TrisKem International

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

TKI Workshop at RRMC 2022

Steffen Happel
03/11/2022

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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
  - Ti-44/5 from Sc 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
- Ac-225
- Ra-226
- Tc-99m from Mo
- CL Resin
- Quality Control – Sheets
- Other on-going R&D

Nuclear Medicine / Radiopharmacy

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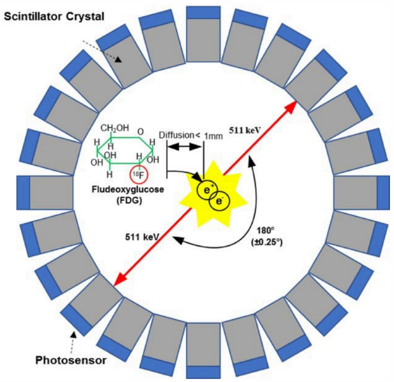
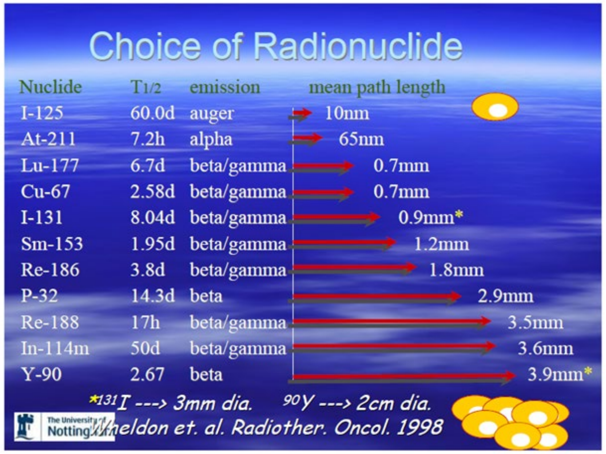
- Use of radioactivity for imaging and treatment
  - Internalisation of radionuclides and distribution in the body
  - Accumulation e.g. in cancer cells
    - Imaging: PET (e.g. ^{18}F-FDG) and SPECT (e.g. Tc-99m)
    - Treatment: I-131 for Thyroid cancer
  - Iodine => first theranostic system (Saul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



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



Choice of Radionuclide

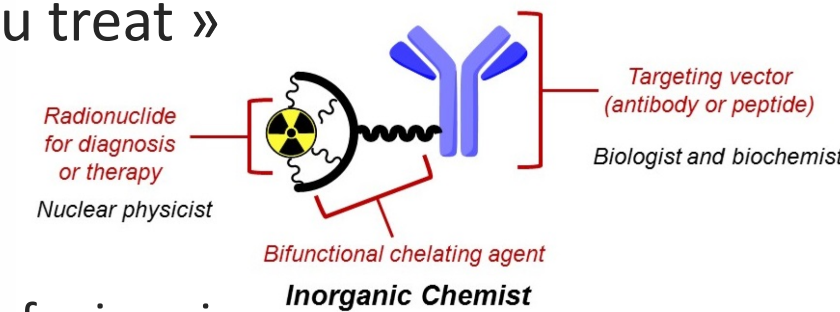
Nuclide	$T_{1/2}$	emission	mean path length
I-125	60.0d	auger	10nm
At-211	7.2h	alpha	65nm
Lu-177	6.7d	beta/gamma	0.7mm
Cu-67	2.58d	beta/gamma	0.7mm
I-131	8.04d	beta/gamma	0.9mm*
Sm-153	1.95d	beta/gamma	1.2mm
Re-186	3.8d	beta/gamma	1.8mm
P-32	14.3d	beta	2.9mm
Re-188	17h	beta/gamma	3.5mm
In-114m	50d	beta/gamma	3.6mm
Y-90	2.67	beta	3.9mm*

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

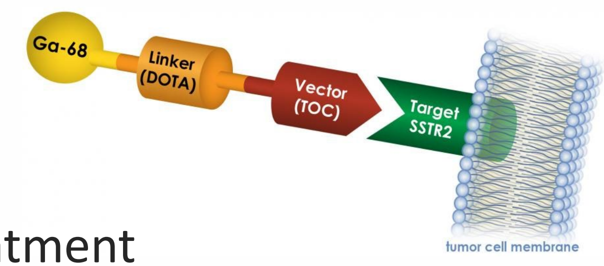
Wheldon et. al. Radiother. Oncol. 1998

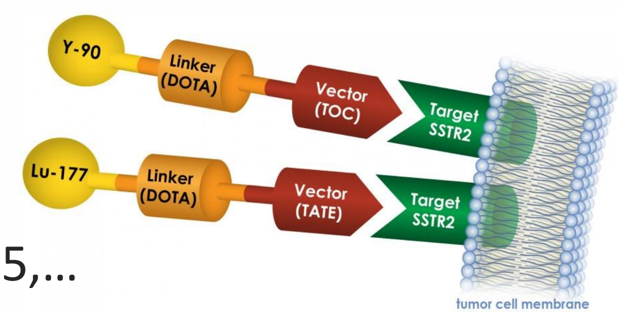
Thera(g)nostics

- « Treat what you see and see what you treat »
  - 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-61/4/7, Sc-44/7, Tb, Pb,…
  - Other theranostic pairs: Ga-68/Lu-177, Ga-68/Ac-225,…
    - Sufficiently similar chemistry



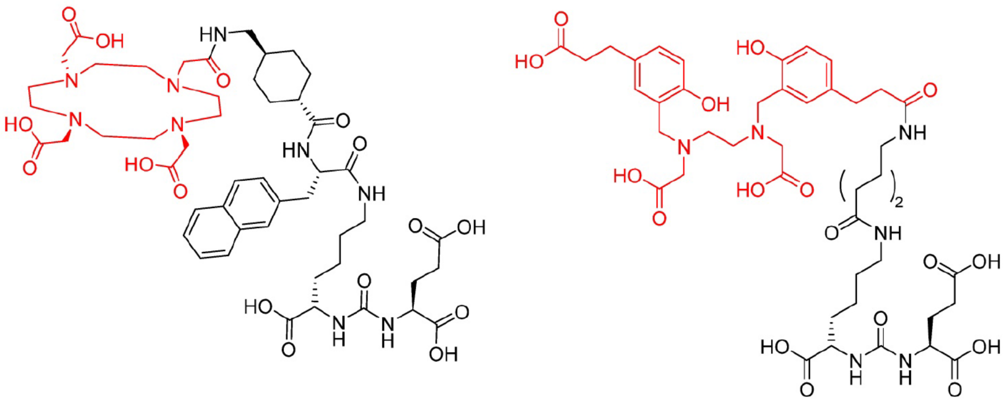
Source: https://wilson.chem.cornell.edu/research/





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

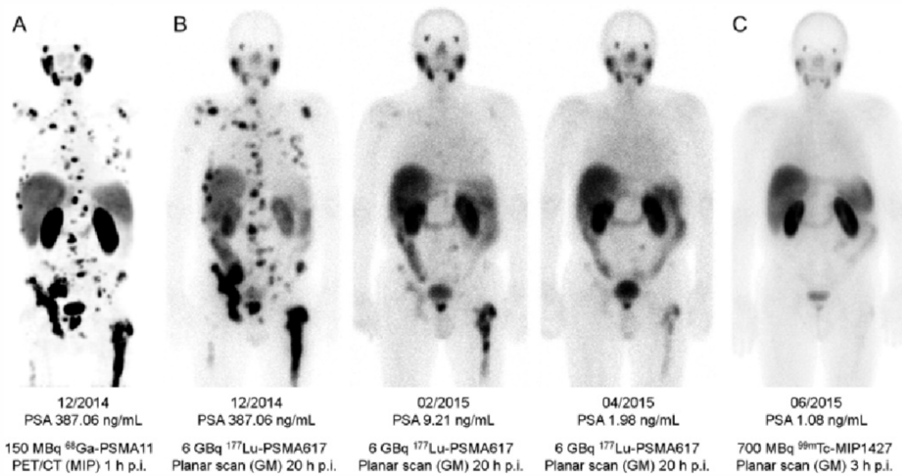
Most promising systems: PSMA & FAPI



(a) (b)

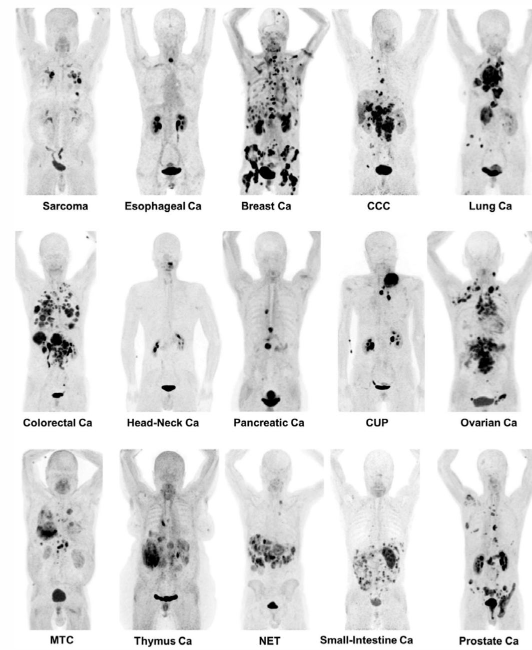
Figure 1. Structures of (a) PSMA-617 and (b) PSMA-11.

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



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

- 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

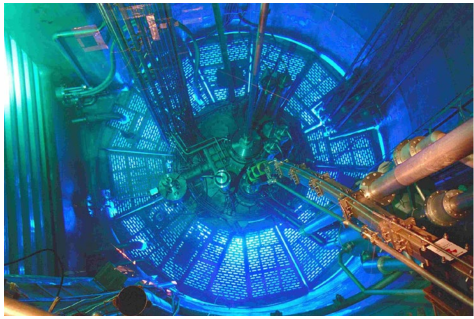


SNMMI image of the year 2019
Kratochwil et al. doi: 0.2967/jnumed.119.227967

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^-

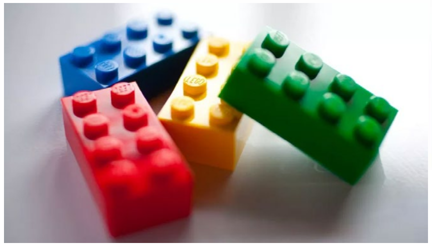


Common challenges:

- Large excess of matrix (target material)
- Very high decontamination factors required
- Especially cyclotron produced radionuclides:
  - generally 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:
    - Criteria
      - » No selectivity for target material, high selectivity for product
      - » Elution under ‘soft‘ conditions in small volume => labelling/injection
      - » Fast kinetics
      - » Stable against radiolytic degradation
    - Combining several resins can facilitate the separation
      - » Conversion (high acid to dilute acid)
      - » Removal of impurities upfront



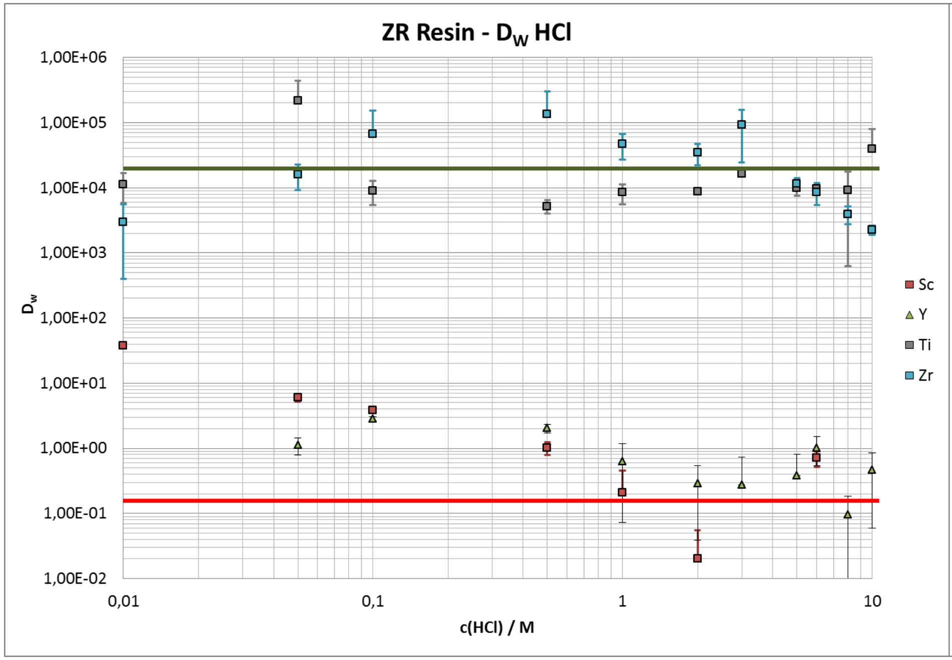
Research interests - Radiopharmacy

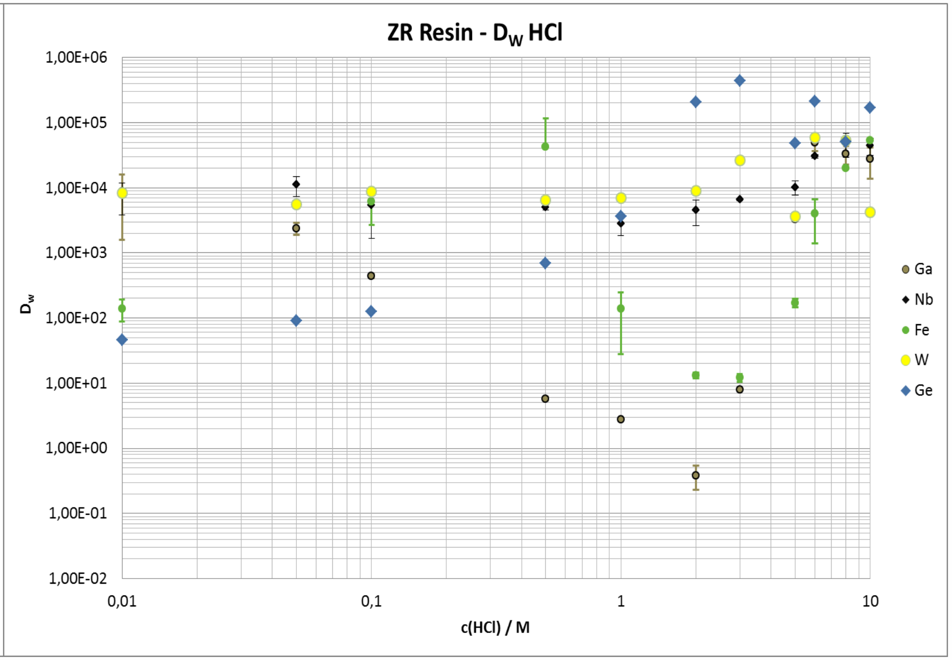
- Quality control
  - Cartridge based methods (e.g. Sr-90 in Y-90,…)
    - Use of “TK-ElScint cartridges”?
  - **“Sheets”**
    - p.ex. DGA sheets (functionalized TLC paper for Ra-223, Ac-225,…. => CVUT Prague), CU Sheets,…
- Decontamination of effluents/waste (Ge-68, lanthanides, radioiodine,…)
- Purification/combination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

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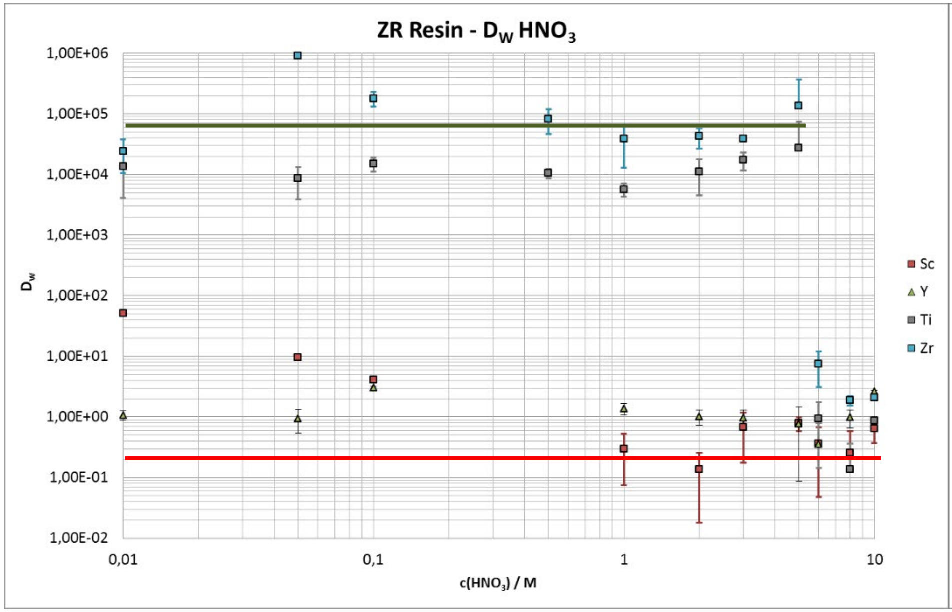
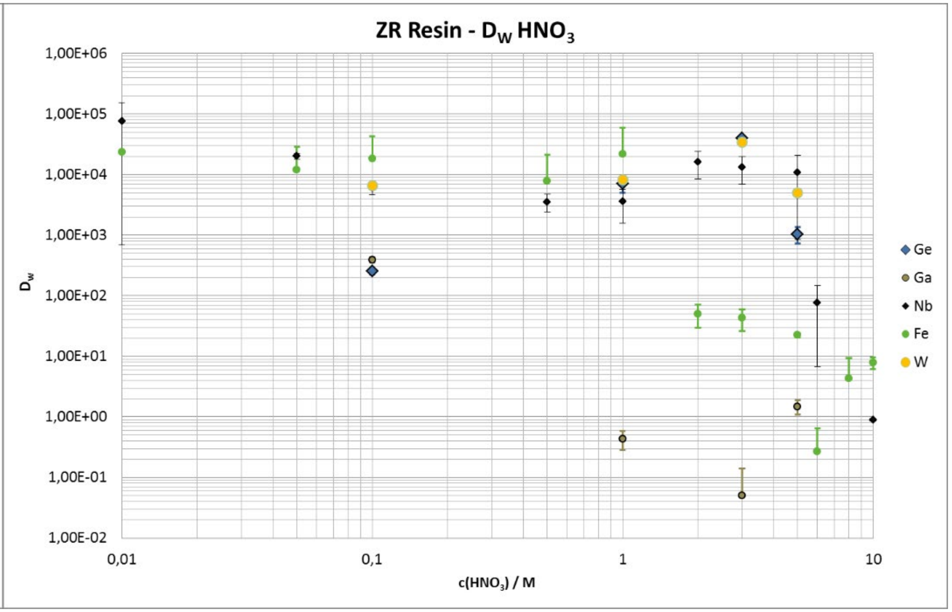


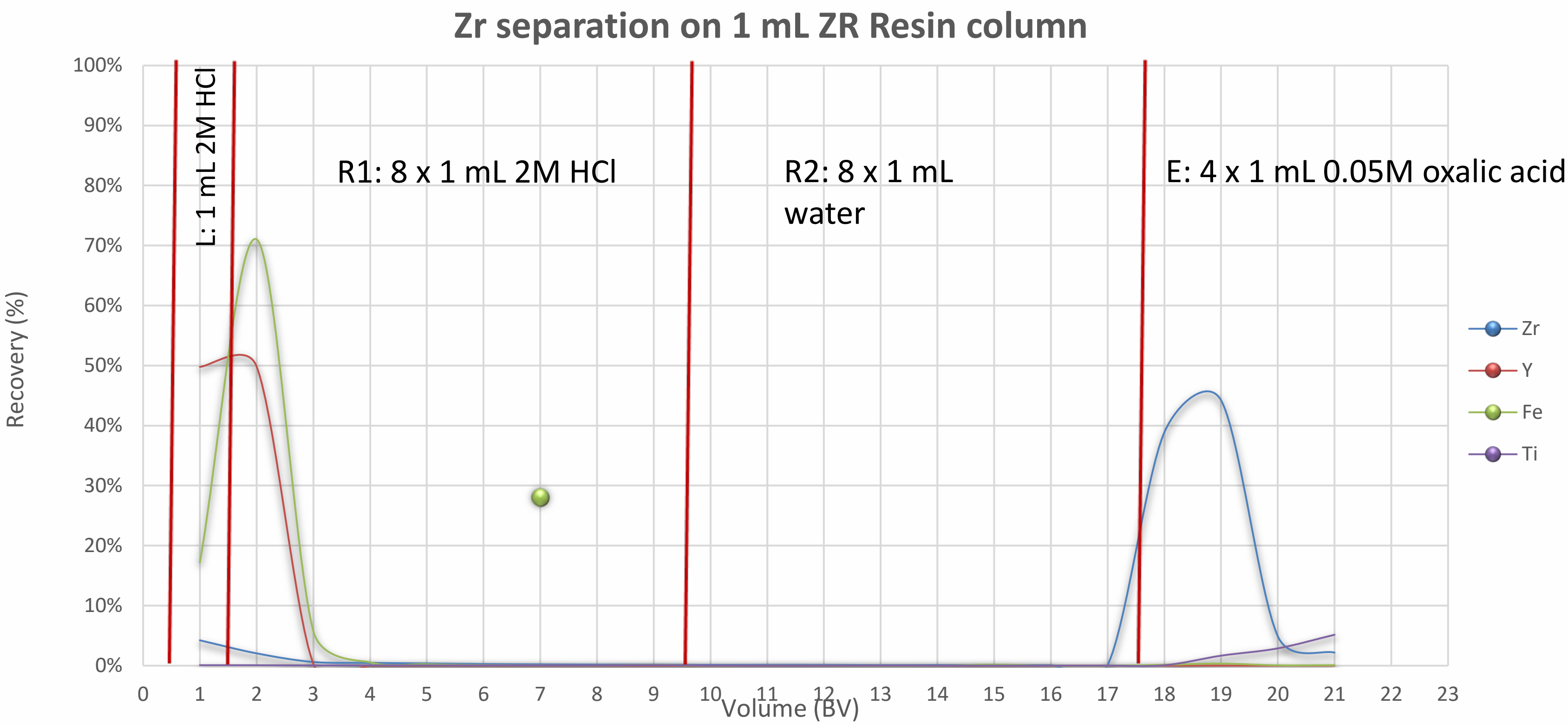


- High selectivity for Zr, Ti, Nb, W over wide HNO_3 concentration range
  - Loss of selectivity at 6M HNO_3

  => Resin shows colour change

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

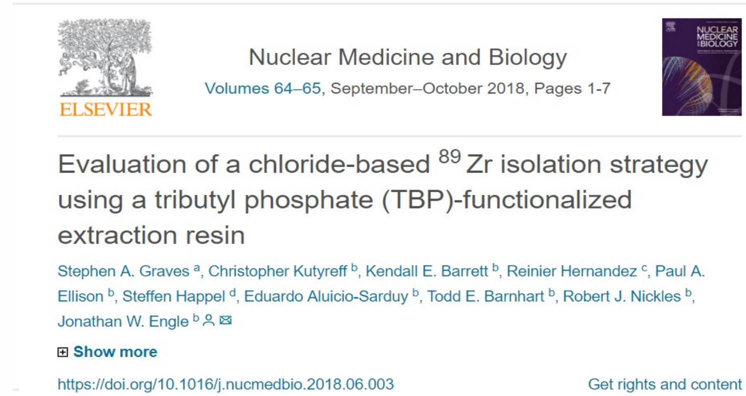
Zr-89 separation from Y targets



- 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)
  - Dissolution in 10 mL conc. HCl
  - 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
  - Stability in dilute acid…
- 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


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]

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

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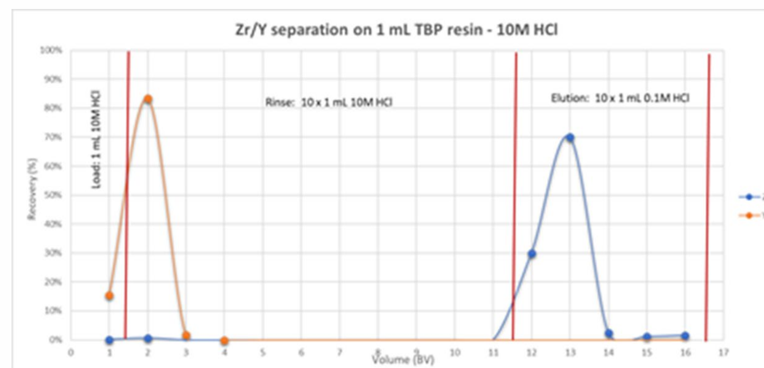
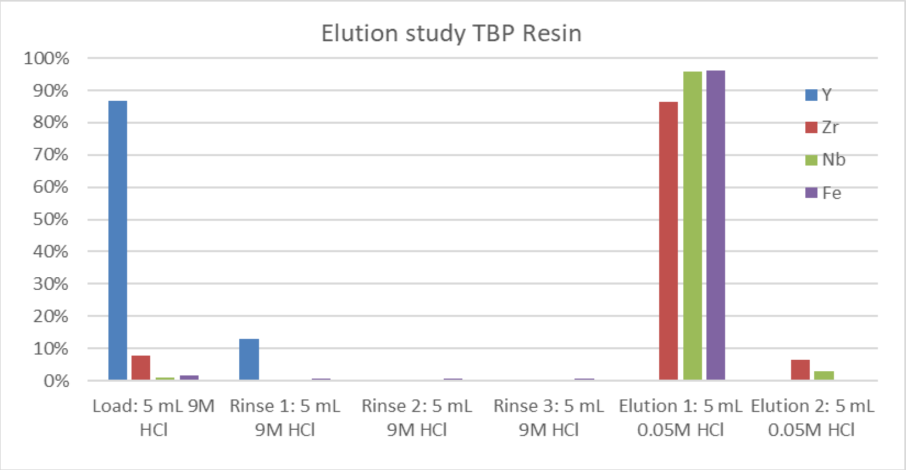
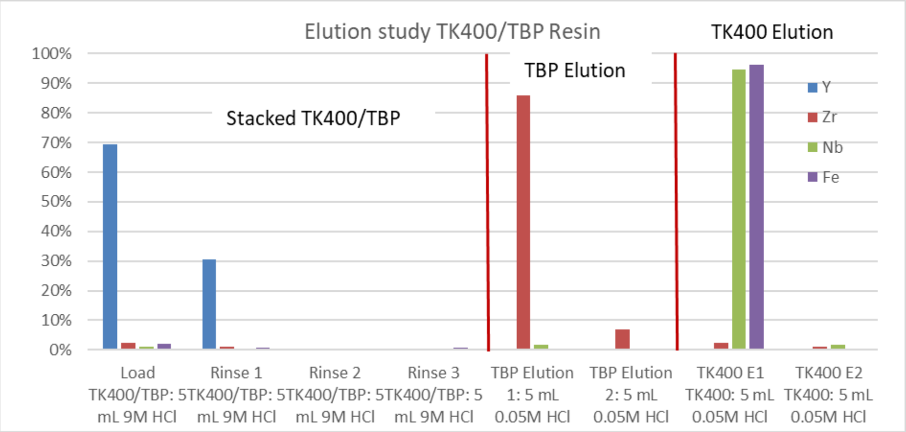


Use of TK400 for Fe/Nb removal

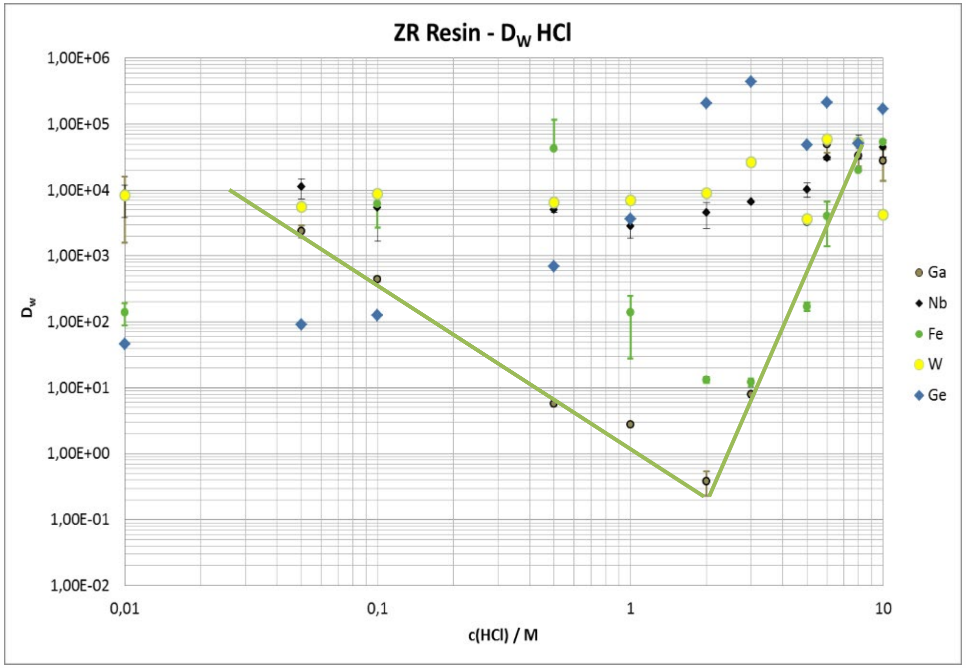


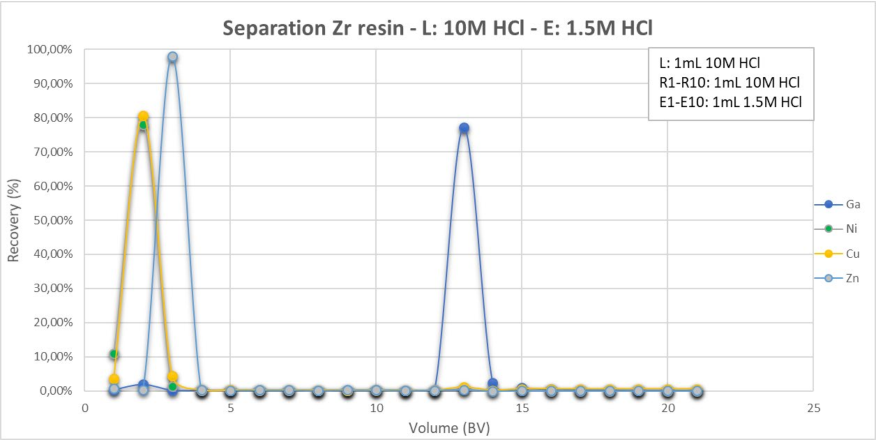


- On-going work
- On TBP only: Fe and Nb follow Zr
- Removal of Fe & Nb upfront possible using TK400 Resin
- Test with stacked 2 mL TK400/TBP cartridges
  - Load and Rinse at 10M HCl with TK400 stacked above TBP
  - Splitting of cartridges and separate elution with dilute HCl
    - TBP => Zr only
    - TK400 = > Fe & Nb
    - Y passes through both
- Removing Fe and Nb using TK400 improves Zr purity

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*]

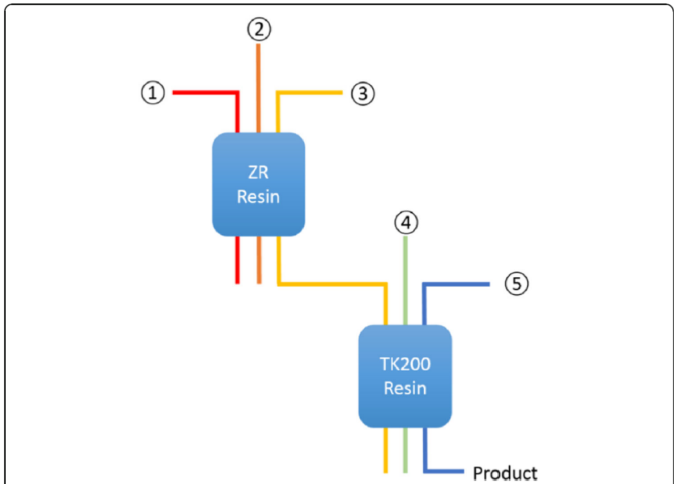


Fig. 4 Two-column approach for ^{68}Ga chemical separation

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 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

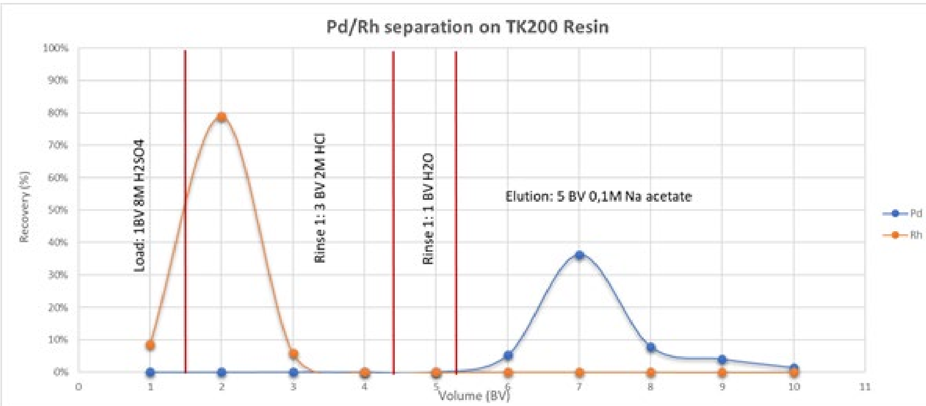
Johan Svedjehed, Martin Pärnaste, Katherine Gagnon *

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

Other separations on TK200

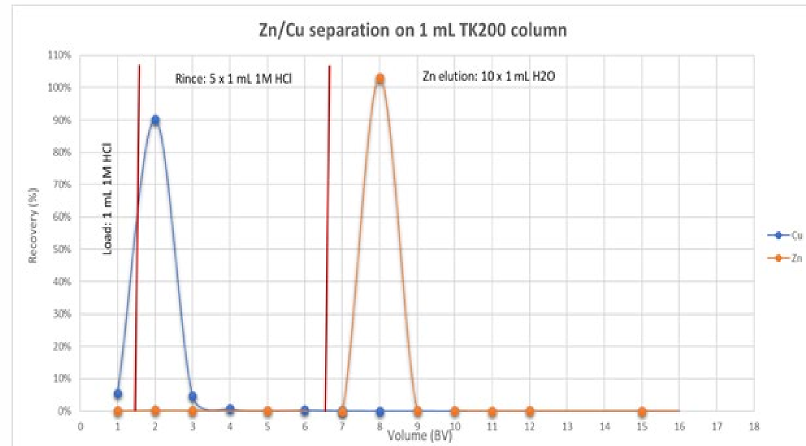
Expertise in Separation Chemistry

- Pd separation from Rh



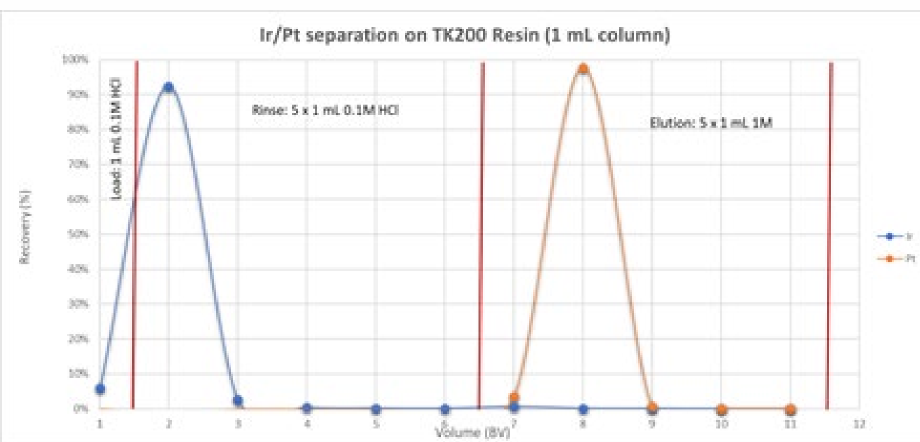
- Pd/Rh separation. Elution study, ICP-MS measurement

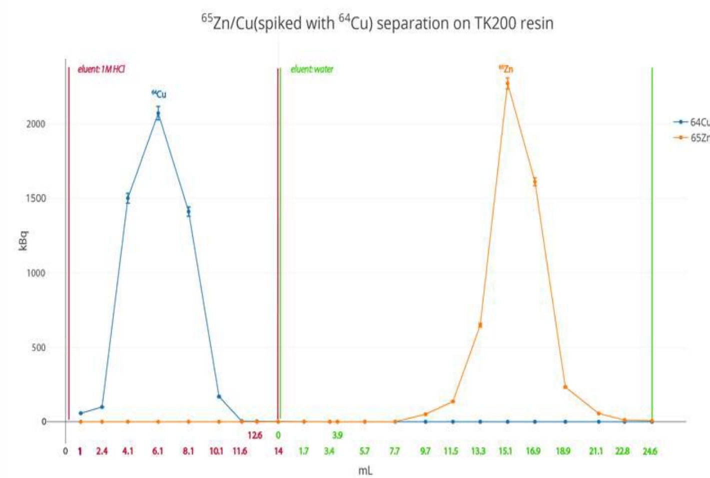
- Zn separation from Cu



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

- Pt separation from Ir

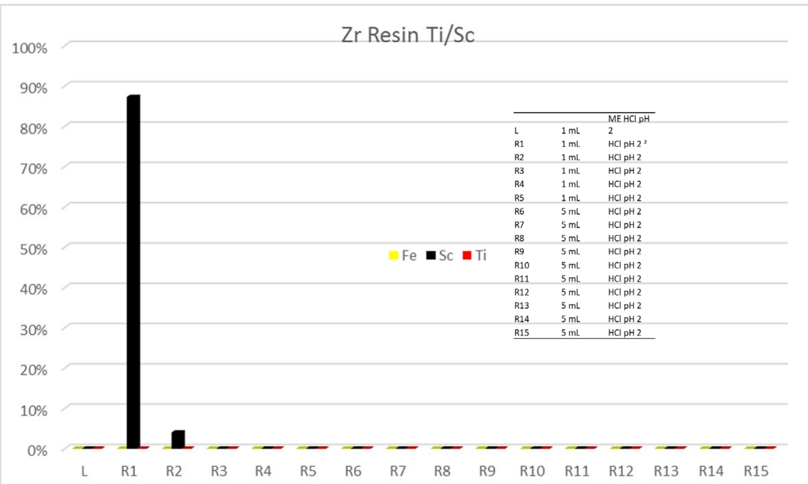




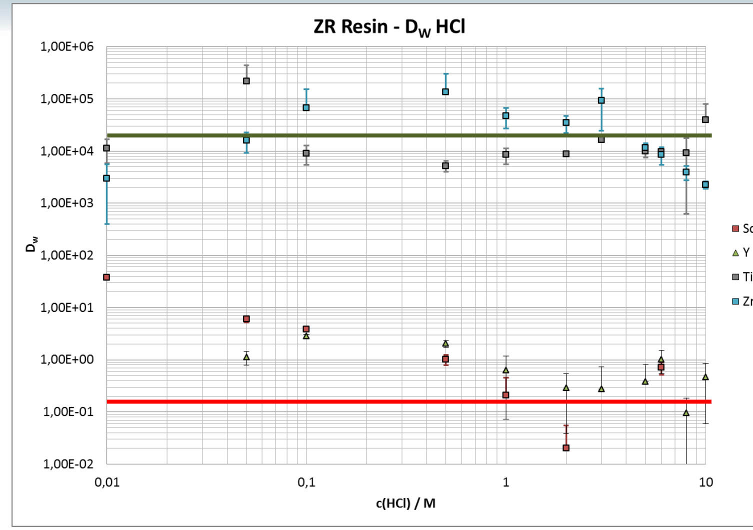
- Pt/Ir separation. Elution study, ICP-MS measurement

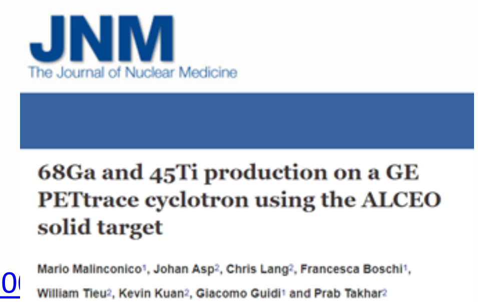
- Zn-65 separation. Data kindly by Fedor Zhuravlev, DTU

Ti-Sc Separation (Ti-44/5)



		ME HCl pH
L	1 mL	2
R1	1 mL	HCl pH 2 ²
R2	1 mL	HCl pH 2
R3	1 mL	HCl pH 2
R4	1 mL	HCl pH 2
R5	1 mL	HCl pH 2
R6	5 mL	HCl pH 2
R7	5 mL	HCl pH 2
R8	5 mL	HCl pH 2
R9	5 mL	HCl pH 2
R10	5 mL	HCl pH 2
R11	5 mL	HCl pH 2
R12	5 mL	HCl pH 2
R13	5 mL	HCl pH 2
R14	5 mL	HCl pH 2
R15	5 mL	HCl pH 2




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 elution with 0.1M citric, >0.2M oxalic acid, 0.1M H_2O_2
- K. Olguin: https://www.triskem-international.com/scripts/files/5fc95b3398a614.0397090 and-purification-of-titanium-45-for-positron-emission-tomography.pdf
- Publication:
  - Malinconico et al.: J Nucl Med May 1, 2018 vol. 59 no. supplement 1 664)
- Ti also retained in dilute acid, Sc not => Ti-44 generator?

Ti-44/Sc-44

Separation of ^{44}Ti from proton irradiated scandium by using solid-phase extraction chromatography and design of $^{44}Ti/^{44}Sc$ generator system

V. Radchenko, C.A.L. Meyer, J.W. Engle, C.M. Naranjo, G.A. Unc, T. Mastren, M. Brugh, E.R. Birnbaum, K.D. John, F.M. Nortier, M.E. Fassbender*

Chemistry Division, Los Alamos National Laboratory, P.O. Box 1663, Los Alamos, NM 87545, USA

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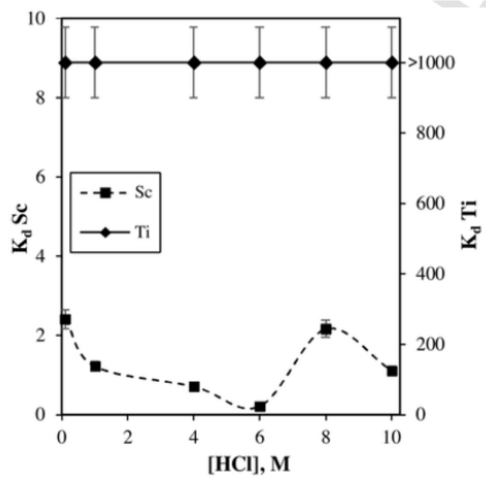


Fig. 3. HCl concentration dependency of K_d for $^{44}Ti/^{46}Sc$ on ZR hydroxamate resin.

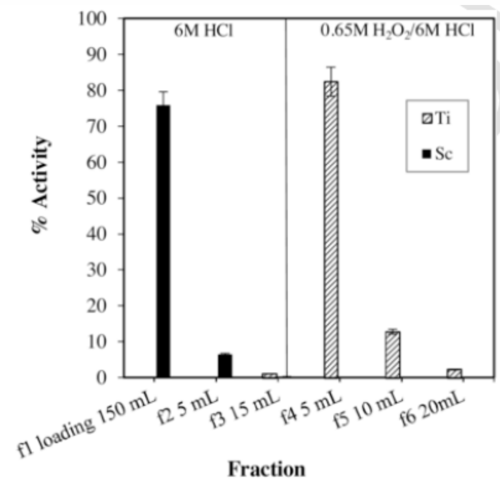


Fig. 5. $^{44}Ti/^{46}Sc$ elution profile using ZR hydroxamate resin with a load of 4 g of scandium.

- **Ti-44 production**
  - 4g irradiated Sc
  - 5 mL Zr Resin
  - Ti-44 yield >95%
  - 65.2 MBq Ti-44
  - D_f(Sc): 10^5

Use of ZR Resin as support in Ti-44/Sc-44 generators

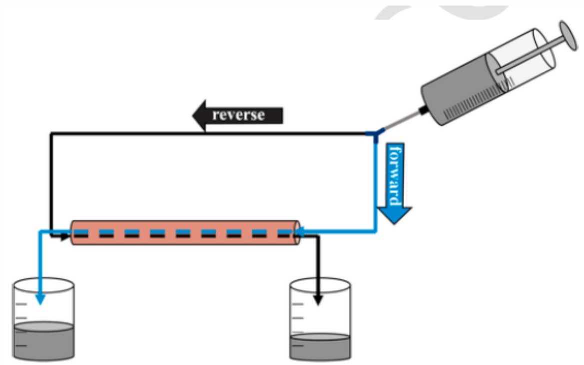
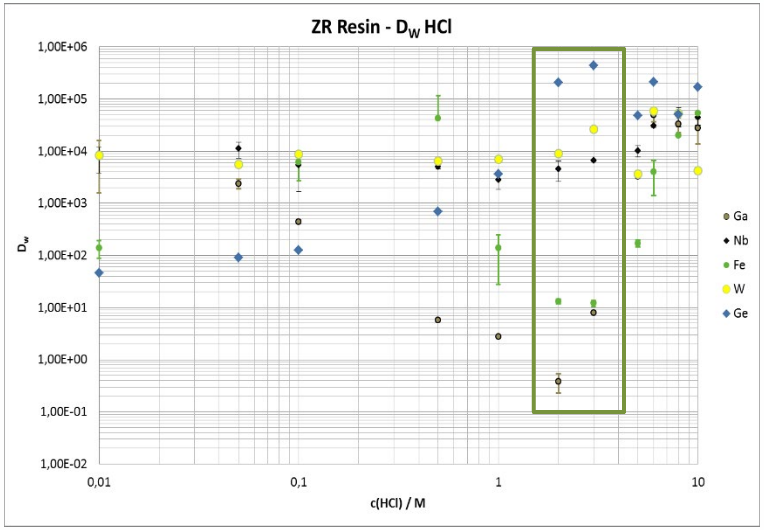


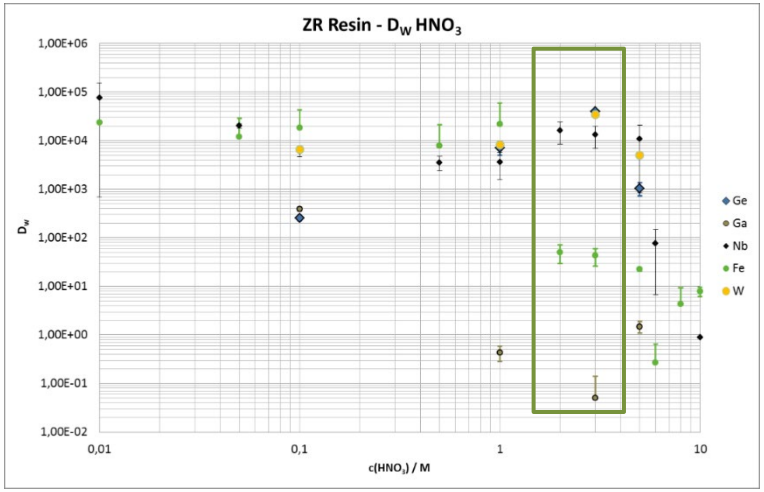
Fig. 1. Schematic concept of a forward/reverse flow radionuclide generator.

- Direct (1 mL ZR) and reverse elution (2 mL ZR)
- 65 column volumes tested up until publication
- High Sc yields, max. Ti-44 breakthrough: 4.1^{E}-4%
- Obtained Sc gave labelling yields > 94%
- Generator been set-up at BNL/SBU => Poster S. Houclier ISRS 2019

Ge-68 separation from GaNi or GaCo

- 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!





Germanium

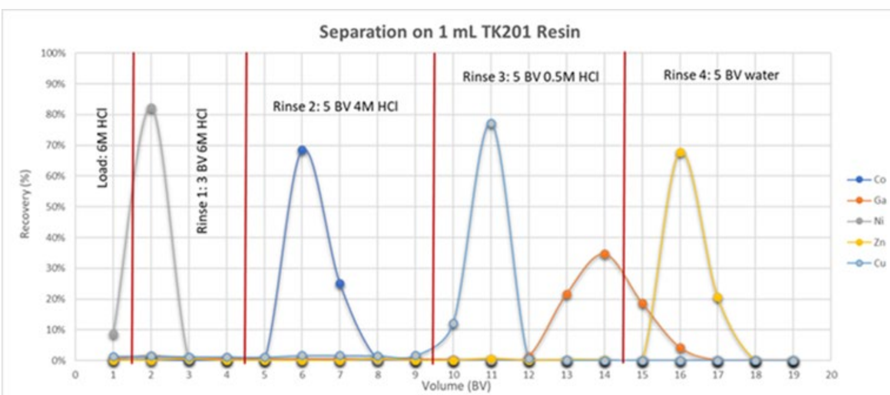
- Ge removal using CeO_2-PAN (TK-GeRem)
  - Extracts Ge from dilute acid, seawater…
    - Decontamination of (reaction) waste
    - Tests on-going: Ge-68 breakthrough elimination from generator effluents
- Combination of several Ge-68 generator eluents
  - Direct ZR/TK200 or
  - Acidification and load onto one TK200
  - Elution in dilute HCl
- Ge recycling
  - Evaluation of possibility to elute Ge from ‘spent’ generators
    - E.g. attack with 9M HCl
    - Use of two subsequent Guard Resins cartridges to collect and purify Ge

Cu-61/4 separation on TK201

Expertise in Separation Chemistry

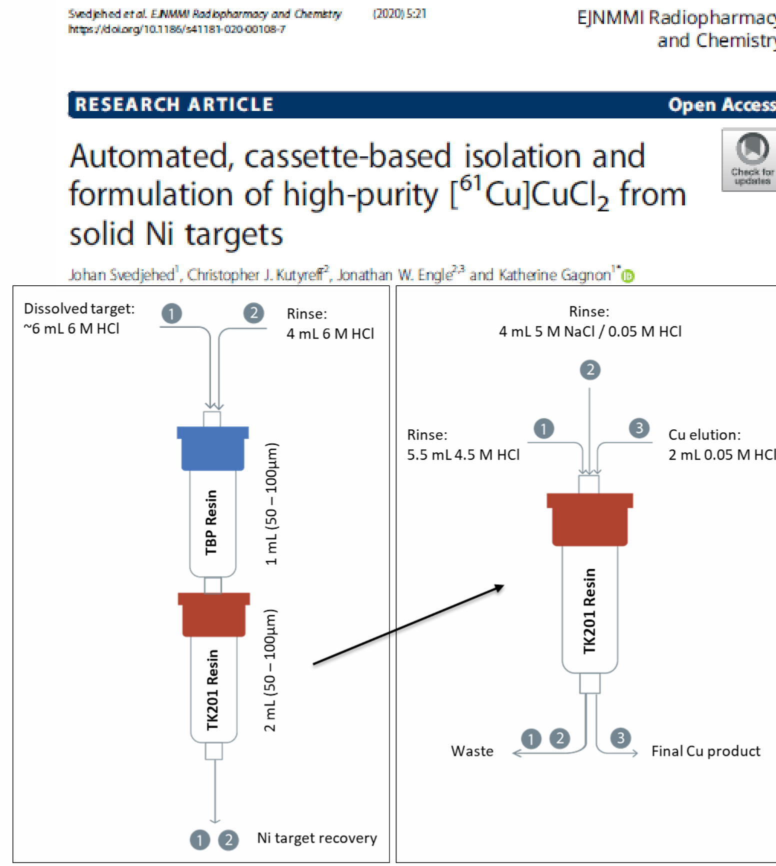
- Cu-64 separation from solid Ni-64 targets
  - Initial tests
  - Target dissolution in high HCl
  - Load and rinse at 6M HCl
    - Ni removal and recovery/recycling
  - Co elution with 4 – 5M HCl => Co separation
  - Cu elution with 0.5M HCl
    - Zn remains retained (Ga and Fe partially co-elute)

    => requires further treatment



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

  => allows for Cu elution in 0.05M HCl

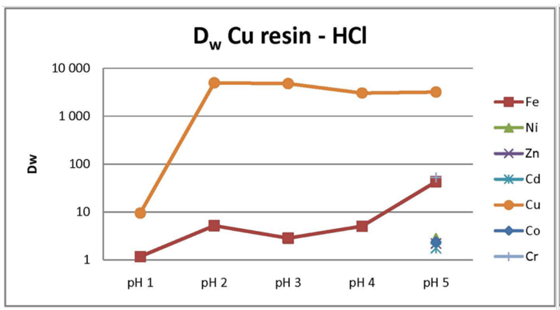


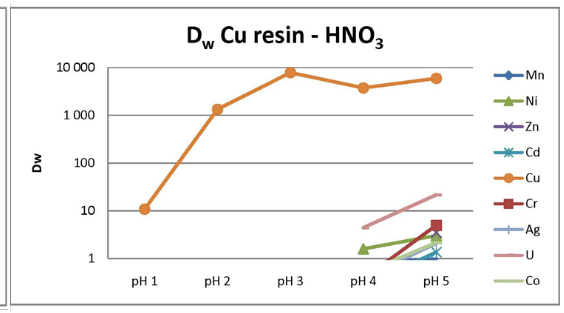
- Gagnon et al. use of NaCl/HCl for better pH control of eluate

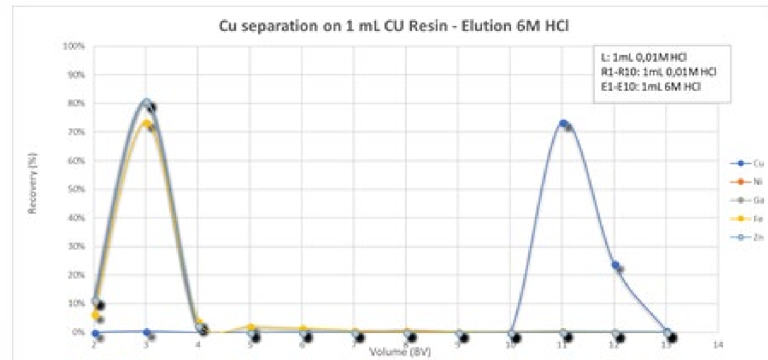
=> Allows for use in TK201/CU/TK201 method

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.

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,*]

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
- 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

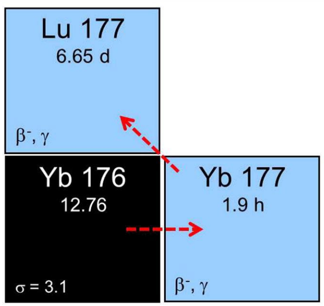
Robust separation that could shorten the overall processing time to separate co-produced radionuclides and large quantities of Zn from radiocopper
Cation and anion exchange columns still needed to suitably purify radiocopper

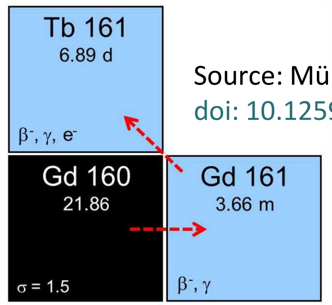
Alternatives to AIX- use of TK201:

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

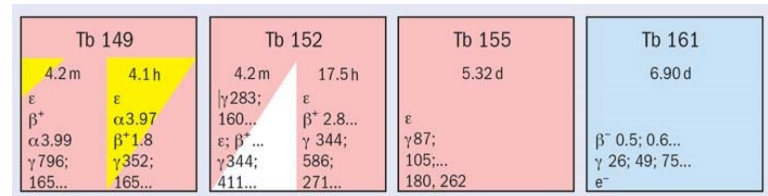
Lu-177/Tb-161

- 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

a


b


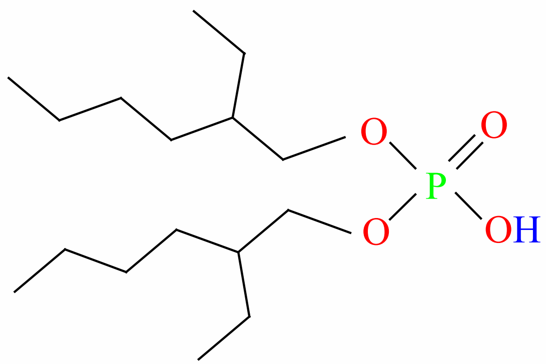
Source: Müller et al. 2018
doi: 10.1259/bjr.20180074



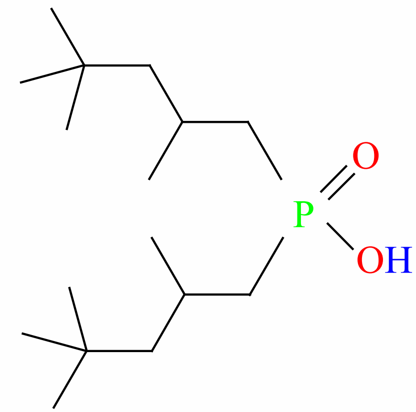
Terbium: a new ‘Swiss army knife’ for nuclear medicine
Source: https://cerncourier.com/a/terbium-a-new-swiss-army-knife-for-nuclear-medicine/

  - 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 (150 mL), 1.5cm x 30cm (53 mL) & 1.1cm x 30cm (29 mL)
  - Connection: ¼’’ 28G, up to ~10bar
  - QC/CoA per column (peak asymmetry) for TK211/2/3
  - TK221 => dry packing

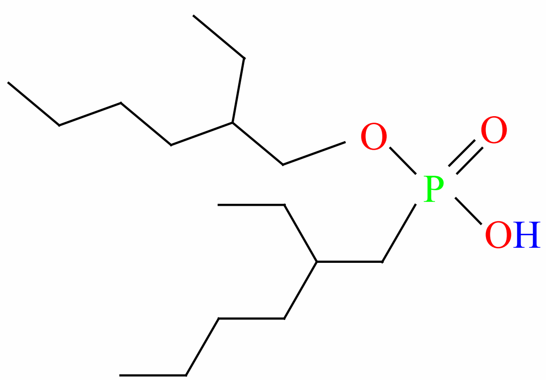
Lanthanide separation on TK211/2/3



HDEHP



H[TMPeP], Cyanex 272



HEH[EHP], PC 88A

Cyanex 572

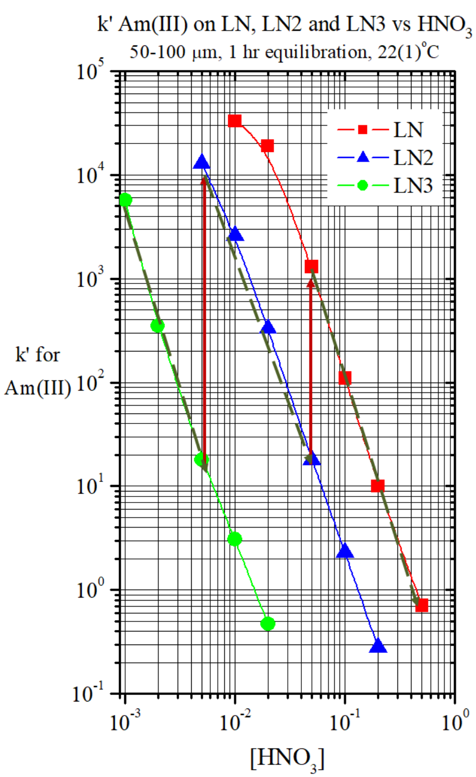
TK211/2/3 Resins

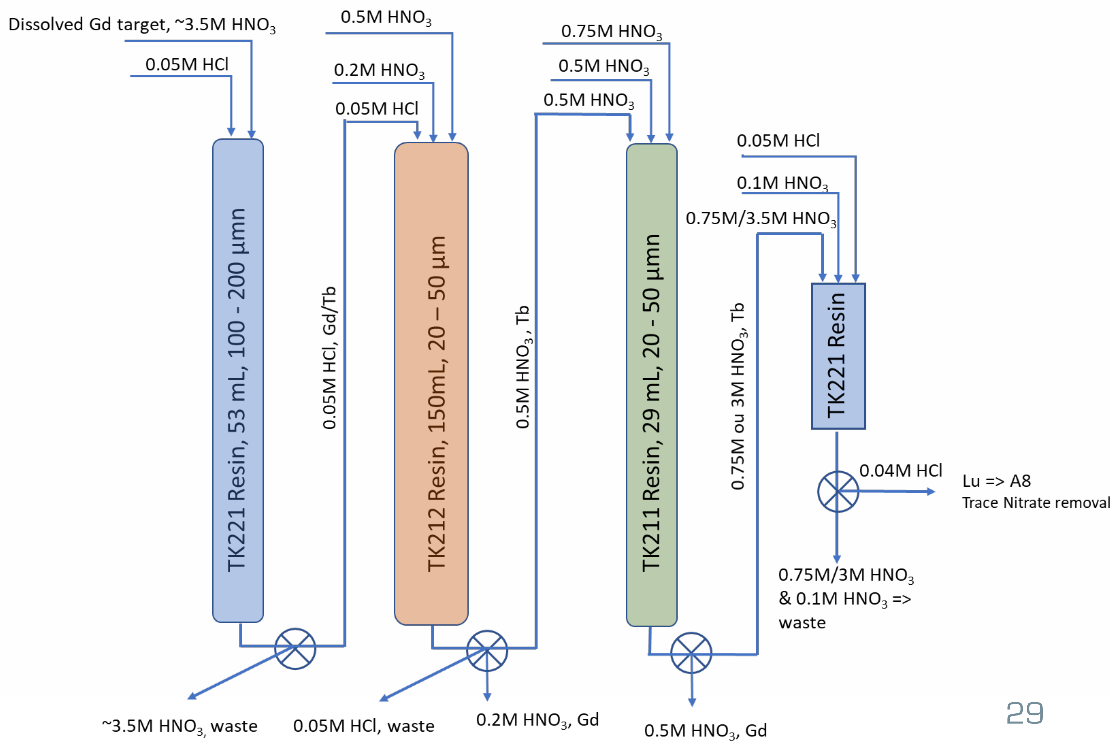
- Mixtures of different extractants
- Modified for higher radiation stability

Tb separation from 1000 mg Gd targets

TRISKEM
Expertise in Separation Chemistry

- Irradiated target typically oxide => dissolved in >3M HNO_3
  - For separation solution needs to be dilute acid
- Conversion via TK221 Resin (TK222 under testing)
- **Sequential separation** on TK212/TK211
- Final conversion to dilute HCl on TK221 + trace nitrate removal on AIX
- Mainly Tb-161, also Tb-155

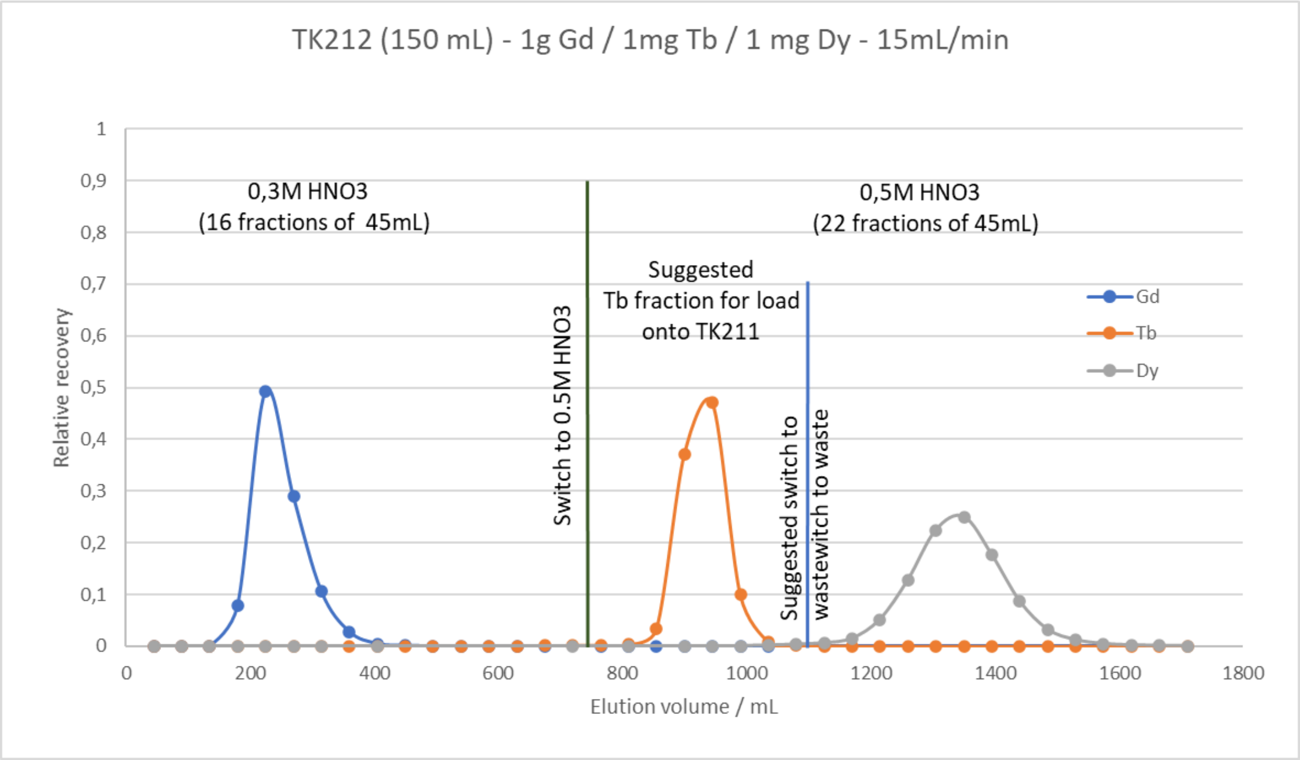




Tb separation from 1000 mg Gd targets

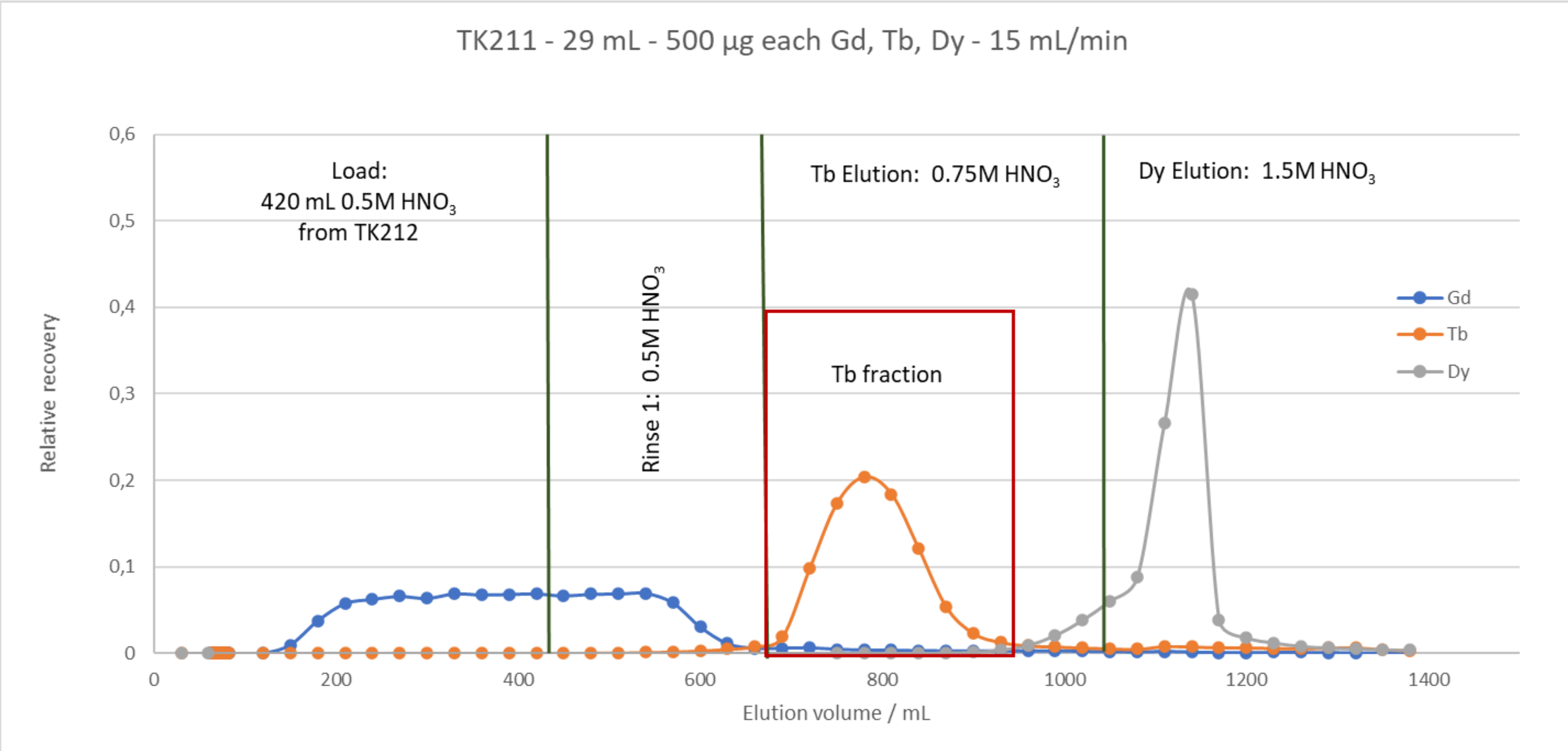
TRISKEM Expertise in Separation Chemistry

- 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 (150 mL column)

Tb purification on TK211

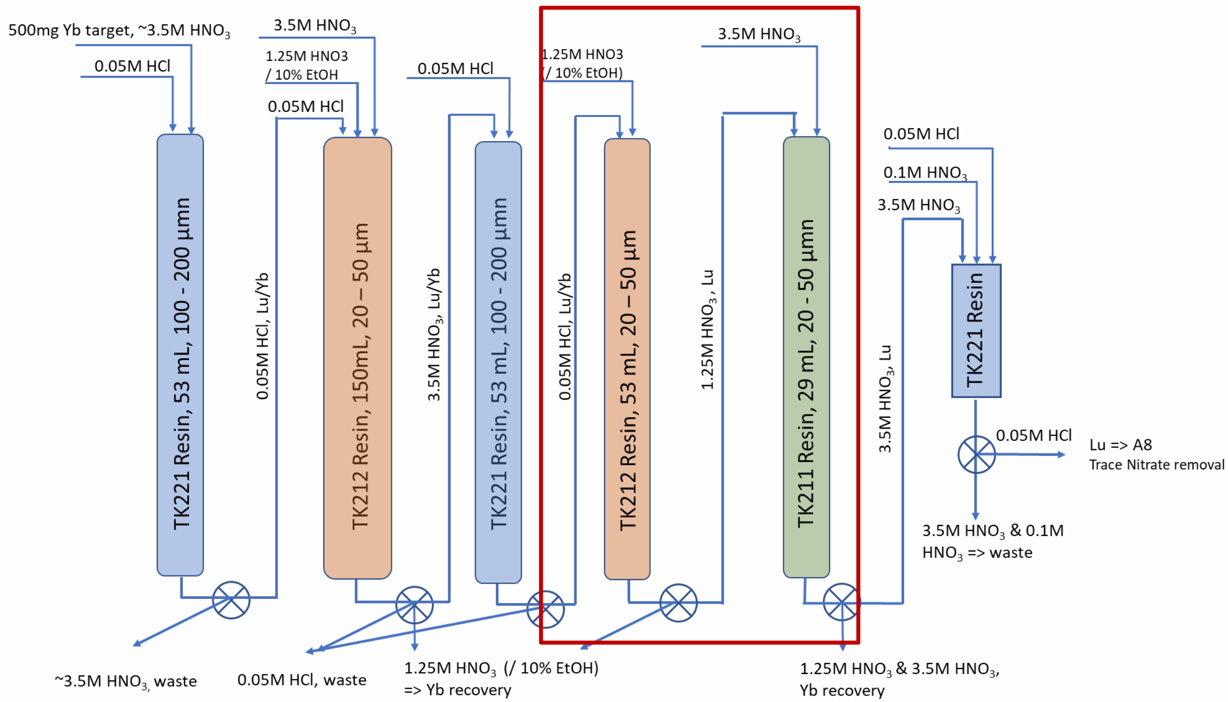


- Direct load of Tb fraction from TK212 onto TK211 (29 mL – 30cm x 1.1cm)
- Gd breakthrough during load & rinse with 0.5M HNO_3 (alternatively HCl)
- Tb elution (Dy sufficiently well removed before) preferably in **>3M HNO_3**
- Conversion to dilute HCl via TK221, A8 for nitrate removal

Lu-177 from Yb targets

TRISKEM Expertise in Separation Chemistry

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



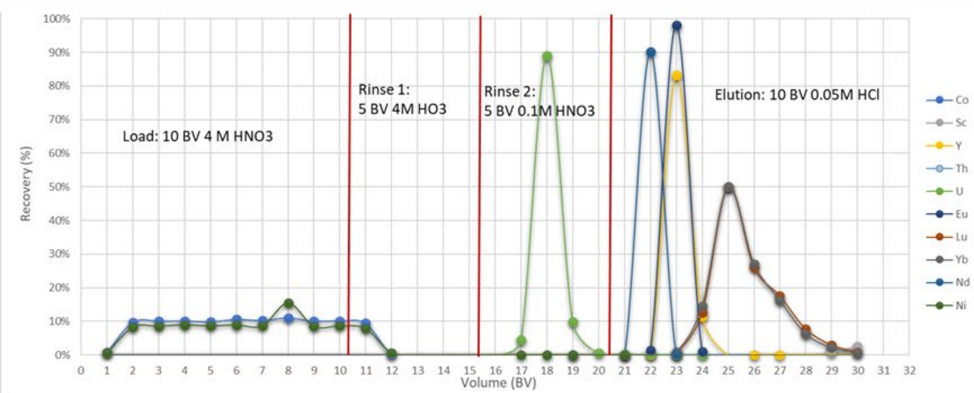
- Sequential separations may be emplyed, too
- Remains more difficult than Tb/Gd
- Addition of **10% EtOH** improves separation
  - Also beginning to be used in analytical applications => Warwick et al.

TK221 Resin

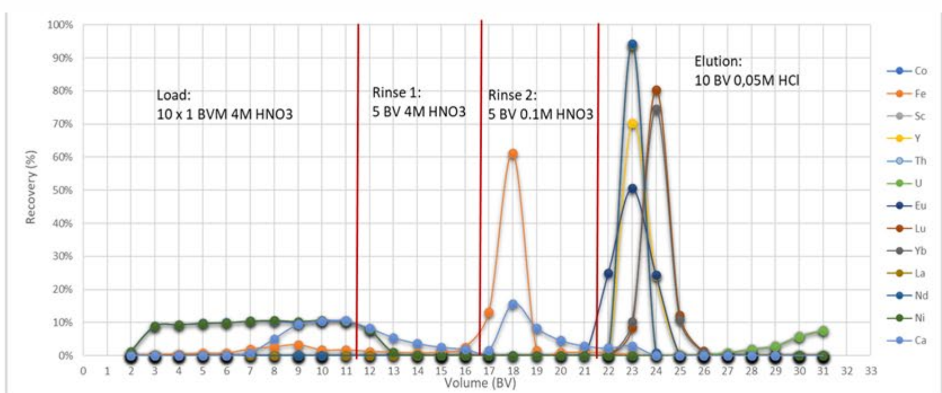
TRISKEM
Expertise in Separation Chemistry

- 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



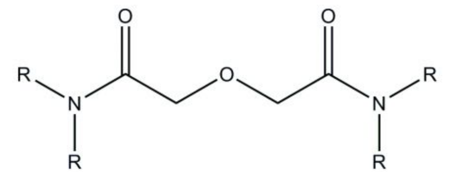
TK221 Resin



- **New: TK225 Resin (TO-DGA + ionic liquid) => lanthanide removal/decontamination**
- **Upcoming: TK222 Resin => DGA/phosphine oxide**

Ac-225 from Ra-226 targets

- Ac-225 separation from irradiated Ra-226 targets
- Ac separation chemistry well established
  - Reference method: DGA, B (e.g. Zielinska et al.)
    - Strong Ac retention, no selectivity for Ra
    - Smaller elution volumes compraed to DGA, N
  - Marsten, Radchenko (LANL)
    - Use of DGA (B/N) allows for Ac/LN separation
    - Ac elutes in 10M HNO_3, LN don't
    - Mainly work on spallation
  - Kotaro Nagatsu et al.:
    - Use of DGA/LN cycles for Ac purification
    - Simplifies several purification cycles
    - 'Ra recycling'
  - Requests for DGA alternative
    - TK221 or TK222 options?



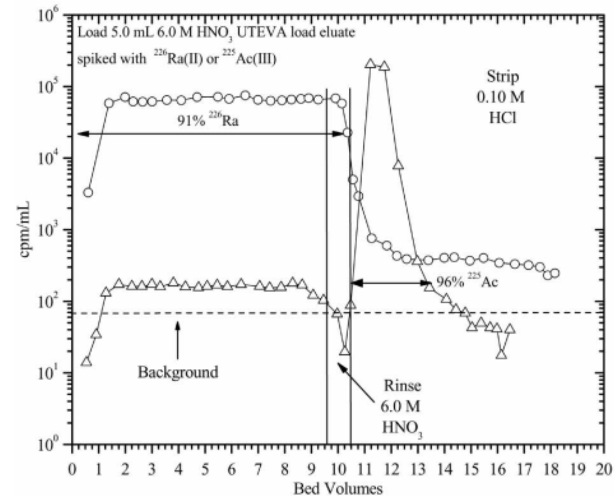


Figure 13. Separation of Ac(III) and Ra(II) on TODGA resin (50–100 μm) with 6.0 M HNO_3 and 0.1 M HCl, 0.5 mL bed volume, flow rate equals 2 mL/min load/rinse, 1 mL/min strip, 22(1)°C.

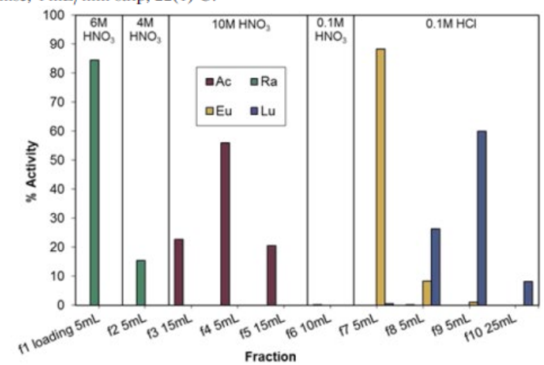
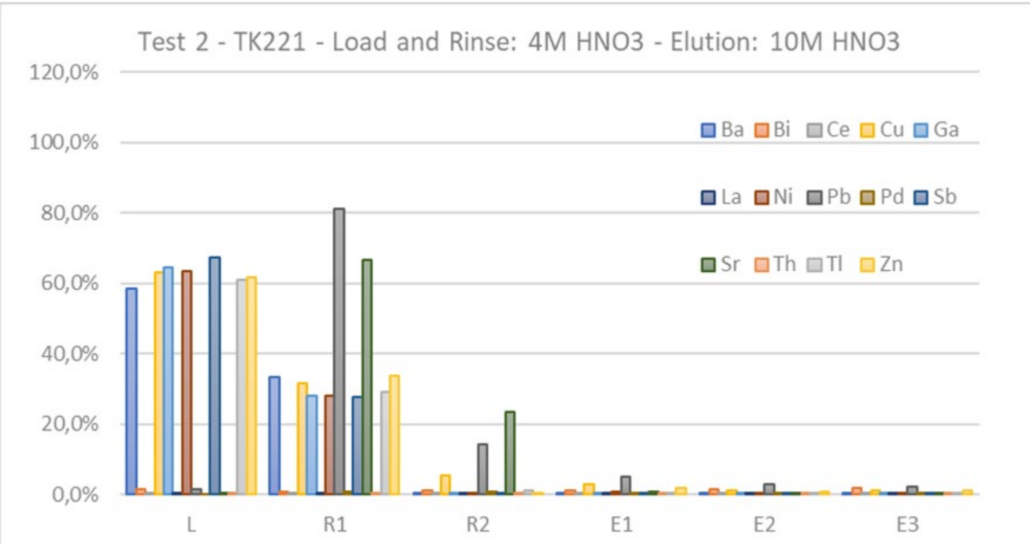


Fig. 4. Elution profile for $^{223/225}Ra$, ^{225}Ac, ^{173}Lu, and ^{155}Eu with TEHDGA resin in HNO_3 media and HCl for lanthanide elution.

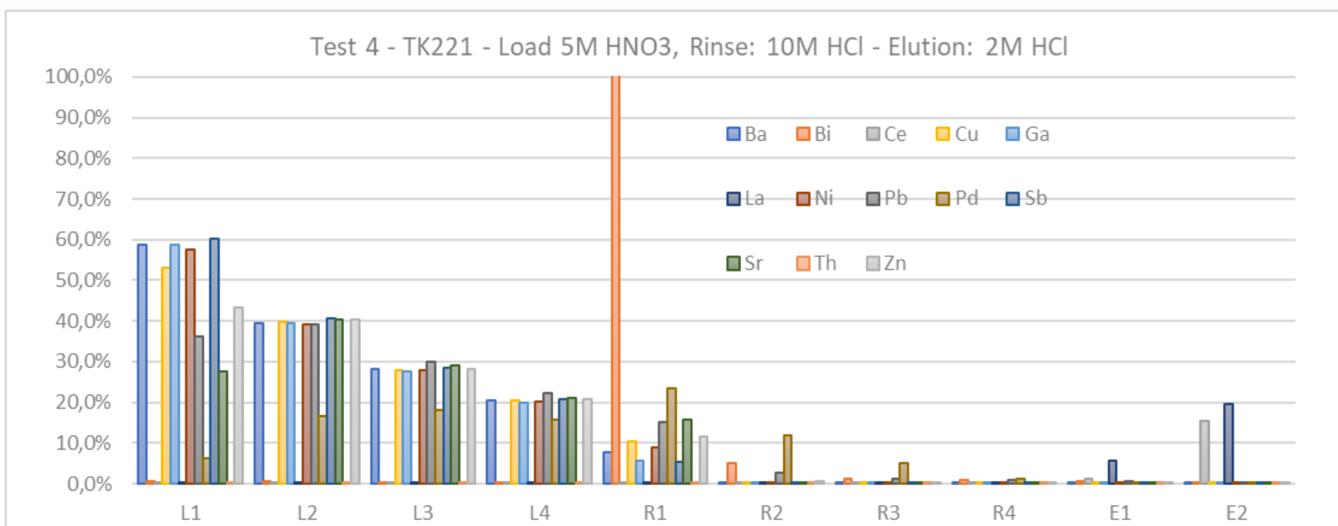
TK221 Resin – Ac separation



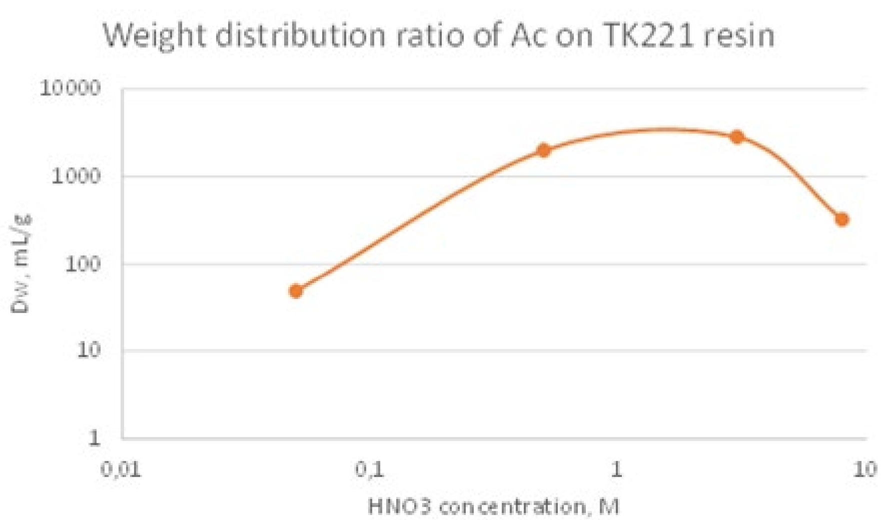
- Two step procedure

- First TK221
  - Load from elevated HNO_3
  - Particular attention to Pb
    - Elution in 4M HNO_3
  - Ac elution in ≥10M HNO_3
  - LNs retained

- Second TK221
  - Dilute x2 => load
  - Bi removal at 10M HCl
  - Ac elution in 2M (additional Pb removal) or 0.05M HCl
  - Additional purification on TK101 (0.05M HCl) or TK102 (2M HCl)
- Alternative: TK222
  - Sharper elution

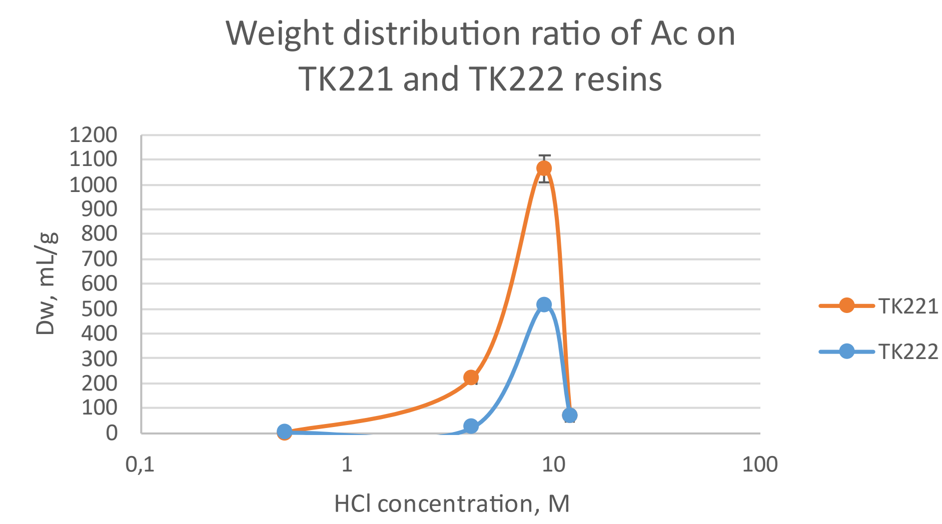


TK221 Resin – Ac separation



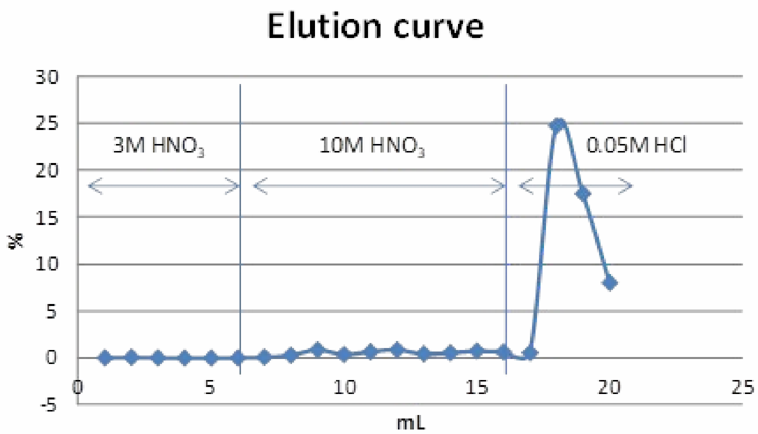
Data courtesy of N. Vajda (RadAnal)

– On-going work

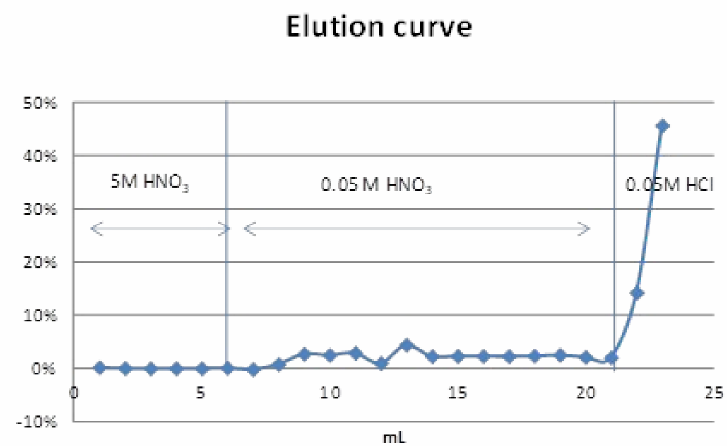


- TK221:
  - High Ac retention from high to low HNO_3
  - Elution in 0.1 – 0.05M HNO_3 not possible
- HCl: Higher retention of Ac on TK221
  - Elution in dilute HCl possible

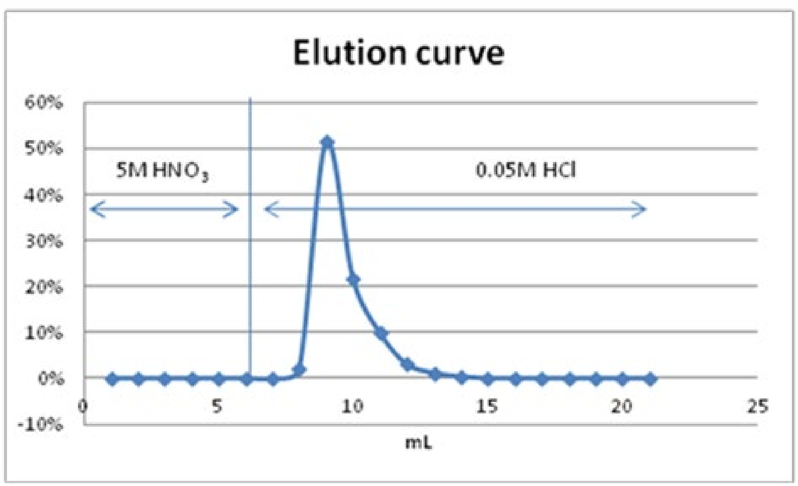
TK221 Resin – Ac separation



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.



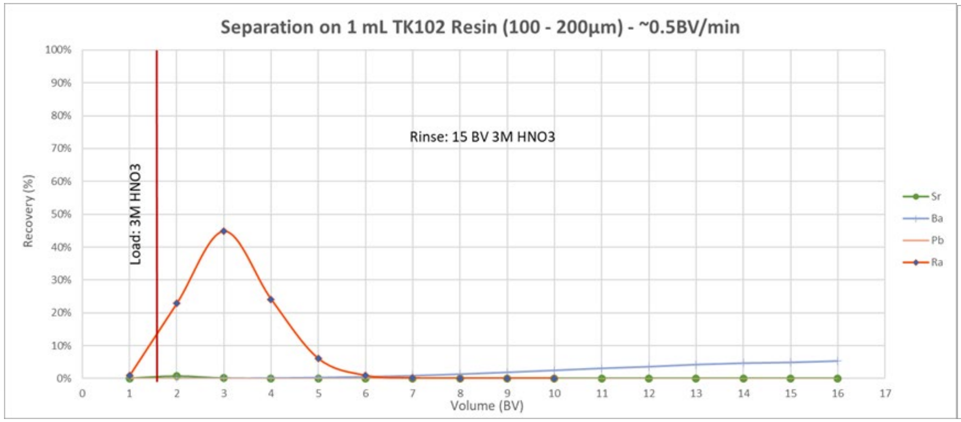
Elution of Ac from TK221 cartridge with 0.05M HCl, 1mL TK221 column, data courtesy of N. Vajda et al.

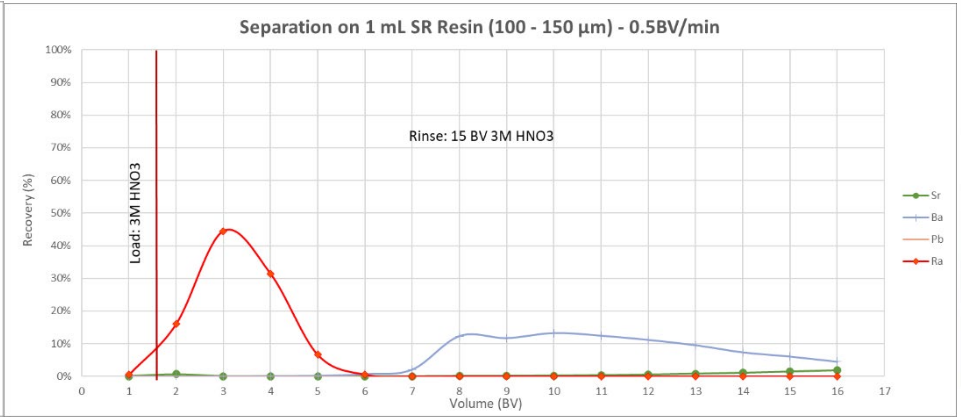
- Ac/LN separation requires 12M HNO_3 => LN remains retained.
- No Ac elution in 0.05M HNO_3
- Elution in 0.05M HCl possible
- HNO_3 => HCl conversion?
- Beta tester: TK222 => sharper elution in dilute HCl

Ra purification / recycling

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

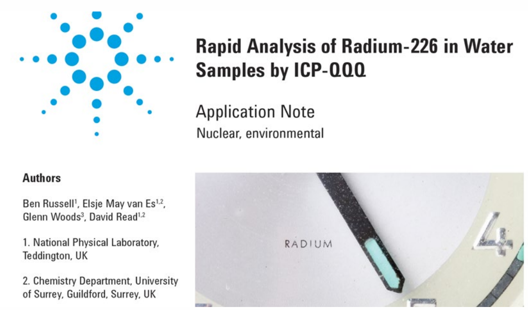
  => Ideal case: only remove impurities, leave Ra in solution
    - E.g. TK221 => alpha emitters, polyvalents et al.
    - TK102 for Ba, Pb and Sr removal from 3M HNO_3
      - Improved Ba/Ra separation
      - Low organics bleeding (hydrophobic solvent)





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
- TK100: SR Resin crown ether / HDEHP mixture => van Es et al., Agilent
  - HDEHP facilitates phase transfer at dilute HNO_3 but also extracts various elements
  - Developed for Sr and Pb uptake also between pH 2 and 7 => Surman et al. (DGT)
  - New publication (DGT) Wagner et al. TK100 discs
  - High Ra/Ba retention from dilute HCl / HNO_3
  - Preconcentration and sequential separation of U, Th, Pb, Sr, Ba, Ra on-going



Rapid Analysis of Radium-226 in Water Samples by ICP-QQQ

Application Note

Nuclear, environmental

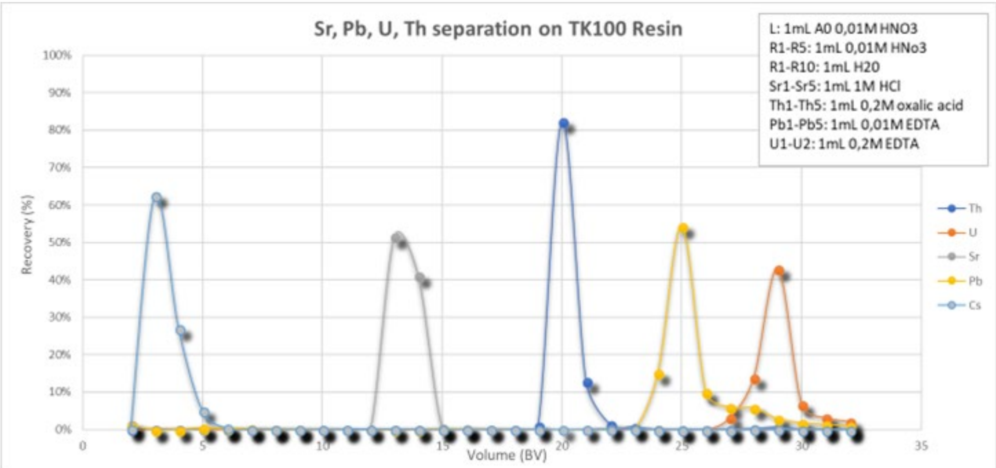
Authors

Ben Russell[1], Elsje May van Es[1,2], Glenn Woods[3], David Read[1,2]

1. National Physical Laboratory, Teddington, UK

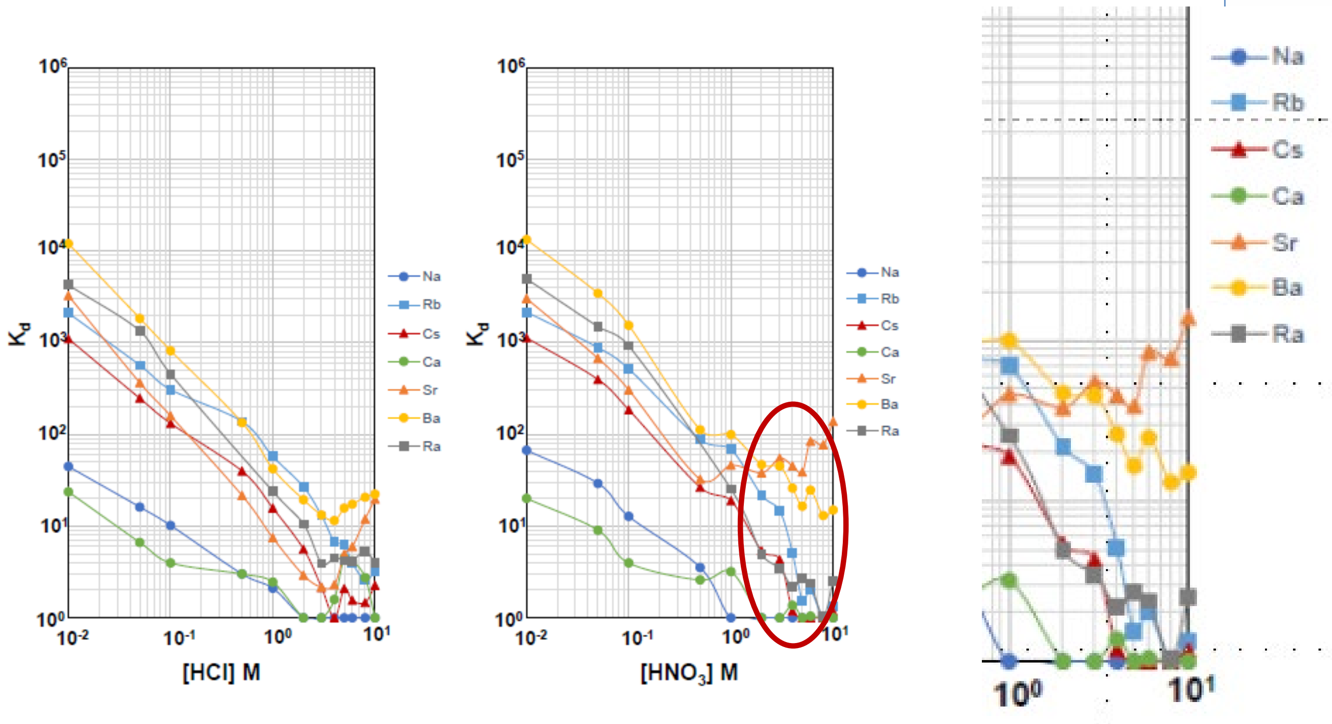
2. Chemistry Department, University of Surrey, Guildford, Surrey, UK

- TK101 => HDEHP replaced by ionic liquid
- Still allows for retention of Pb, Sr, Ba, Ra,… from water to dilute acid (0.5M)
- Without extensive extraction of other elements



TK101 - Radium

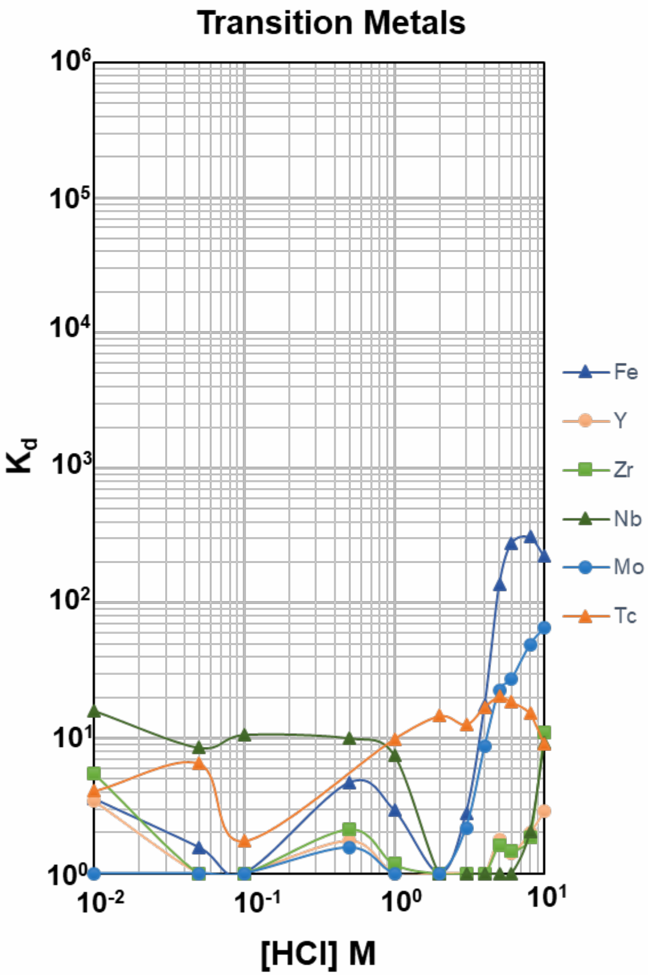
TK101 Group 1 and 2

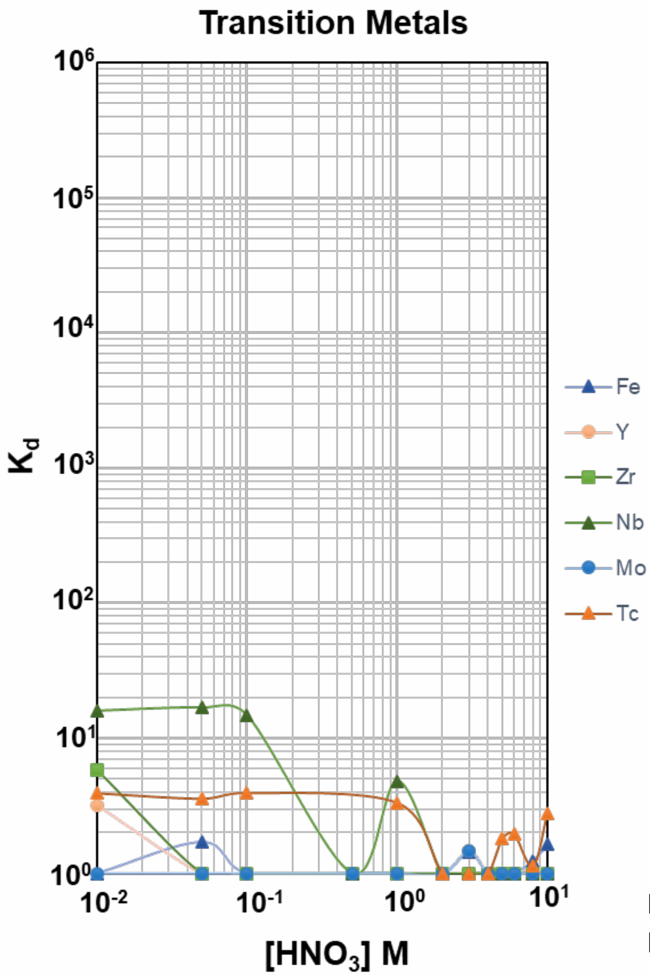


Data provided by
Russel et al. (NPL)

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

TK101 Transition Metals

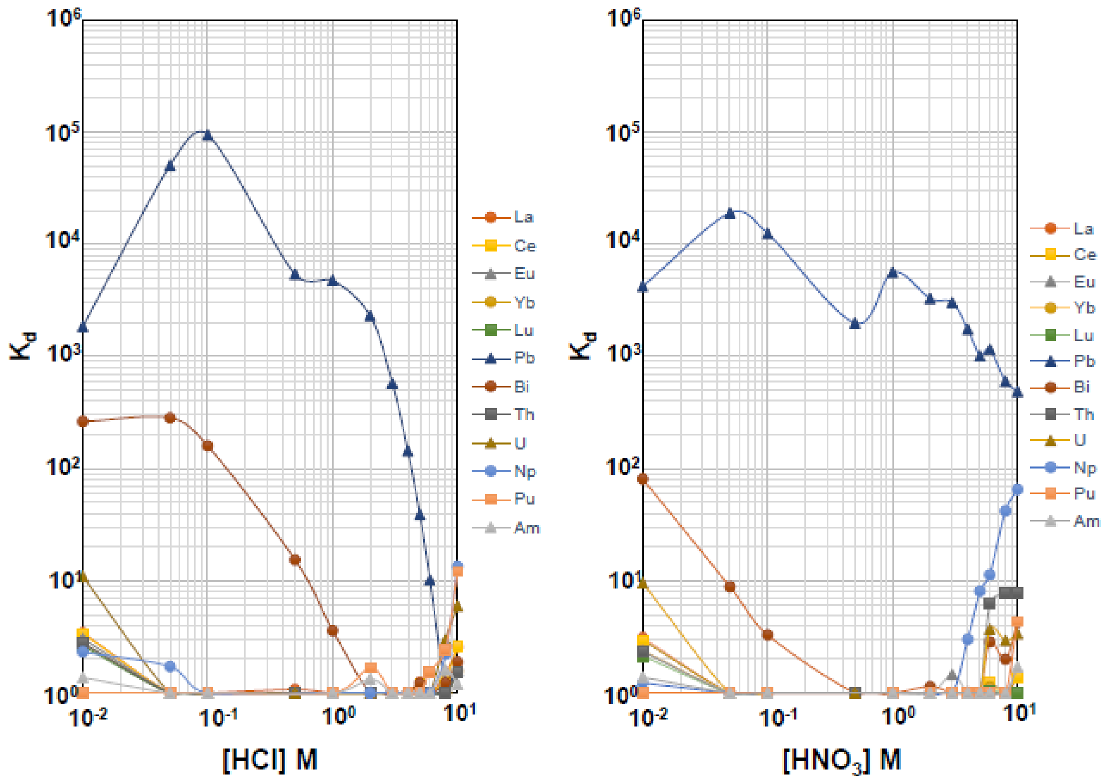




Data provided by Russel et al. (NPL)

TK101 - Ra

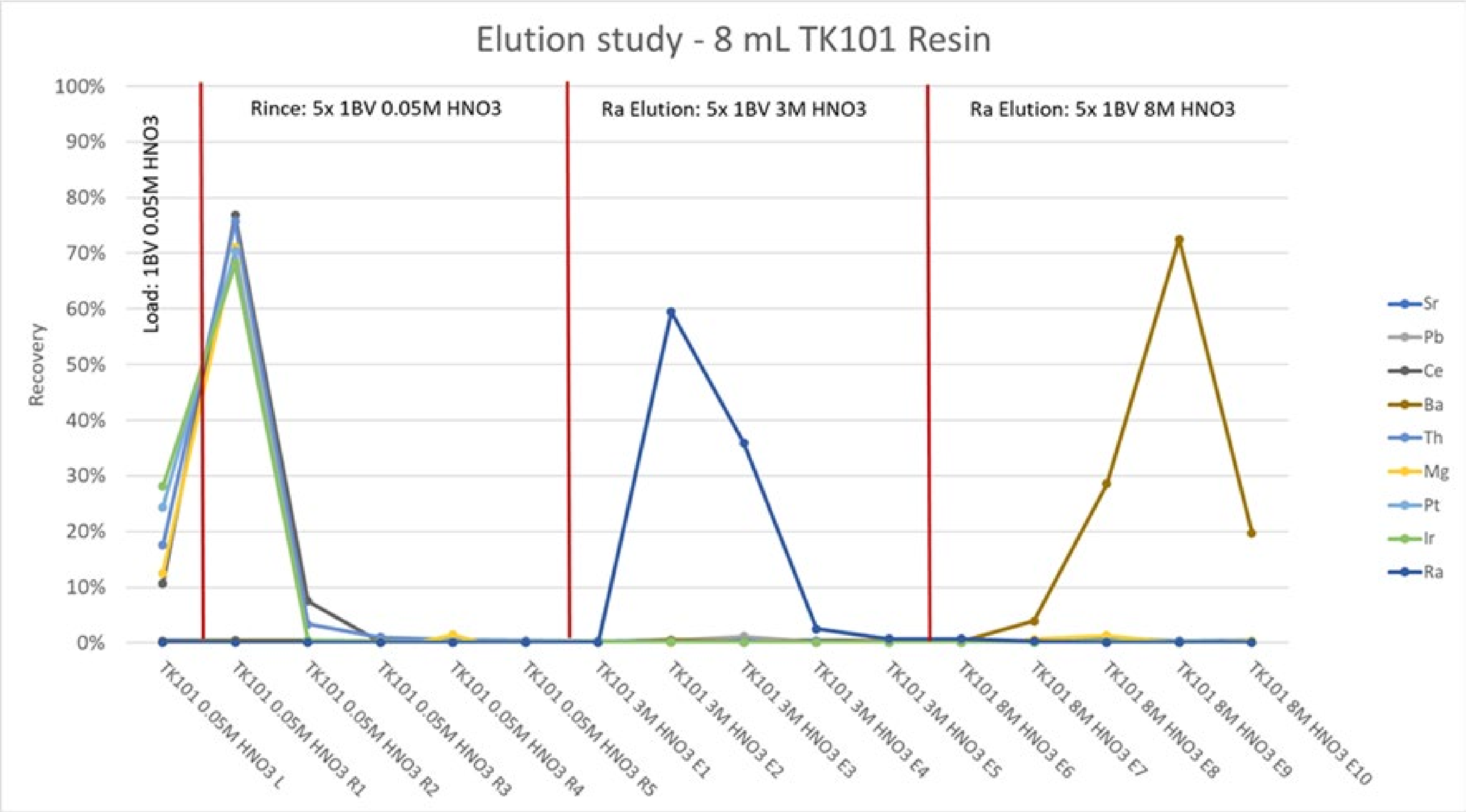
TK101 Lanthanides and Actinides (+ Bi and Pb)



Data provided by Russel et al. (NPL)

- No selectivity for Th/U
- Very strong Pb retention => elution in high HCl or citrate

Ra separation on TK101

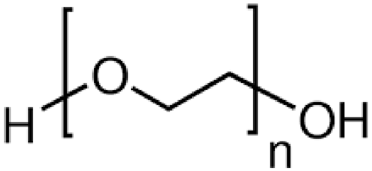


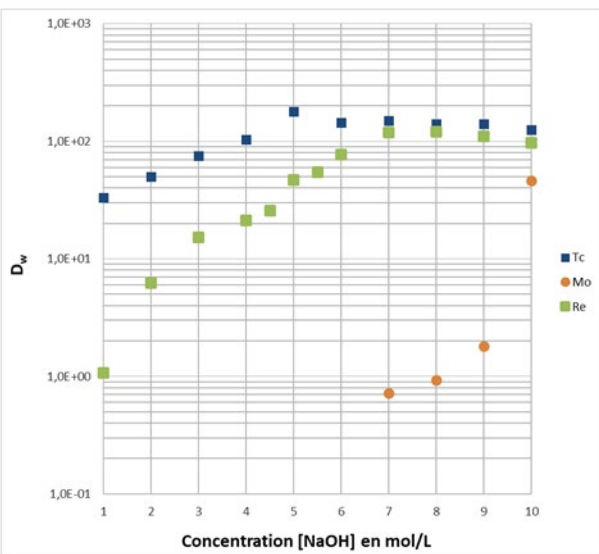
- Good Ra separation when loading from dilute HNO_3/HCl
- Ra purification (e.g. needles):
  - Ra/Ba Sulfate treated with carbonate
  - Dissolution in dilute HNO_3
- Ra elution in 3M HNO_3, Ba, Pb, Sr remain retained
- No retention of U, Th, Pt, Ir,…
- Ba eluted in 8M HNO_3

Tc-99m - new TK202 Resin

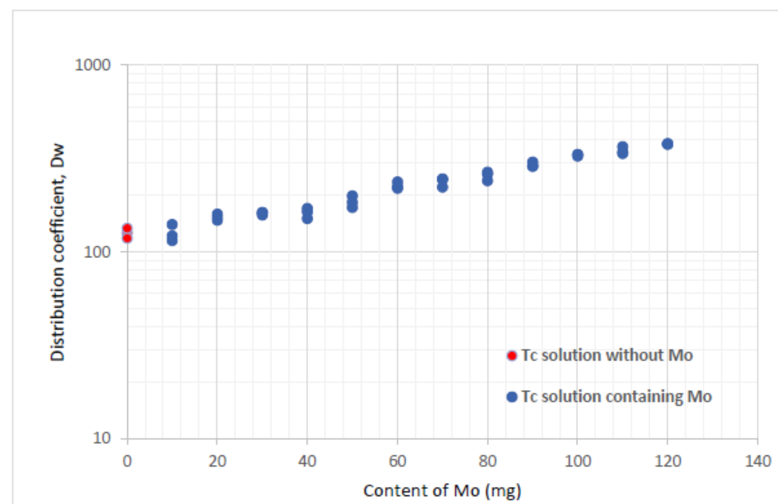
TRISKEM
Expertise in Separation Chemistry

- 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



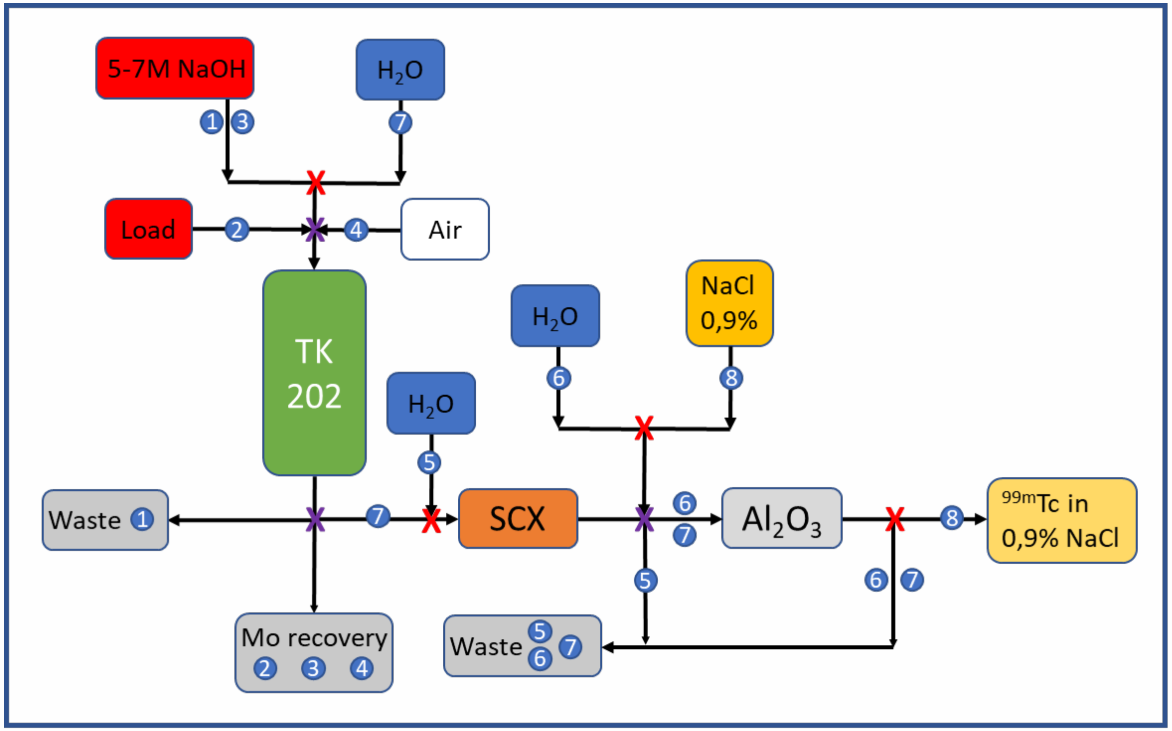


Dw values for Tc, Re and Mo on TK202 Resin, at varying NaOH concentrations. Tc data taken from Cieszykowska et al.(2).



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

Tc-99m separation from Mo targets – suggested scheme (following 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

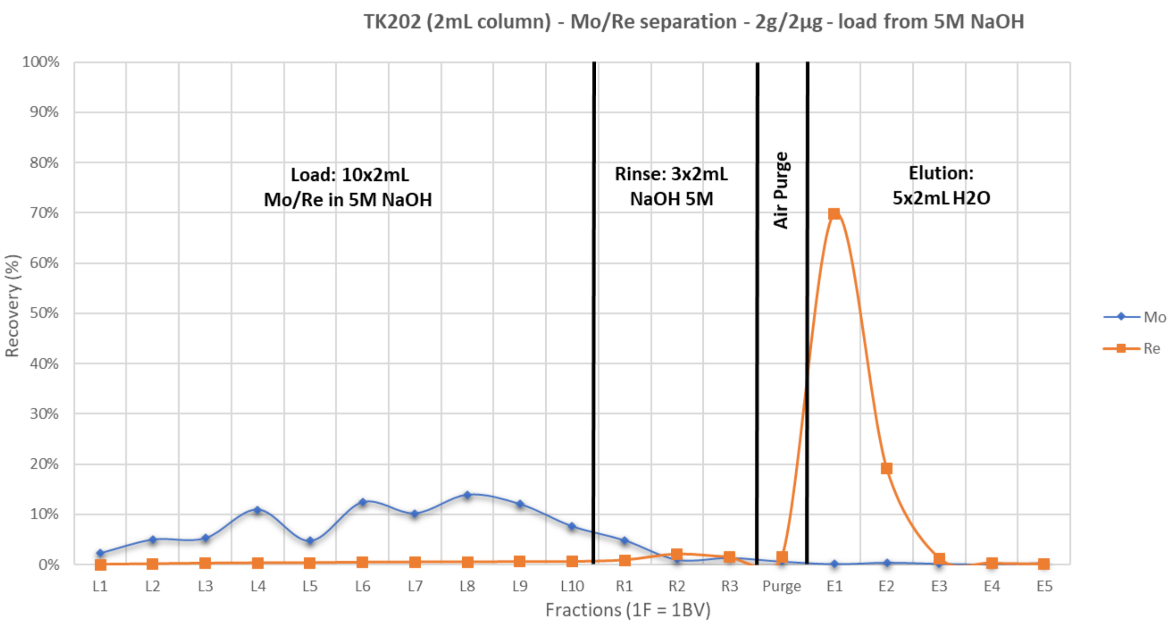
TK202 : 35-75 or 75-150µm
X : 3-ways valve
X : 4-ways valve
SCX : Strong Cation Exchange
Al_2O_3 : Acidic Alumina

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 via cyclotron route

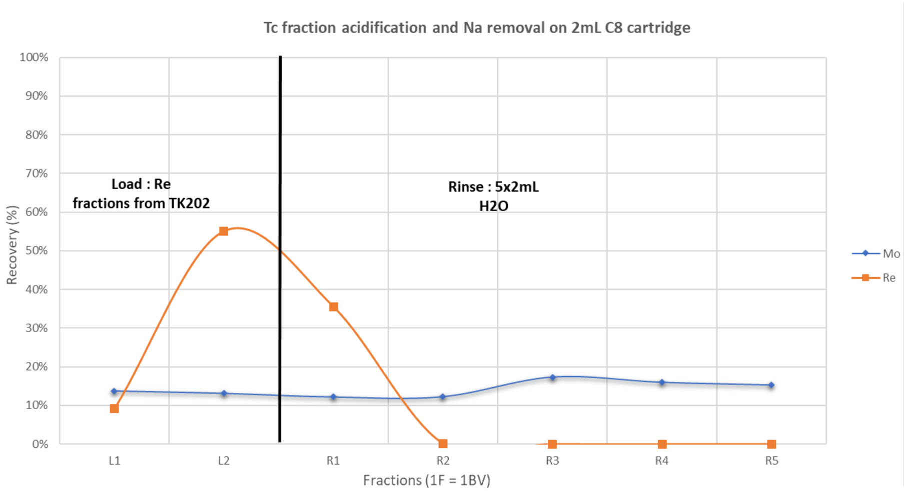


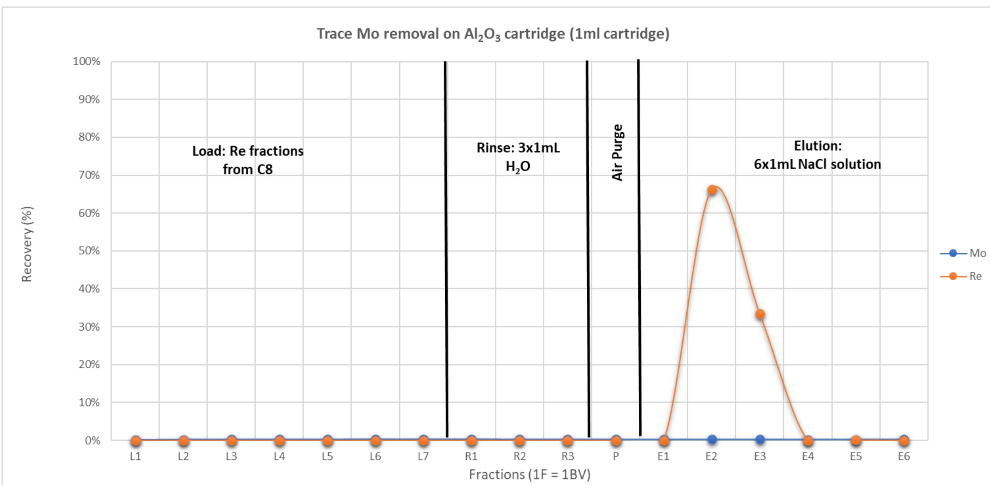
Tests performed cold with 2g Mo and 2 µg Re

- 2 mL TK202 cartridge
- 2 mL C8 cartridge
- 1 mL AlOxA cartridge

Method similar to Zeisler et al.

High Re yield (~90%) in 2 – 3 mL 0.9% NaCl solution





On-going :Tc-99m from large Mo targets

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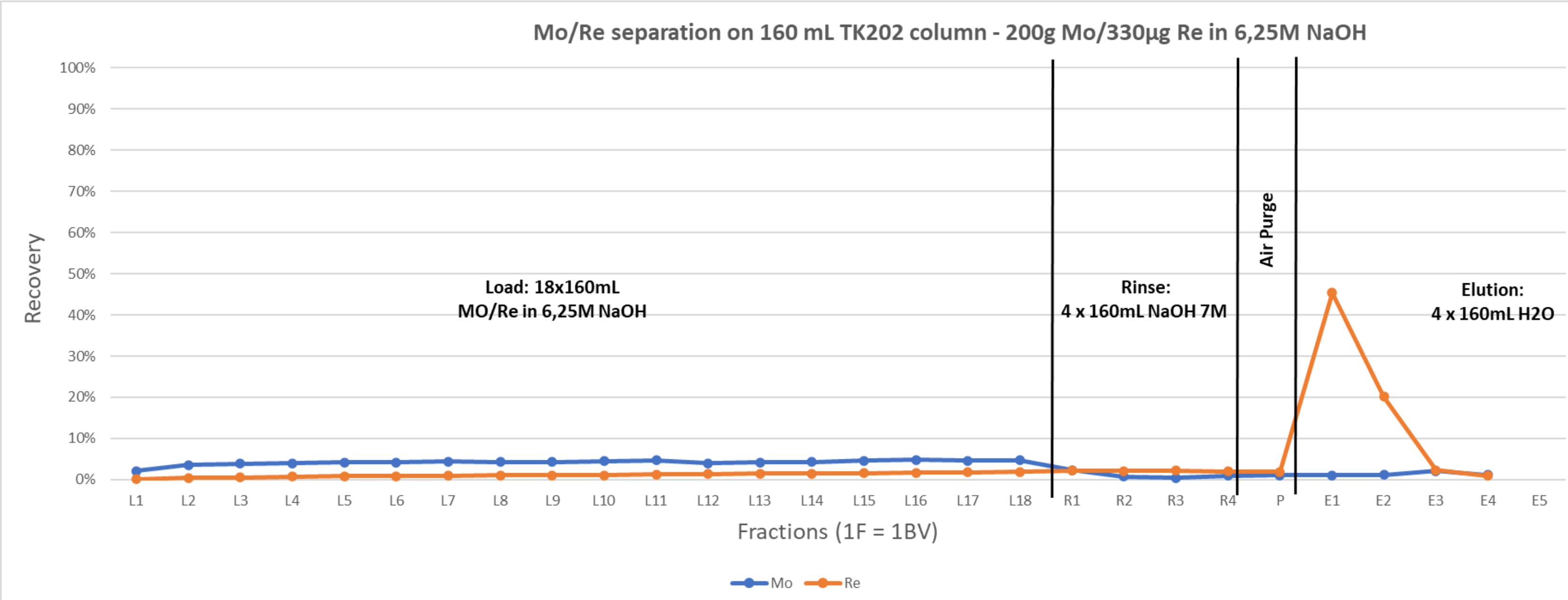
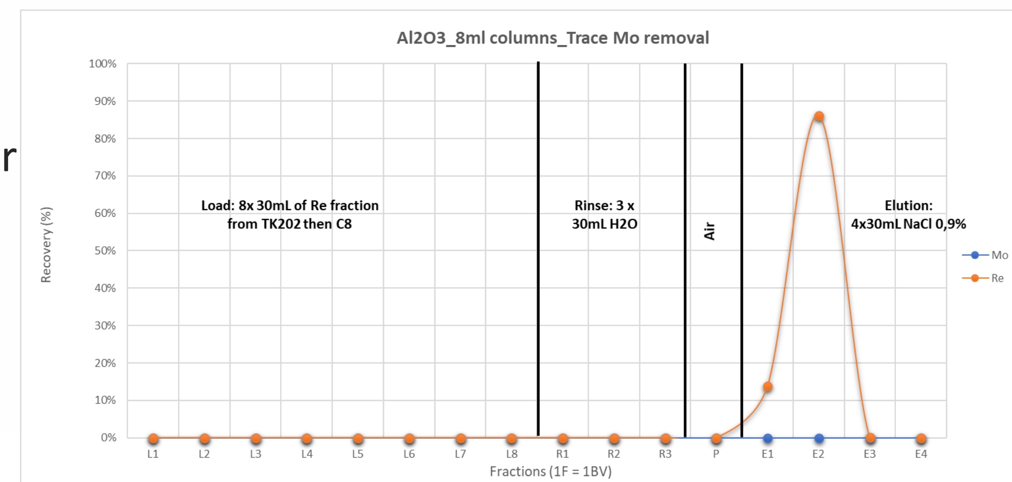


- On-going work on 200g Mo
- ~160 mL TK202 column
- Load from 6 - 7M NaOH - elution in water
- Pass through C8 cartridge for acidification and Na removal
- Final concentration/conversion to 0.9% NaCl on 8 mL AlOxA cartridge



CL Resin - Iodine removal from effluents

Decamp et al.: Iodine removal from elevated sample volumes[§]

- Treatment of complex process effluents
  - > 10 L radioactive effluent (1M HNO_3)
- Issues with rad. waste storage
  - Storage as liquid waste challenging
  - Preferably stored as solid waste
- Use of mixed-bed columns
  - 3g Ag loaded CL resin (plus 4g XAD-4 resin)
- Flow rate up to 180 mL/min
- Radio-iodine retention: 89% - 98%
- Retention of up to 2000 GBq radio-iodine per 7g column

Example for decontamination of effluents

[§] C. Decamp (IRE), S. Happel: Utilization of a mixed-bed column for the removal of iodine from radioactive process waste solutions, Journal of Radioanalytical and Nuclear Chemistry, online April 2013, DOI: 10.1007/s10967-013-2503-1

CL Resin

Chromatographic separation of the theranostic radionuclide ^{111}Ag from a proton irradiated thorium matrix

CrossMark

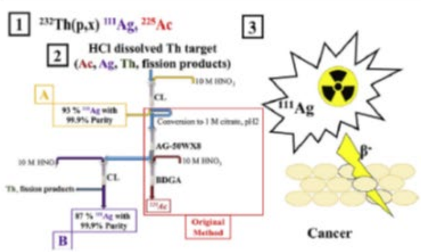
Tara Mastren [a], Valery Radchenko [a,1], Jonathan W. Engle [a,2], John W. Weidner [a], Allison Owens [b], Lance E. Wyant [b], Roy Copping [b], Mark Brugh [a], F. Meiring Nortier [a], Eva R. Birnbaum [a], Kevin D. John [a], Michael E. Fassbender [a,*]

[a] Chemistry Division, Los Alamos National Laboratory, P.O. Box 1663, Los Alamos, NM 87545, USA
[b] Nuclear Security and Isotope Technology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831, USA

H I G H L I G H T S

- Chromatographic recovery of medical isotope ^{111}Ag from proton irradiated thorium targets.
- First-time measured equilibrium distribution coefficients for silver and ruthenium on CL resin.
- ^{232}Th (p, fission) cross-section data for the formation of ^{111}Ag and ^{110m}Ag.

G R A P H I C A L A B S T R A C T



Anal. Chem., 2018, https://pubs.acs.org/doi/10.1021/acs.analchem.8b01380

Separation of protactinium employing sulfur-based extraction chromatographic resins

Tara Mastren†, Benjamin W. Stein†, T. Gannon Parker†, Valery Radchenko†#, Roy Copping‡, Allison Owens‡, Lance E. Wyant‡, Mark Brugh†, Stosh A. Kozimor†, F. Meiring Nortier†, Eva R. Birnbaum†, Kevin D. John†, Michael E. Fassbender†*

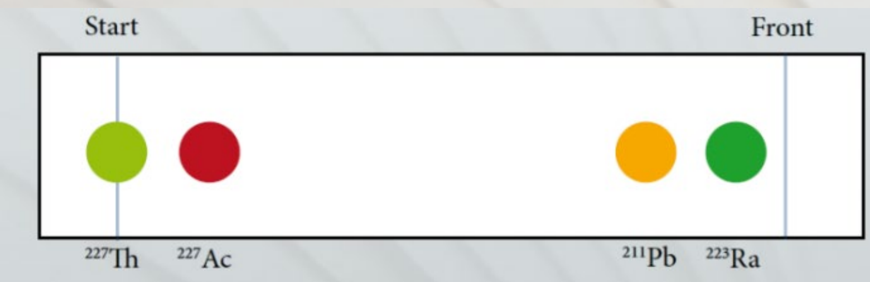
†Chemistry Division, Los Alamos National Laboratory, P.O. Box 1663, Los Alamos, NM 87545, USA
‡Nuclear Security and Isotope Technology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831, USA

#Current Address: Life Sciences Division, TRIUMF, 4004 Wesbrook Mall, Vancouver, BC, V6T2A3, Canada

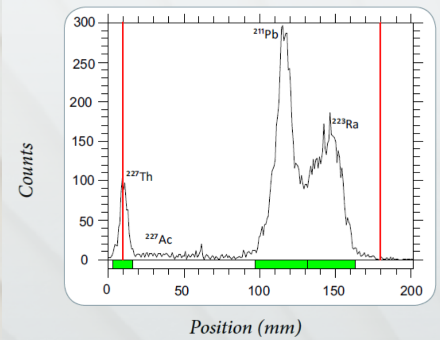
DGA Sheets

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

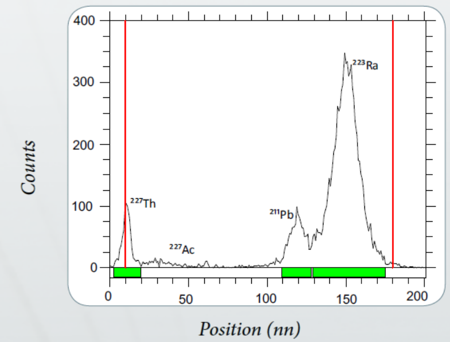
(p.ex. Ra-223, Ac-225/Bi-213, Pb-212, Ge-68/Ga-68 …)
  - TLC scanner or radiometer/LSC or HPGe after cutting
- Run under acidic conditions => radionuclidic purity



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.

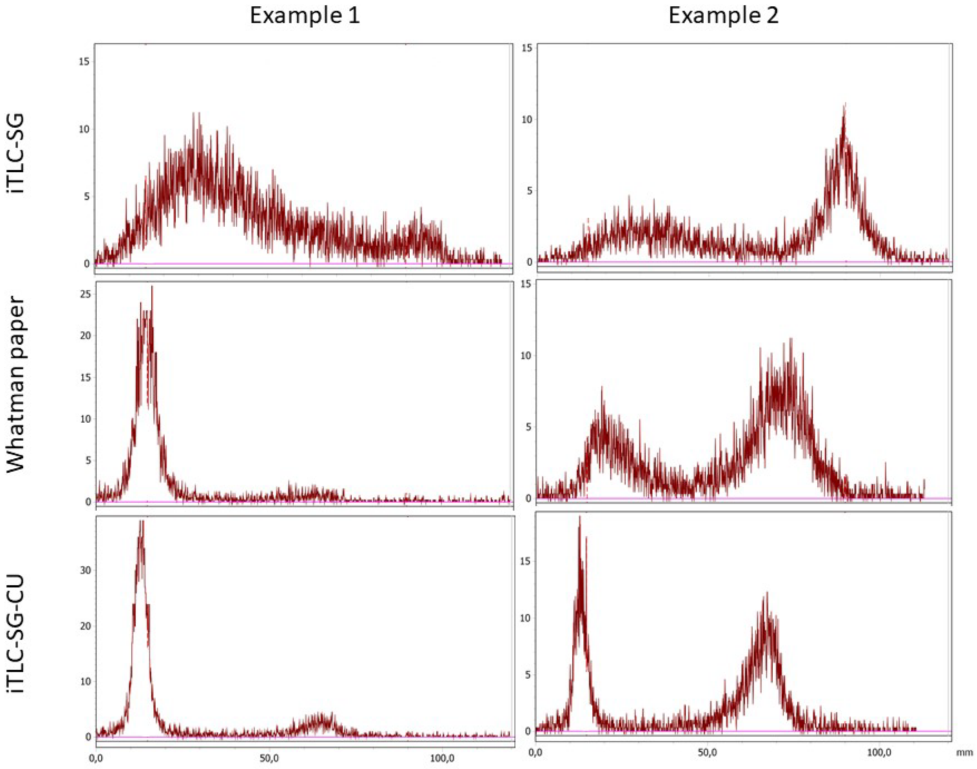


Radiochromatogram measured one hour afer separaton. Decay and ingrowth of ^{211}Pb is clearly visible.

- More types of sheets under development (selectivities, geometry, support)
  - ZR, TK201,…
  - 2D TLC for radionuclide screening ?

Upcoming - CU Sheets

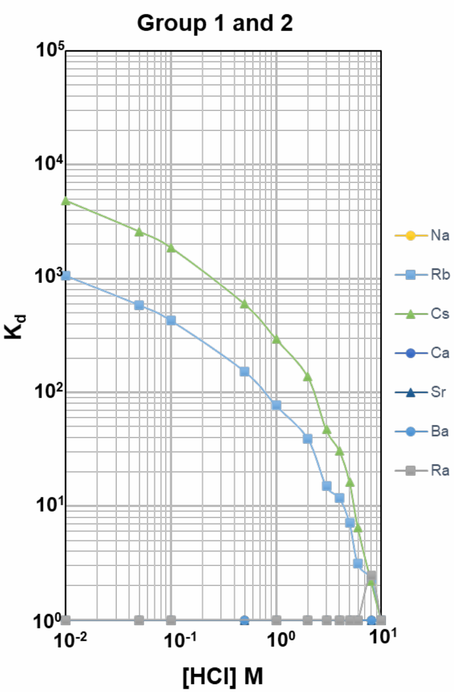
- Poster presented at Terachem 2022 (Svedjehed et al.)
- QC of Cu radiolabeled peptides (labeled vs free Cu)
  - Shown: [^{61}Cu]Cu-NOTA-octreotide
- Spotting/run on three different papers after labeling:
  - Whatman and iTLC without modification and
  - CU extractant impregnated iTLC paper.
- Both iTLC paper (impregnated/non-impregnated) developed in less than 10min, Whatman took 25 – 30 min.
- CU extractant impregnated iTLC paper showed superior resolution

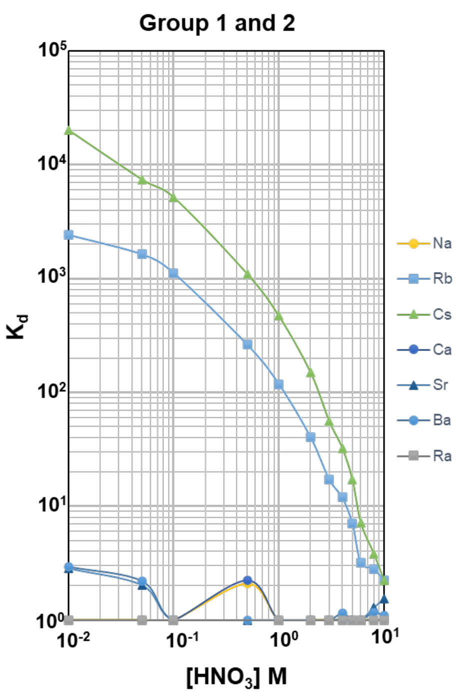


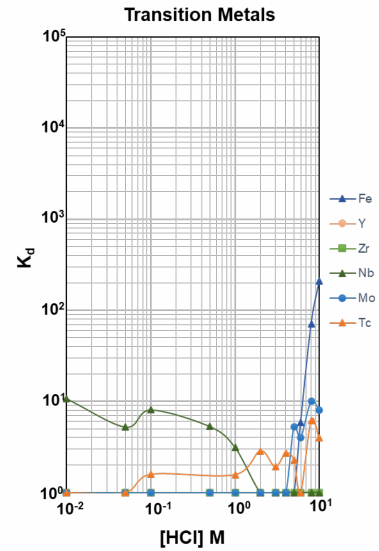
- Other systems under development/testing

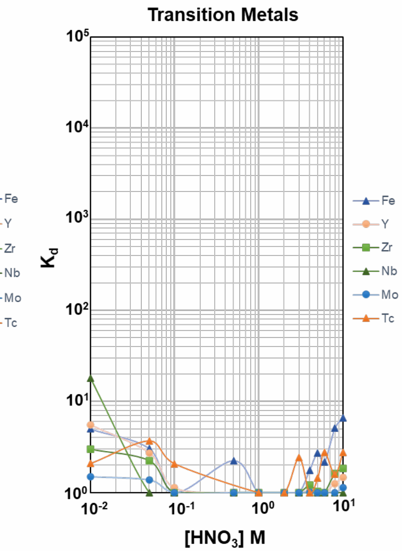
Under Development - TK300 Resin

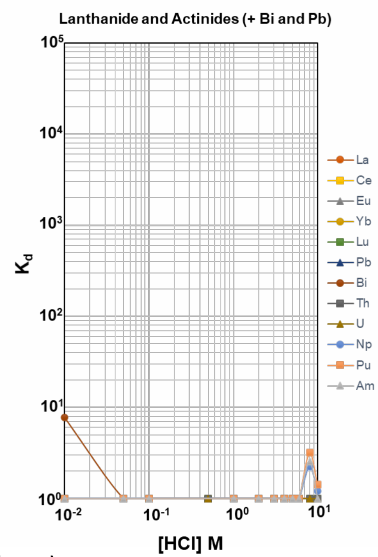
- Macrocycle based Resin
- Cs and/or Rb separation
- Selectivity for Cs and Rb over other elements tested in HNO_3 and HCl
  - Incl. Ba

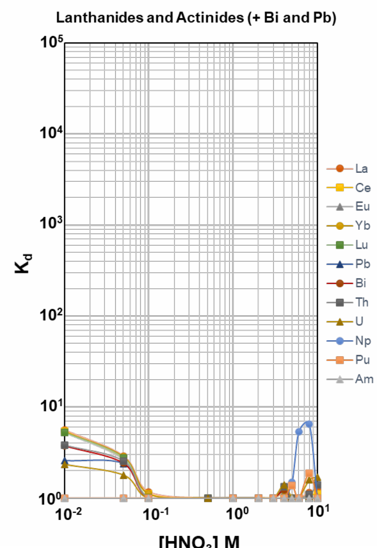












Data provided y B. Russel (NPL)

Under Development - TK300 Resin

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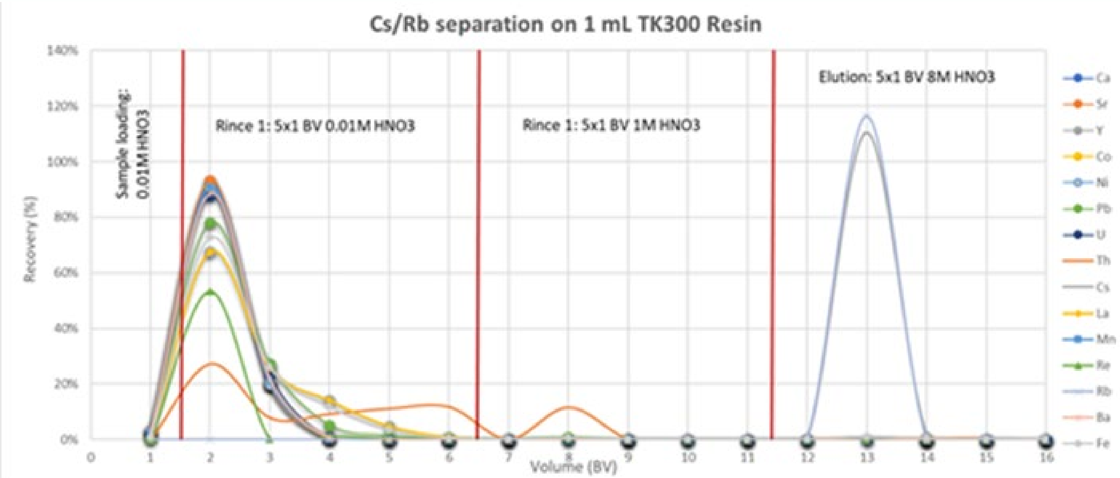
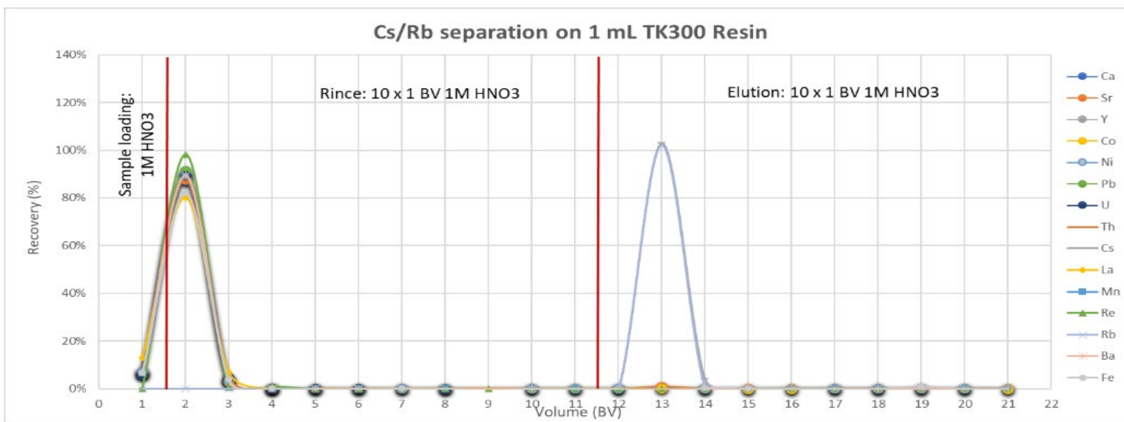


Elution study, Cs and Rb separation from selected elements on TK300 resin, loading from dilute acid.



Elution study, Cs and Rb separation from selected elements on TK300 resin, loading from 1M HNO3

- Separation of Cs and Rb
- Retention over wide pH range (up to 1M HNO_3)
- Cs/Rb separation possible
- Elution in >3M HNO_3
  - Alternative => push resin into LSC vial (=>TEVA)
  - Membrane filters
- Current limitations:
  - Limited Cs capacity
  - Interference by K
  - Limits use for environmental samples
- Improvement ongoing

➢ Rather suitable for decommissioning samples

Some other on-going projects

- Further upscale of radiolanthanide separations
- Scandium separation
  - TK200, TK221, TK222
- Other radiometals
  - Mn, V, In, Auger (Sb, Pd, Hg,…)
- At separation
  - TK400, Rn-211/At-211 generator,…
- Improvement of radiolysis stability
- 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
- 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,…
- In-field preconcentration
  - Impregnated membranes
  - Cartridges

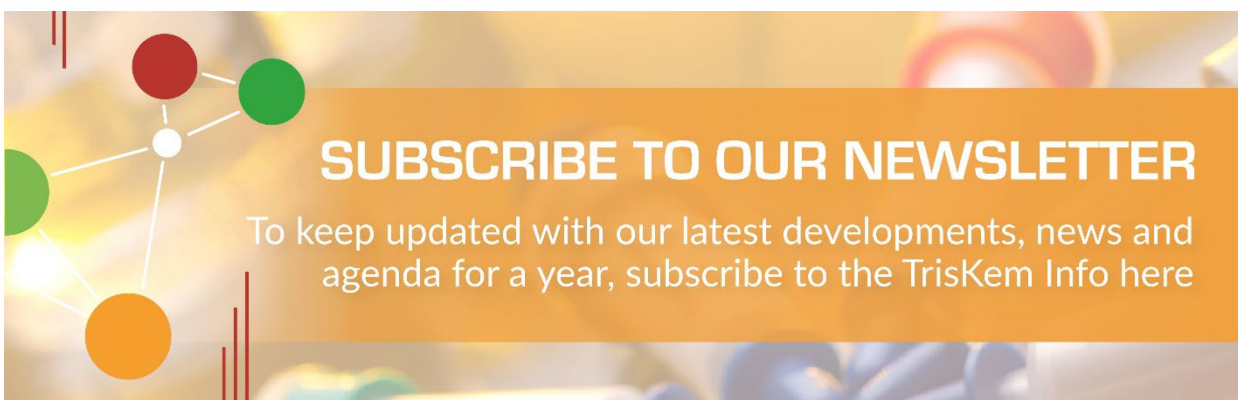
Some other on-going projects

- Rapid tests
  - Impregnated PSm resins
  - Impregnated membrane filters
  - Range of ‘Test sticks’
    - Suitable impregnated support
    - JCU => rapide isotope ratio analysis by MS (metallomics)
    - Uni Southampton/NPL
      - Ideally multiple layers of resins for multi RN screening
      - LSC measurement
      - Scintillating supports for non-LSC options
      - Decommissioning/screening

- Separation of DTM
  - SE Resin
  - Zr-93, Fe, Mo, Nb,…
- Decontamination
  - PAN based materials (e.g. AMP-PAN)
- Microfluidics
- Other ’geometries’ &

‘Non-resin’ separation materials

Thank you for your attention!



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Cyclotron production of Ga-68

- Riga et al. Physica Media 2018
- Liquid target: 1.7M $^{68}Zn(NO_3)_2$ in 0.2M HNO_3
- GE PETtrace at 12MeV, 32 min, 46 µA
- Modular Lab (EZAG)
- 4.3 ± 0.3 GBq EOB
- Separation on ZR Resin and TK200 Resin (t~40 min)
  - Loading of ZR Resin at <0.1M HNO_3,
  - Rince with 9 mL 0.1M HNO_3.
  - Ga Elution with 5 mL 2M HCl directly onto 100 mg TK200
  - Ga Elution from TK200 with water
- Chemical yield >75%,
  - 2.3 ± 0.2 GBq after separation
- Purity: 99.976 ± 0.002% => Ph. Eur.
- Target material recovery 80 – 90%
- For solid targets: single cartridge method (TK400) also under evaluation

Original paper

Production of Ga-68 with a General Electric PETtrace cyclotron by liquid target

Stefano Riga[a,*], Gianfranco Cicoria[b], Davide Pancaldi[a], Federico Zagni[a], Sara Vichi[c], Michele Dassenno[d], Luca Mora[e], Filippo Lodi[e], Maria Pia Morigi[d], Mario Marengo[a]

S. Riga et al. Physica M

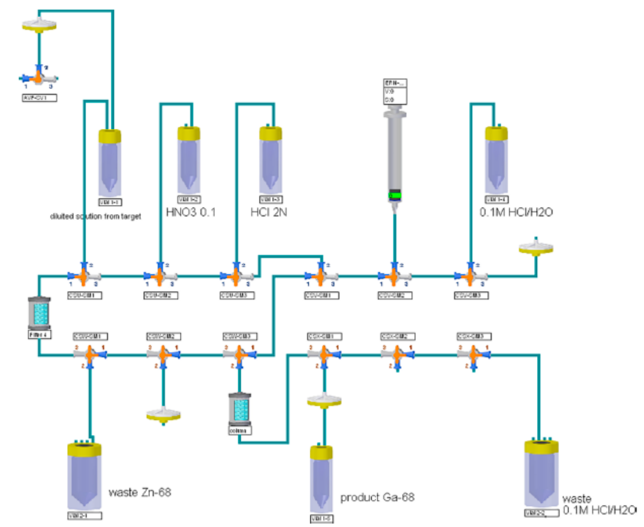
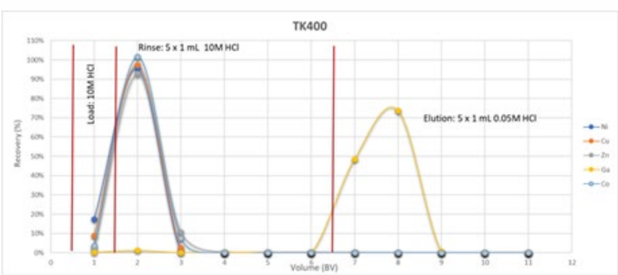


Fig. 4. Schematic diagram of the separation process (Modular Lab, Eckert & Ziegler, Berlin).



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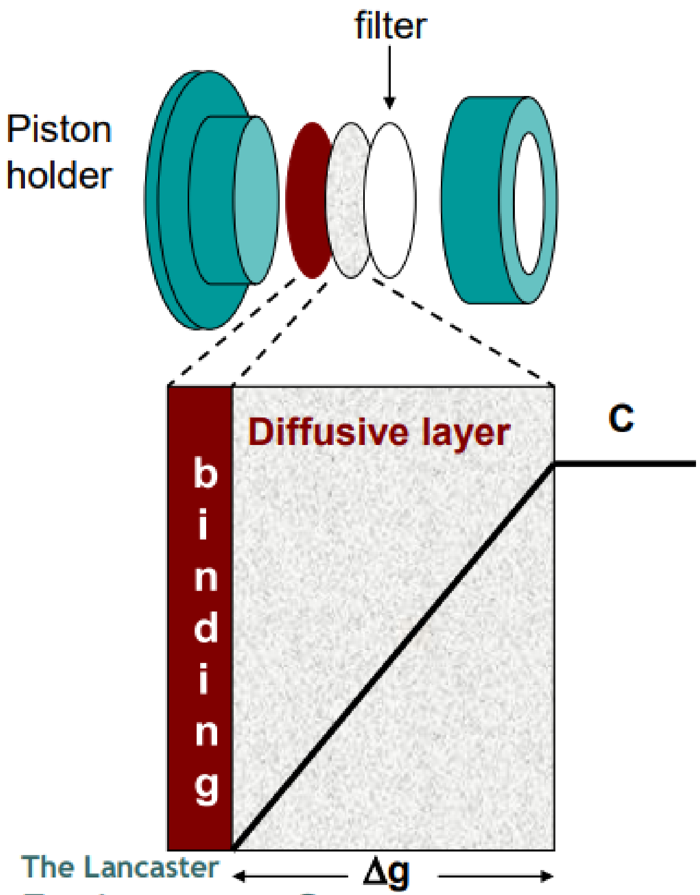
Diffusive Gradients in Thin Films



F = M/At

F = DC/Δg

C = MΔg/DAt

F = flux (ng cm^{-2} s^{-1})

M = mass (ng)

A = area (cm^2)

t = exposure time (s)

D = diffusion coefficient (cm^2 s^{-1})

C = ng cm^{-3} (ppb) / Bq l^{-1}

Δg = cm

The Lancaster
Environment Centre