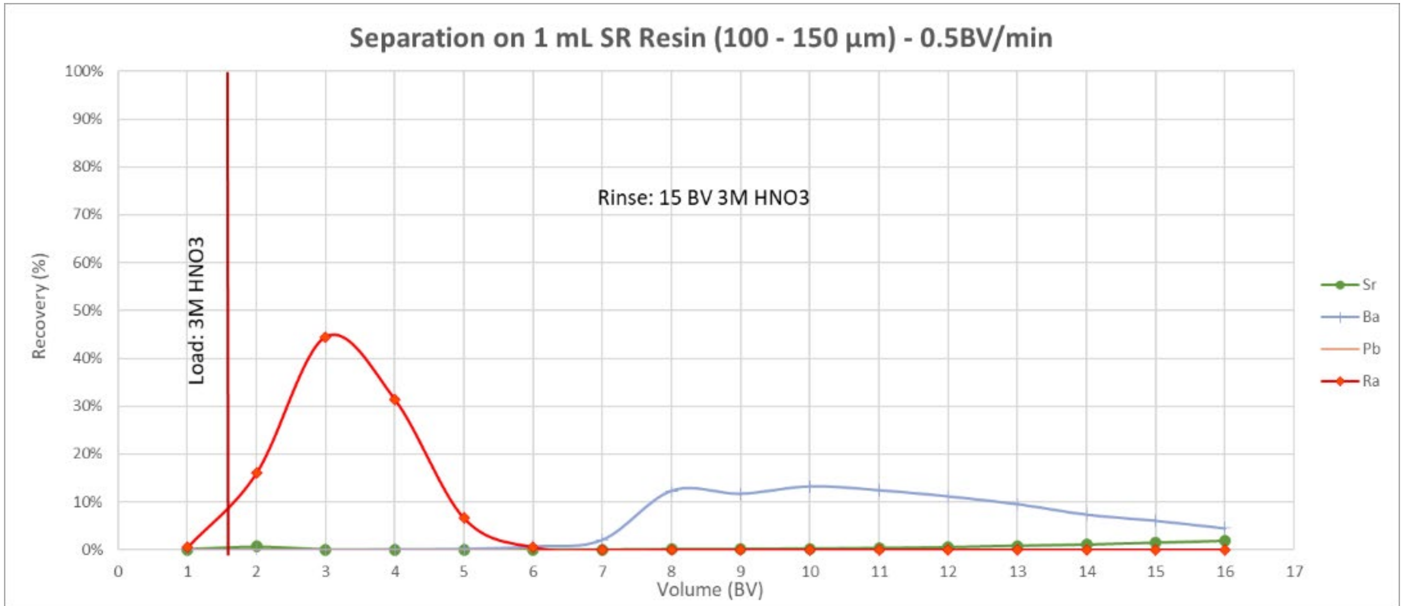
Ra eluted in 3M HNO_3

Further Ba removal via TK102 possible

Tl and Ba eluted in 8M HNO_3

TK102 - Ra purification / recycling





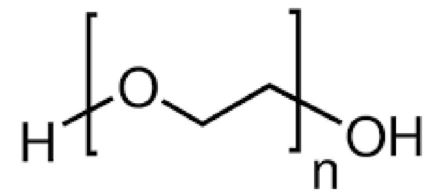
- SR Resin: high Ba breakthrough starts after 7 – 8 bed volumes
- TK102 Resin: significantly lower Ba breakthrough
- TK102 shows less bleeding than SR Resin

Tc-99m - TK202 Resin

Based on Polyethylene Glycol (PEG)

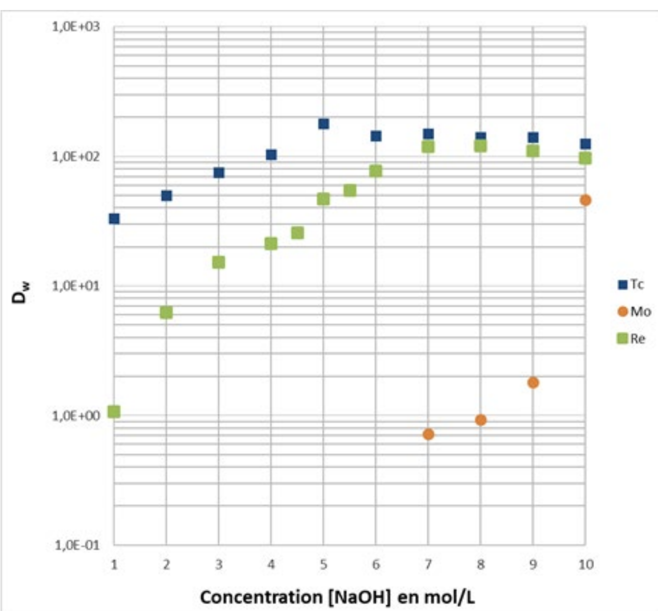
Less swelling/shrinking than crosslinked PEG

Aqueous Biphasic System (ABS)

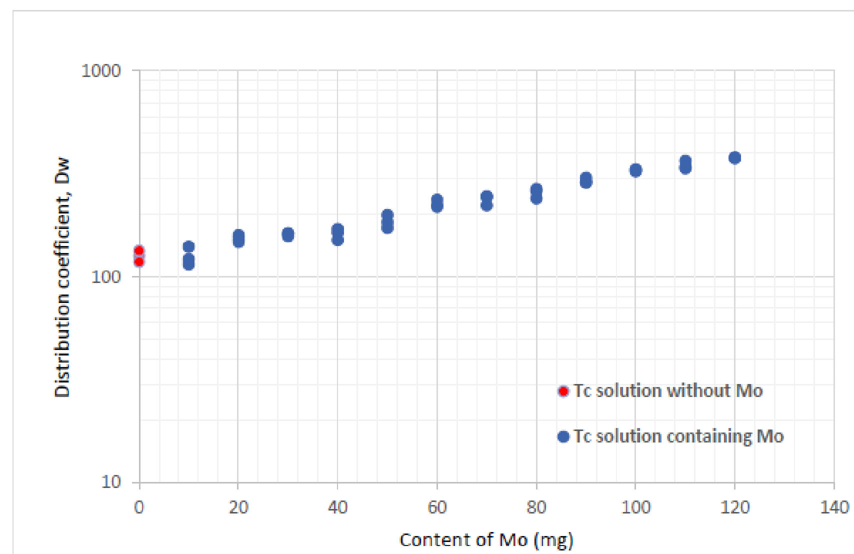


Retention of chaotrophic anions like TcO_4^- in presence of kosmotrophic anions (SO_4^{2-}, CO_3^{2-}, OH^-, MoO_4^{2-},…)

- Separation of Tc-99m from high masses of Mo
- Separation of Re from W (and Ta) possible, too

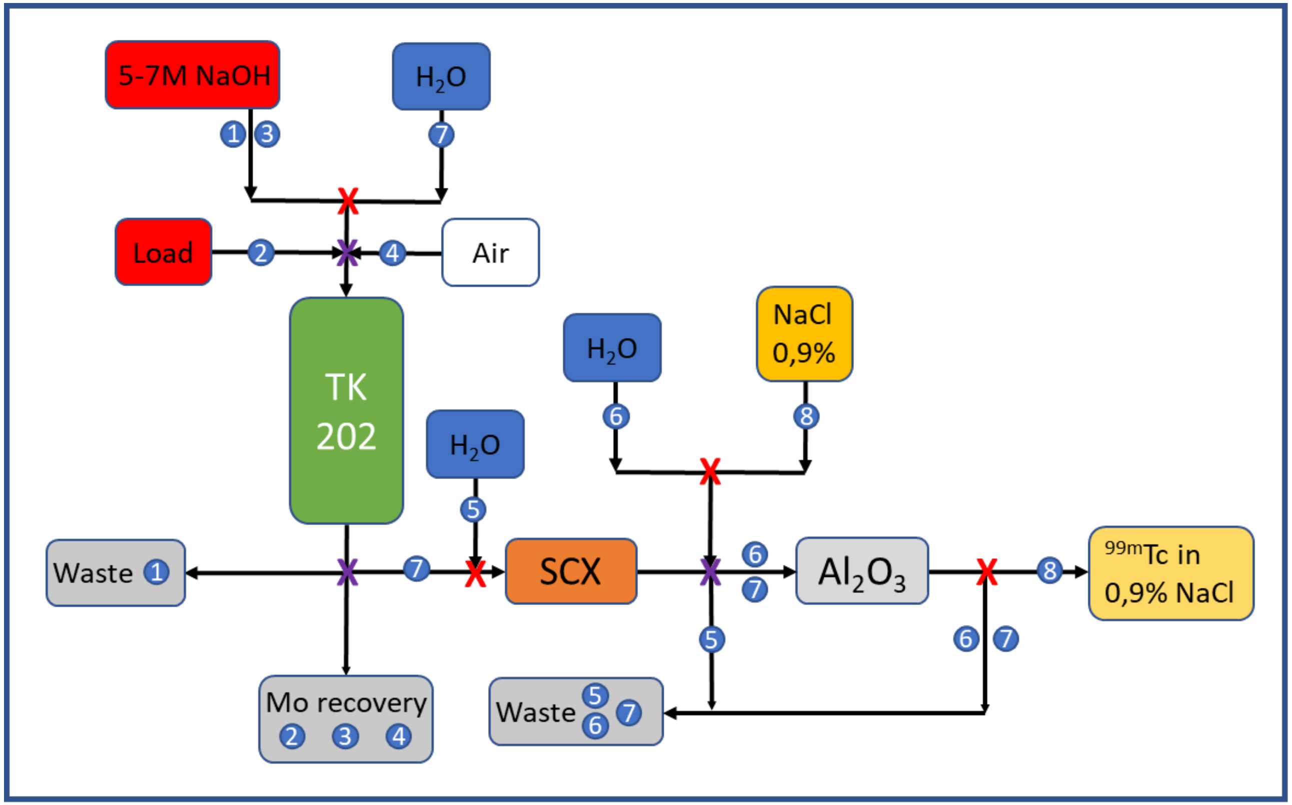


Dw values for Tc, Re and Mo on TK202 Resin, at varying NaOH concentrations. Tc data taken from Cieszykowska et al.(2).



Dw values for Tc in 5M NaOH using 40 mg TK202 Resin, increasing amounts of Mo. Data taken from Cieszykowska et

Tc-99m separation from Mo targets – suggested scheme (similar to Zeisler et al.)



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

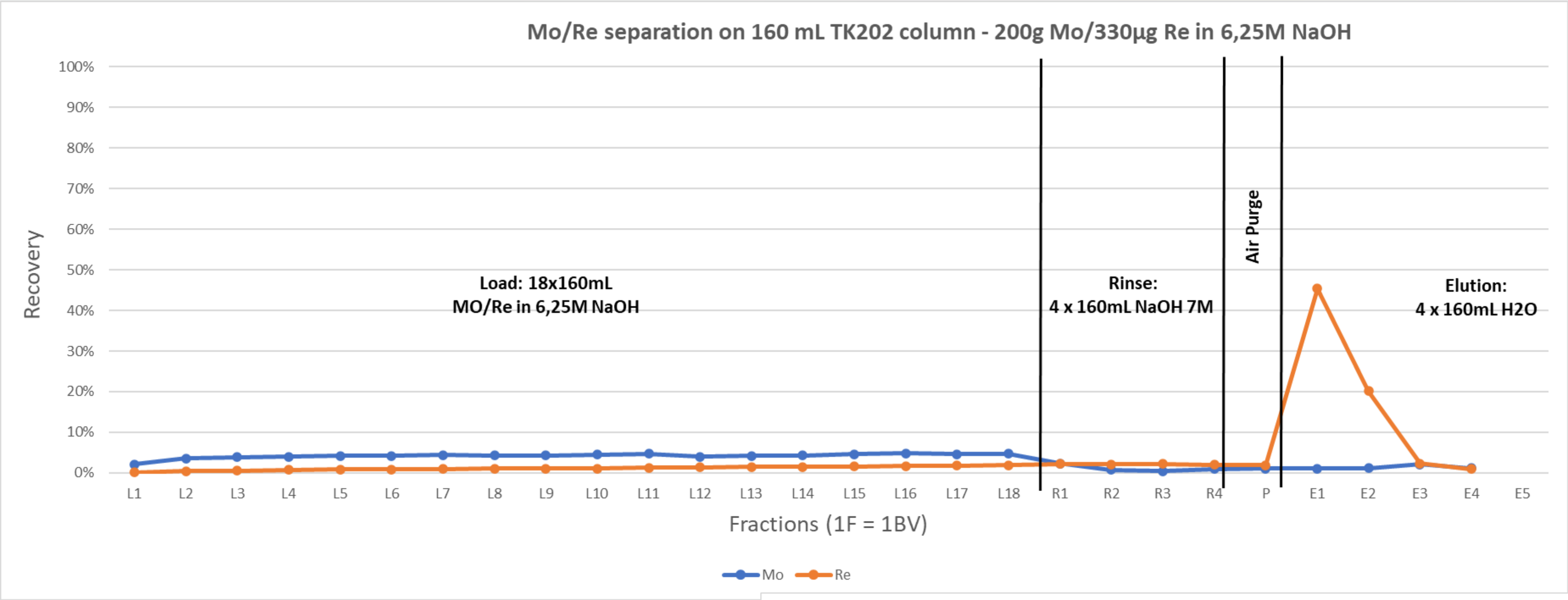
TK202 : 35-75 or 75-150µm
X : 3-ways valve
X : 4-ways valve
SCX : Strong Cation Exchange
Al_2O_3 : Acidic Alumina

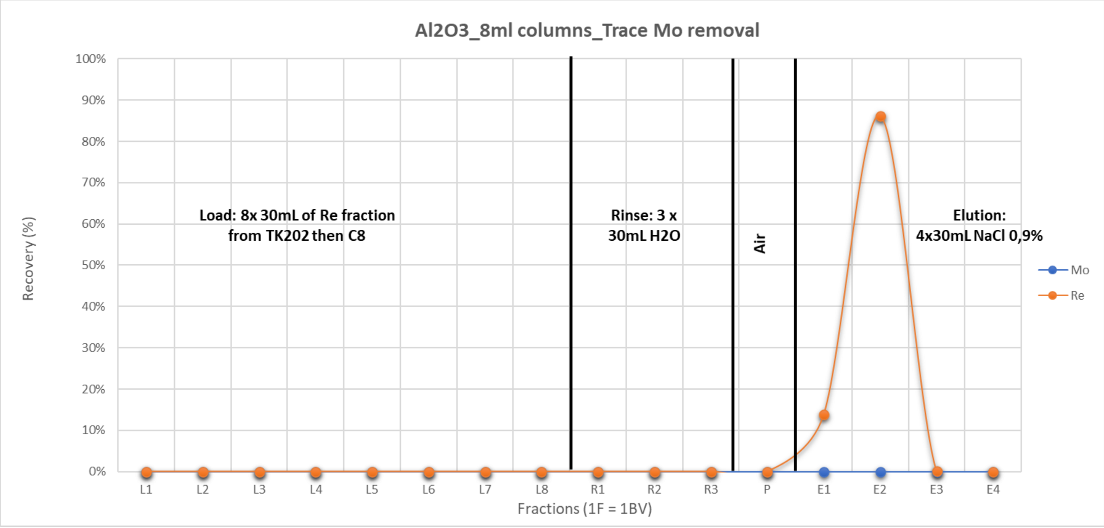
Developed with ReO_4^- as TcO_4^- surrogate

Re recovered on saline solution from alkaline

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

Tc-99m from large Mo targets





Test with 200g Mo

~160 mL TK202 column

Load from 6 - 7M NaOH - elution in water

Pass through C8 cartridge for acidification and Na removal

Final concentration/conversion to 0.9% NaCl on 8 mL AlOxA cartridge

DGA Sheets

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

- Developed at CVUT (Kozempel et al.)

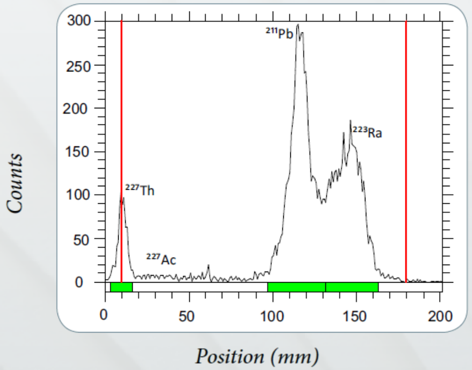
QC of radionuclides and generator eluents

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

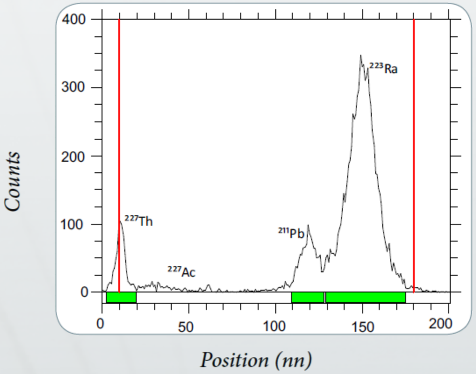
- TLC scanner or radiometer/LSC or HPGe after cutting

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)

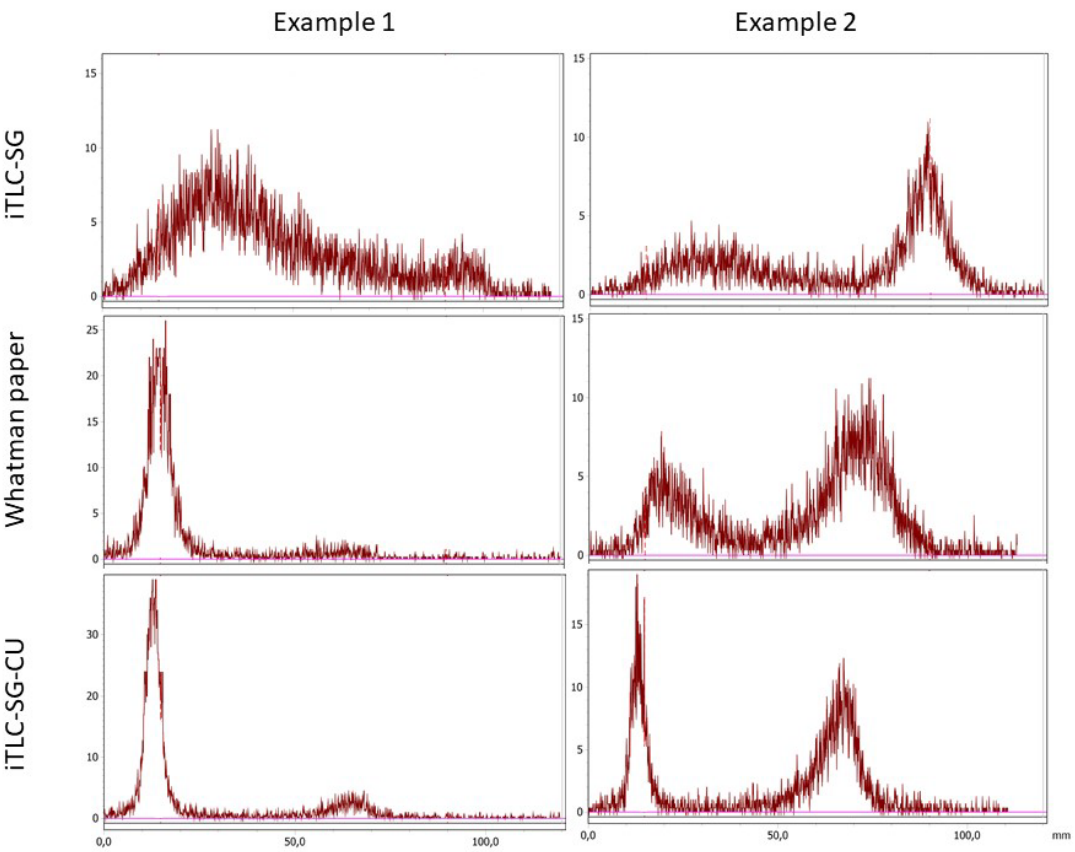
- Shown: [^{61}Cu]Cu-NOTA-octreotide

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, Whatmn took 25 – 30 min.

CU extractant impregnated iTLC paper showed superior resolution



- Other systems under development/testing

Some other on-going projects

- Ac rapid purification and ‘resalting’ via TK222, TK221
- Improvement of radiolysis stability
- Additional ‘Sheets’
- Further upscale of radiolanthanide separations
- Scandium separation
  - TK200, TK221, TK222
- Improved Cu separation
- Other radiometals
  - Mn, V, In, Auger (Sb, Pd, Hg, Ag,…)
- At separation
  - TK400, Rn-211/At-211 generator,…
- Decontamination
  - Effluents and reaction wastes
- Fate’ of RN in the environment
  - Separation methods
  - Mainly longer lived RN (=> therapy)
    - Ac-225/7, Lu-177(m), radioiodine,…
  - Quantification

Thank you for your attention!

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