TrisKem International

An overview over some new extraction chromatographic resins and their application in radiopharmacy

Steffen Happel

04/06/19

TRISKEM
Expertise in Separation Chemistry

TrisKem International

- Based in Rennes (France)
- Independent company since 02/07
    - Formerly part of Eichrom Europe
    - ISO 9001 since 2007
- Staff : 23
- R&D and TechSupport group:
    - 3 RadChem PhD, 2 OrgChem PhD, 1 Engineer and 3 Technicians
- R&D: Development of new resins, techniques and applications
- Several domains:

R&D TrisKem International

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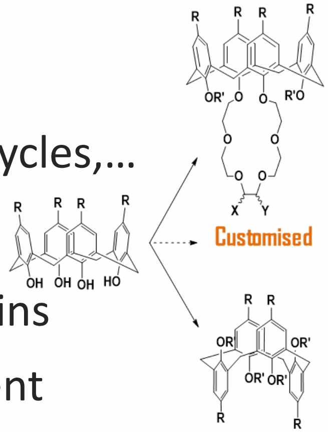
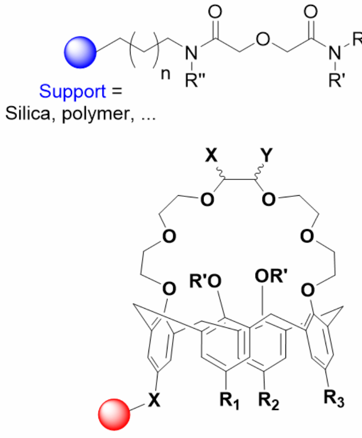
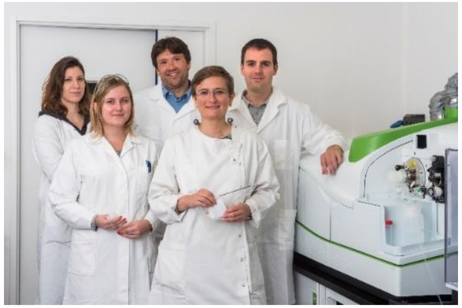
- Two R&D labs:
  - Synthesis Lab (new resins and extractants)
    - Incl. grafted resins (silica or polymers), macrocycles,…
  - Application Lab
    - Preparation of extraction chromatographic resins
    - Resin characterisation and method development





- Equipment:
  - ICP-MS, IC, TOC, TGA, IR, automatic desiccator, benchtop NMR (43 MHz), surface area and pore size volume analyser, size and shape analyser, pycnometer
  - Production and packing lab with four 20L reactors

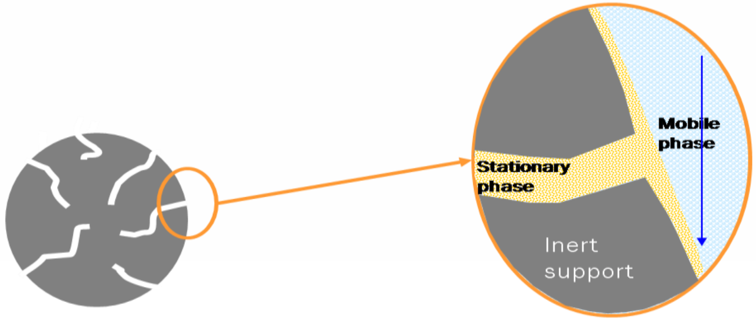


- No handling of radioactivity => R&D cooperation
  - Resin and method development “cold” => R&D partner

Extraction chromatography

Organic extractant impregnated onto inert support

- « Supported Solvent Extraction » / « Solvent Impregnated Resins »
  - Distribution between two non-miscible phases
  - High density of functional groups
  - Fast kinetics/small volumes => rapid separations
  - High variety of selectivities:
    - Pure extractants, synergetic mixtures, solid extractants in diluents
  - Aim: selectivity for product, no selectivity for target material
  - Elution under 'soft' conditions in small volume => labeling/injection
  - Bleeding might need to be adressed (Prefilter, AIX, CEX,…)



Domains and applications

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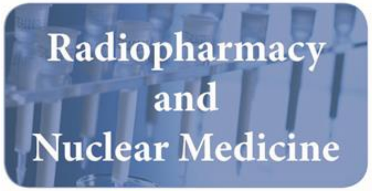
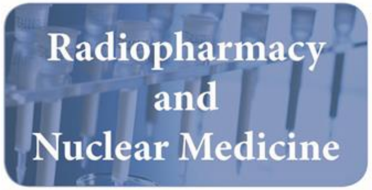
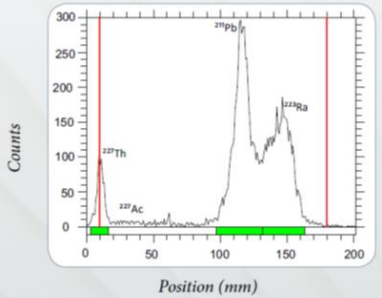


- Radiopharmacy/Nuclear Medicine
  - Radionuclide production
    - Cooperation with cyclotrons & reactors (NL, RN producers,…)
    - Equipment provider (targetry, synthesizer,…)
    - Separation of radionuclides from irradiated targets
      - » Diagnostics: Zr-89, Cu-64, Ga-68, Ge-68, Ti-44/5, Tc-99m, Sc-43/4…
        - **ZR Resin, CU Resin, TK200 Resin, TK400, TK201, TK202,…**
      - » Therapy: alpha emitters, Lu-177, Cu-67, Sn-117m, Sc-47…
        - **TK400, TK200, TBP Resin, CU Resin, TK211/2, TK221,…**

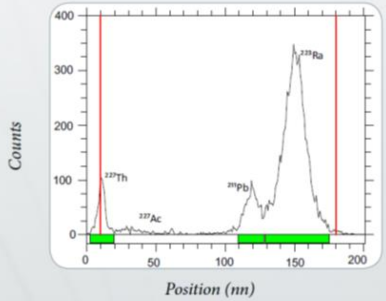
Domains and applications



- Radiopharmacy/nuclear medicine
  - Purification of generator eluates => under development
  - Decontamination of contaminated effluents => **CL Resin,...**
  - Quality control
    - Cartridge based methods
    - **DGA sheets** (functionalized TLC, Ra-223, Ga-68, Pb-212,…. => CVUT Prague)



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



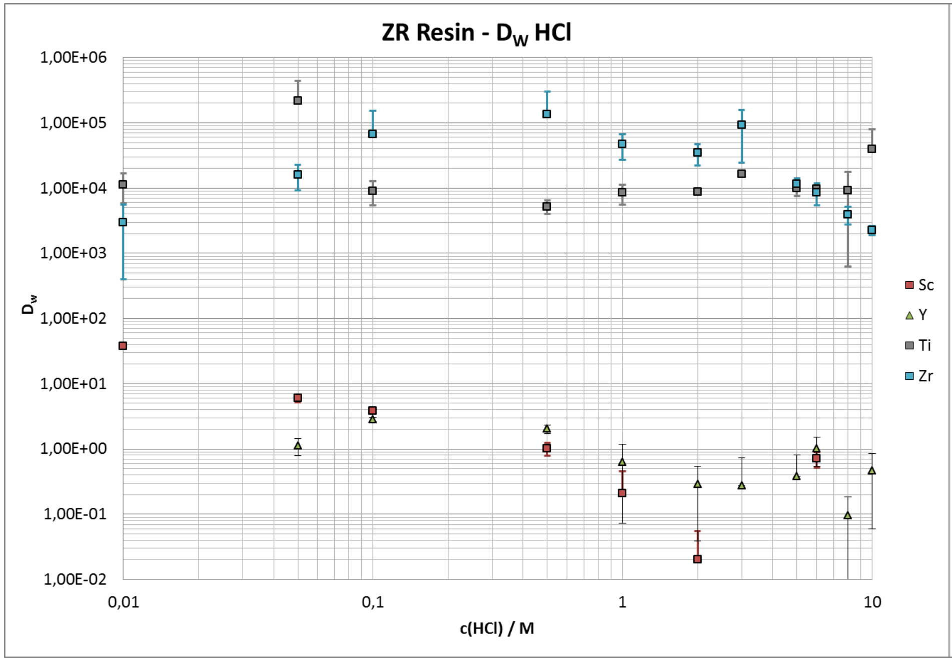
Radiochromatogram measured one hour afer separaton. Decay and ingrowth of ^{211}Pb is clearly visible.

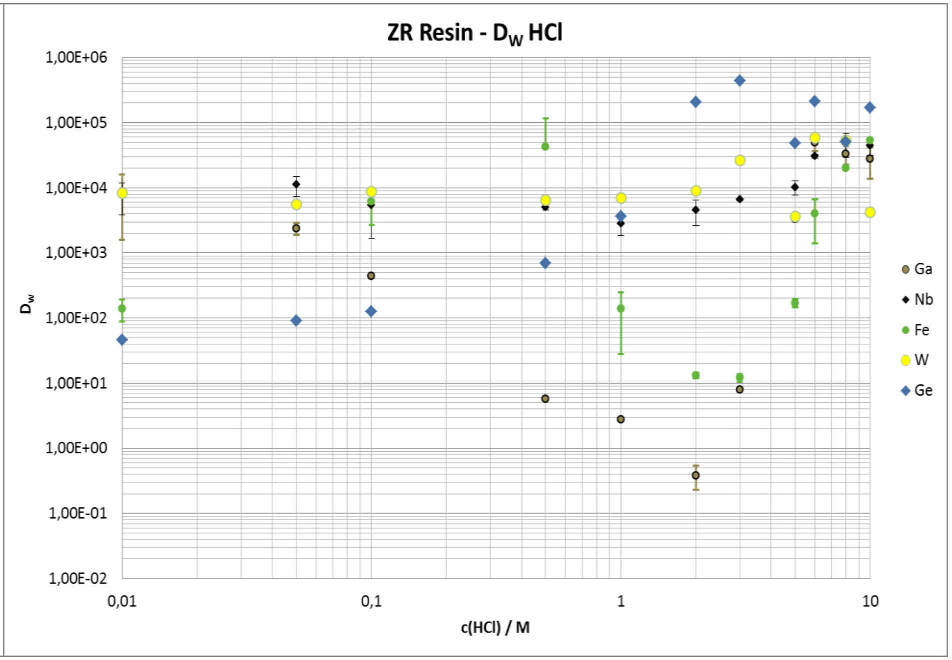
A scheme of chromatographic separaton of mixture of ^{227}Ac and his daugther´s niclides. ^{227}Th remains on start, ^{227}Ac has the retenton factor ca 0.2, ^{211}Pb ca 0.7 and ^{223}Ra ca 0.9.

ZR Resin

- Original scope: Hydroxamate based resin
    - 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

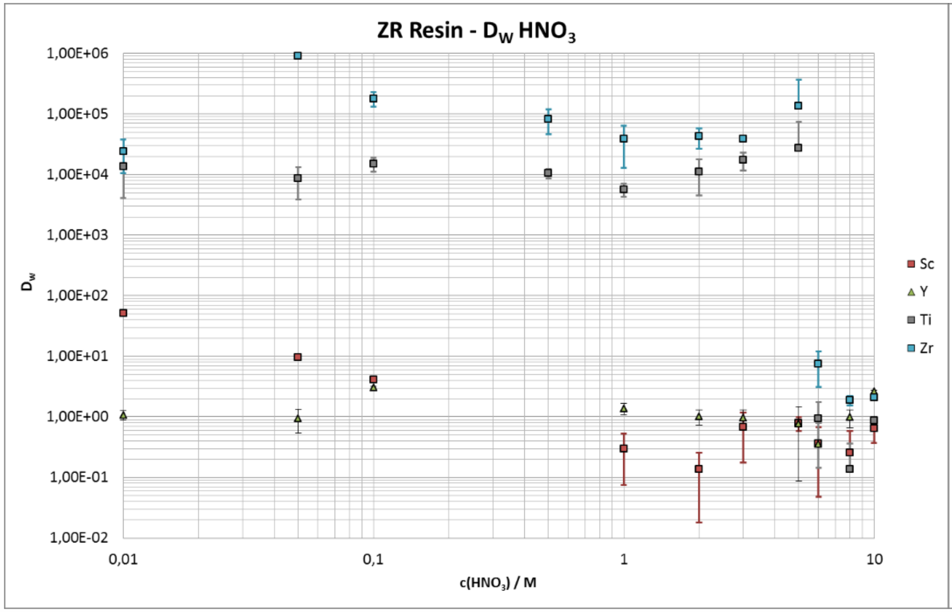
ZR Resin – HCl

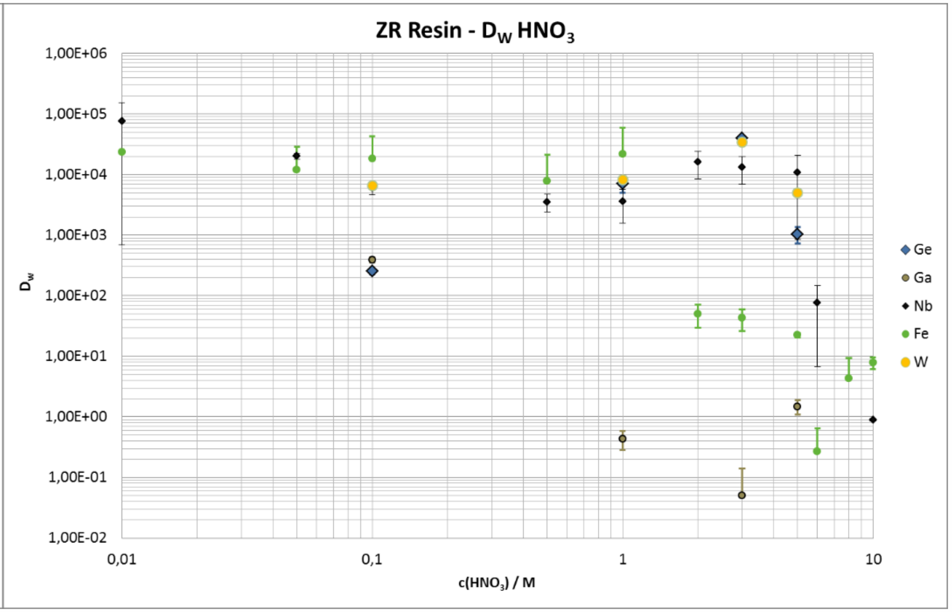




- No selectivity for Y, Sc
- High Ge/Ga selectivity at elevated HCl
- High selectivity for Zr, Ti, Nb, W over wide HCl conc. range
- No selectivity for alcalines and earth alcalines
- Lanthanides not retained
- Fe retention (dip at 2 – 3M HCl)

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

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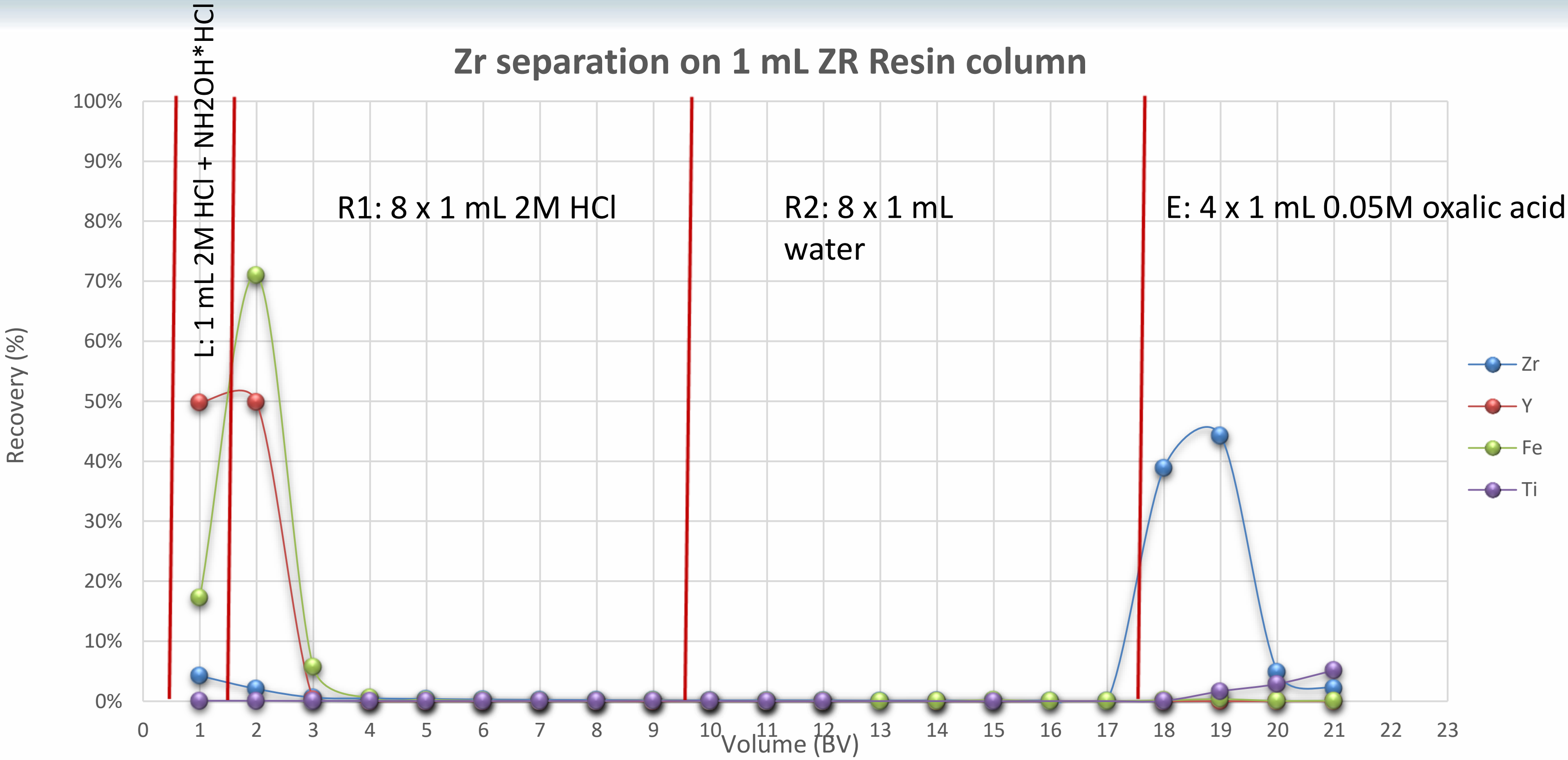

- Load from 2 – 6M HCl
- Rinsing described by Holland may be used
- No activation with acetonitrile
- Quantitative Zr elution in 1.5 - 2 mL ≥ 0.05M oxalic acid
- Clean Fe removal
- Use in commercial systems
  - Taddeo, Pinctada,…

Zr-89 separation on TBP Resin

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- 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
- Zr yield: 89 ± 3%, Y decontamination: 1.5×10^5
- Other applications of TBP Resin:
  - Sc isotope production (=> presentation EANM'18, Polatom)
  - Sn-117m from Cd targets
  - Sn-121m and Sn-126 determination in decommissioning samples

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]

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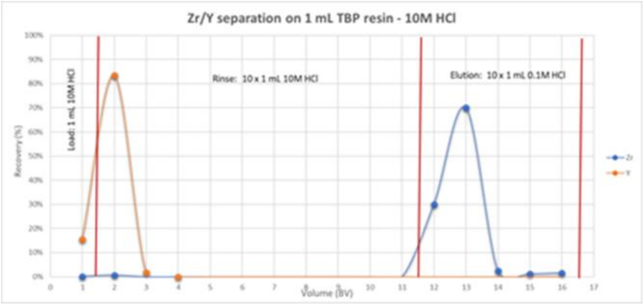
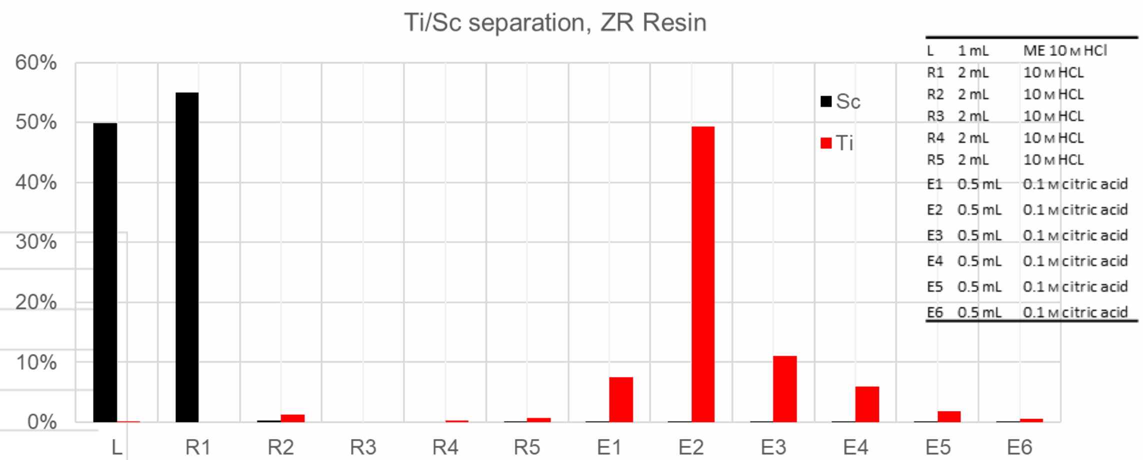
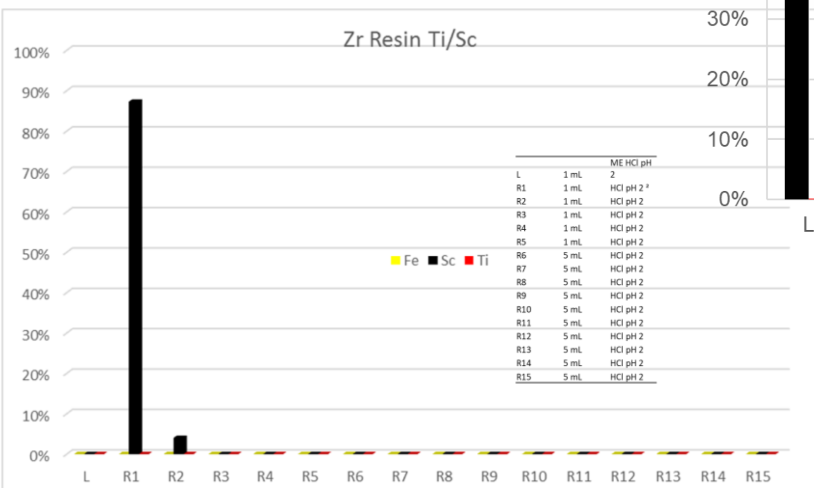


Ti-Sc Separation (Ti-44/5)





- 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
- Publication: Malinconico et al. use of 1M oxalic acid

(J Nucl Med May 1, 2018 vol. 59 no. supplement 1 664)


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-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

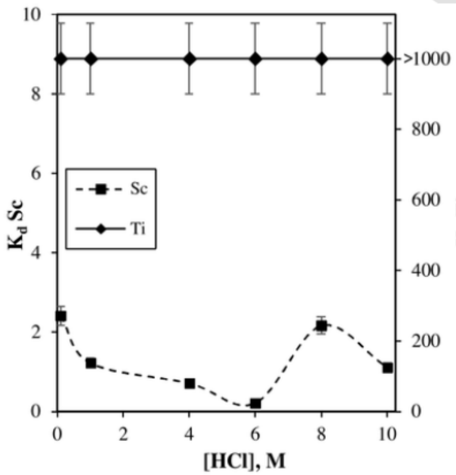


Fig. 3. HCl concentration dependency of K_d for $^{44}Ti/^{46}Sc$ on ZR hydroxamate resin.

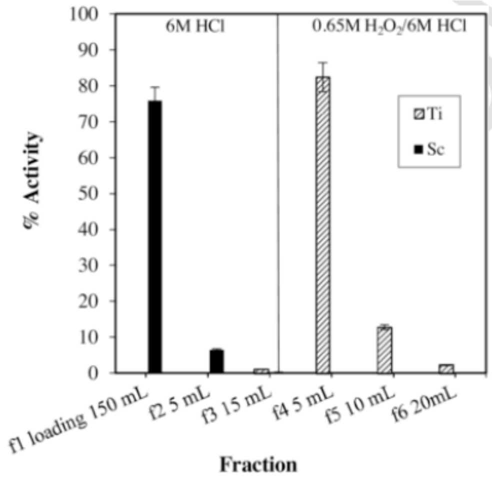


Fig. 5. $^{44}Ti/^{46}Sc$ elution profile using ZR hydroxamate resin with a load of 4 g of scandium.

- **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

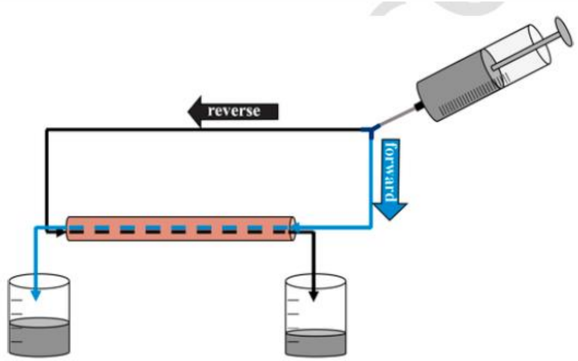


Fig. 1. Schematic concept of a forward/reverse flow radionuclide generator.

- 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/GaCo targets

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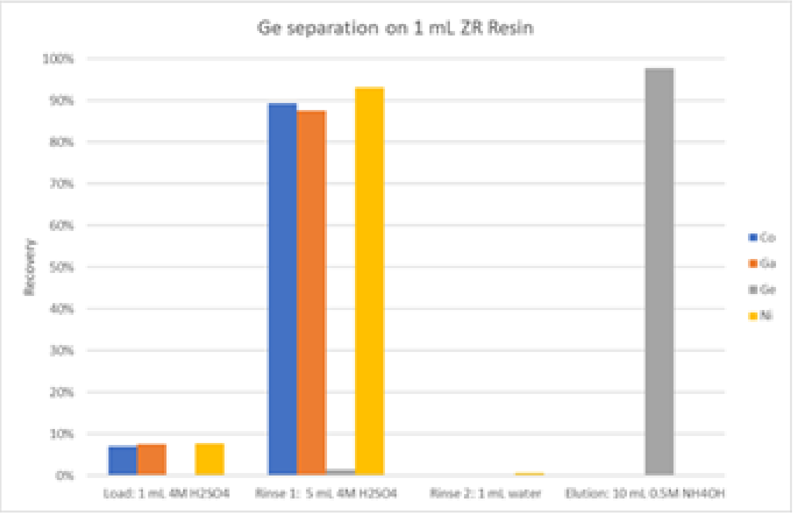
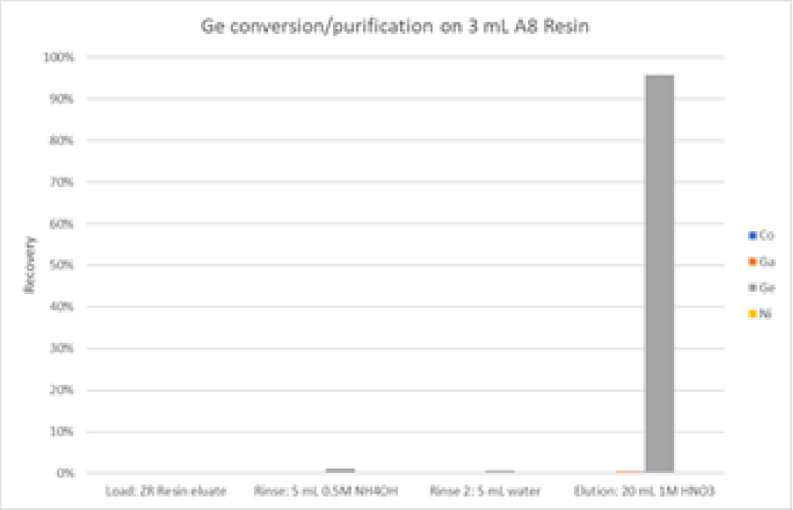
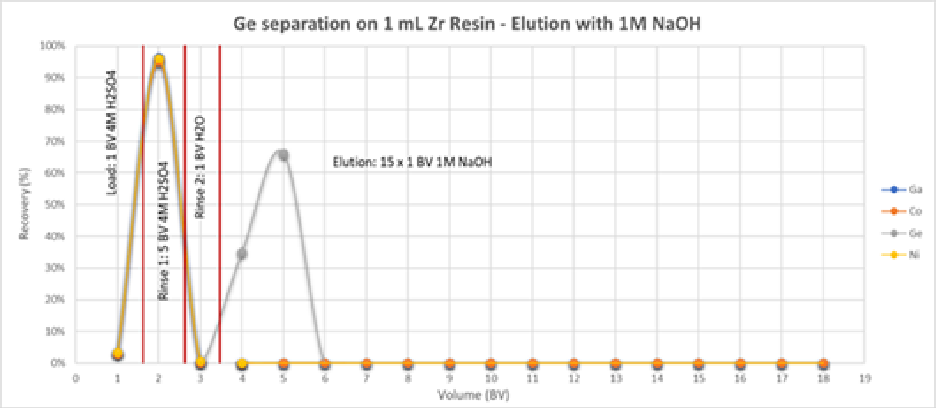
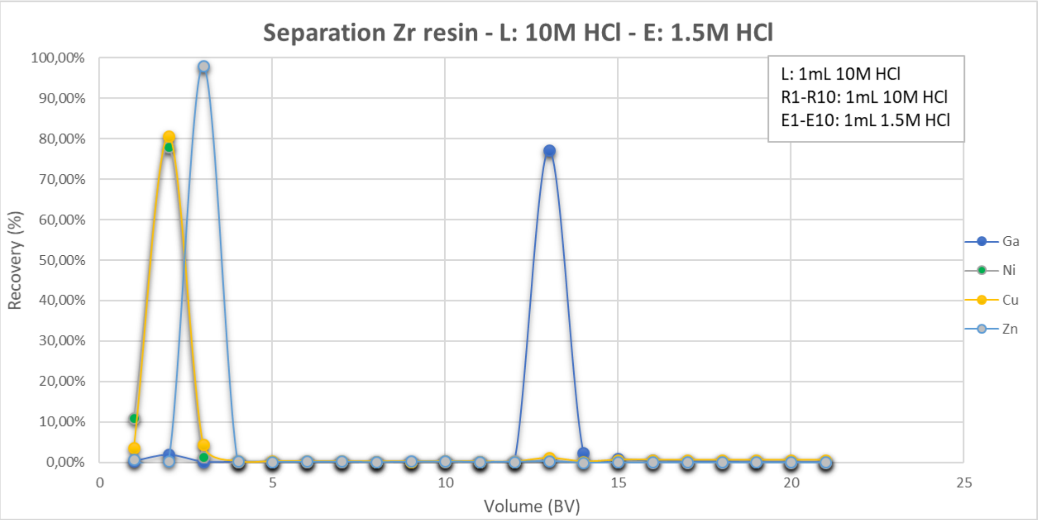
- Ge separation from GaNi or GaCo
  - Cold test on sev. 100mg GaNi per mL ZR Resin
- ZR Resin: Loading from HNO_3, HCl or H_2SO_4
  - HNO_3 & **H_2SO_4** preferred => $GeCl_4$ volatile
  - High retention/purification
- Most efficient elution e.g. NaOH or NH_4OH
- Additional purification via AIX => use of NH_4OH.
- Elution via 0.1M oxalic acid
- Acidification to 9M HCl then
- Conversion to 0.05M HCl via TK400 or PF







Ga-68/Ga-67 separation from Zn targets



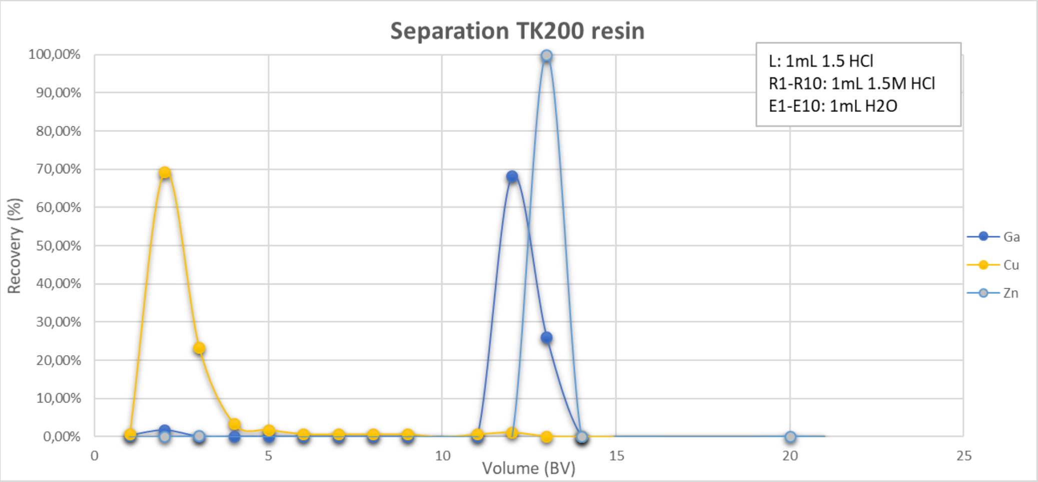
- Loading from:
  - dilute HNO_3 (liquid targets)
  - > 6M HCl (solid targets)
- Ga separation on ZR Resin
- Elution with 1.5M HCl
  - Too high for labeling/injection
- Ga conversion step on TK200 (TOPO)
- TK200 load from 1.5M HCl, elution in 2 – 3 BV water

Presentation EANM '17: Ga-68 from liquid targets by K. Gagnon (GEHS) et al.

Poster ISRS 2019: Ga-68 from solid targets by K. Gagnon (GEHS) et al., Tieu et la. (MITRU)

Publication Riga et al. Physica Media 2018

- Liquid target: 1.7M $^{68}Zn(NO_3)_2$ in 0.2M HNO_3, 12MeV, 32 min, 46 µA
- 4.3 ± 0.3 GBq EOB
- Chemical yield >75%, t = 40 min
- Purity: 99.976 ± 0.002% => Ph. Eur.



=> New IAEA TechDoc: https://www-pub.iaea.org/books/IAEABooks/13484/Gallium-68-Cyclotron-Production

Cyclotron production of Ga-68

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- Riga et al. Physica Media 2018 (in press)
- Liquid target: 1.7M $^{68}Zn(NO_3)_2$ in 0.2M HNO_3
- GE PETtrace at 12MeV, 32 min, 46 µA
- 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]

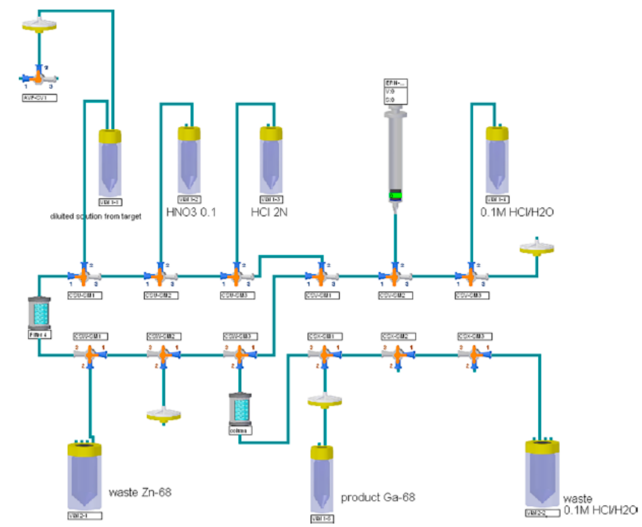
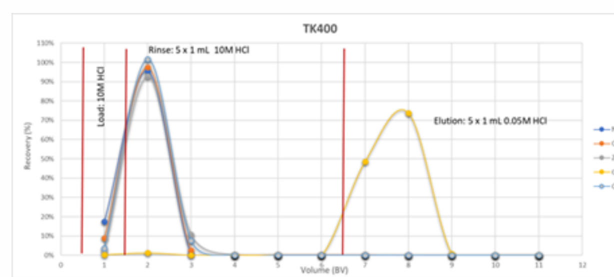
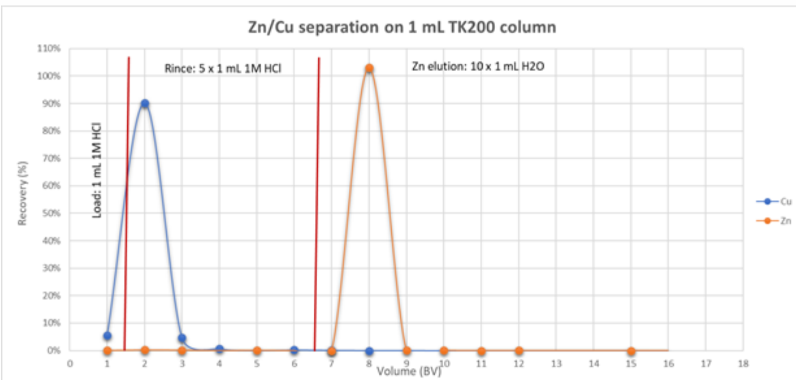


Fig. 4. Schematic diagram of the separation process (Modular Lab, Eckert & Ziegler, Berlin).



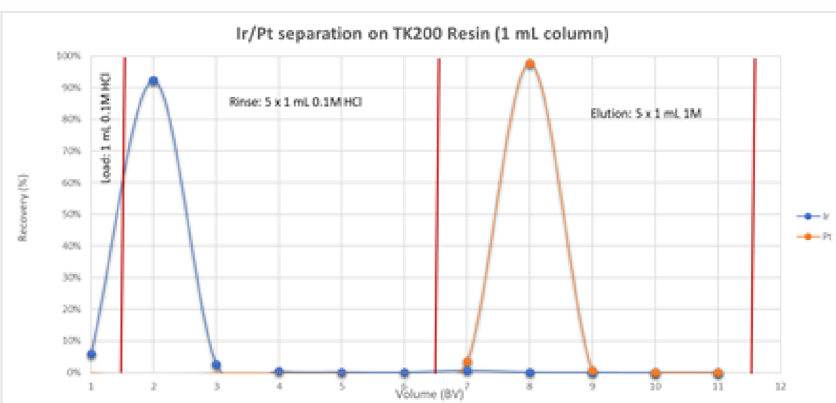
Other examples for separations on TK200

- Zn separation from Cu



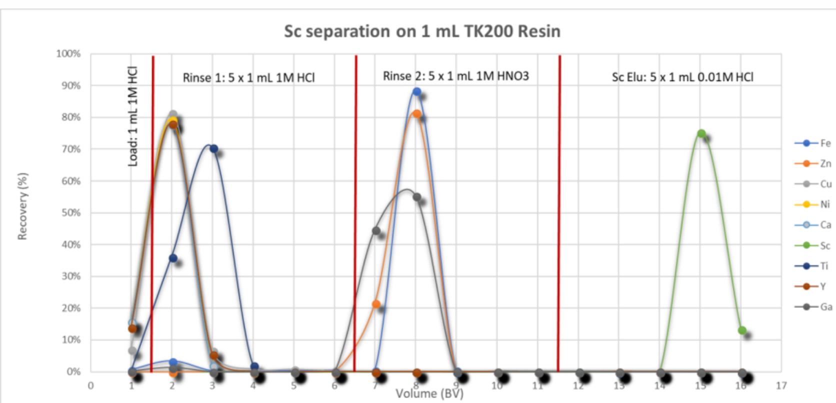
- Zn/Cu separation. Elution study, ICP-MS measurement
- Zn-65 separation. Data kindly provided by Fedor Zhuravlev, DTU

- Pt separation from Ir



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

- Sc from Ca



- Elution under rather soft conditions
- Potentially in combination with TBP Resin

CU Resin

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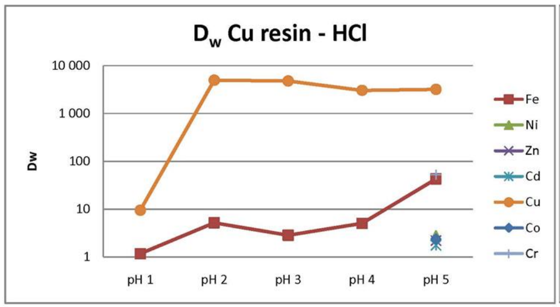
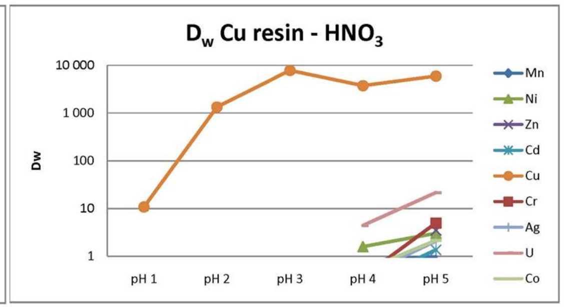
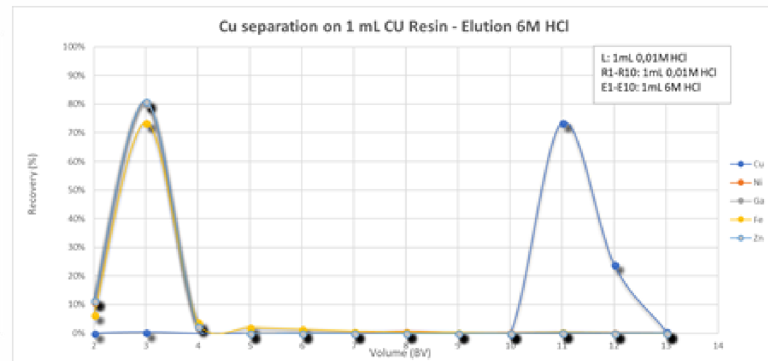
- Oxime based resin
- High selectivity for Cu
  - Especially with respect to Zn and Ni
  - Widely used in mass spectrometry (Cu isotope ratio measurement)







- Load from pH >2, elution in high acid (2 – 8M)
  - Very suitable for liquid targets
  - Used for (large) solid Zn targets (=> Cu-67)
  - Loading not ideal for solid Ni targets (usually high HCl)
  - Elution in high HCl not compatible with labelling/injection
    - Evaporation or conversion
  - High purity and labelling yields

Cu-67 at BNL (DeGraffenreid et al.)

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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 ZnCL2 onto 2.4g CU Resin column => 8 mL
- Rinse with 80 mL pH2 HCl
- Eluiton 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

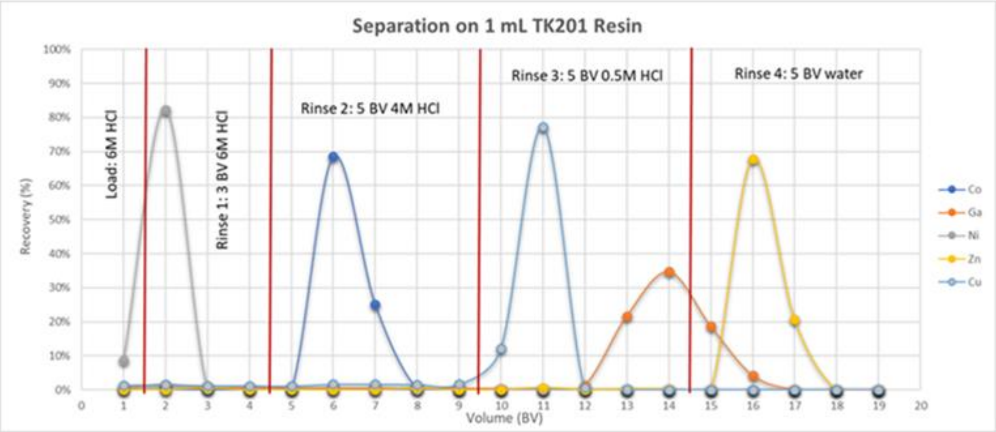
Alternatives:

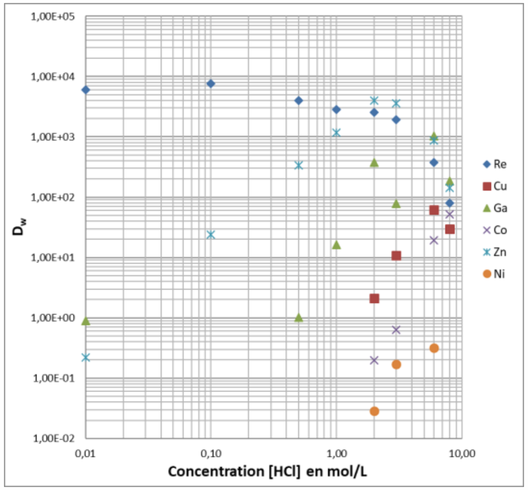
- TK200: used for Zn separation from Cu targets => Cu recovered in 2M HCl
- TK201: prefered option, allows for obtaining Cu in dilute acid

Cu separation /conversion on TK201

- Cu separation from solid Ni targets and conversion usually done using AIX
  - Shrinking/swelling, trace Zn removal, elution volumes
- Under beta testing: use of TK201 (amine)

➢ Cu conversion: Loading onto TK201 at 6M HCl, elution in dilute acid
  - Additional Ni (& Co) removal





➢ Two methods for Cu-64 separation from solid Ni targets under development:
  - Direct Cu purification on TK201 for small targets and "standard" purity
  - Combined TK201/CU Resin method for high purity Cu-64
    - TK201 => direct loading onto CU Resin => pH control!

• Other on-going developments

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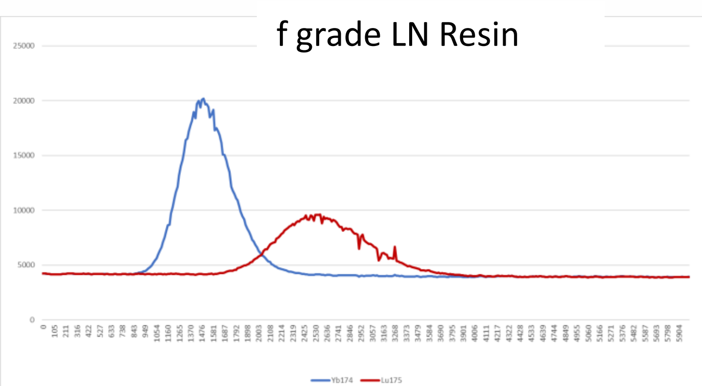
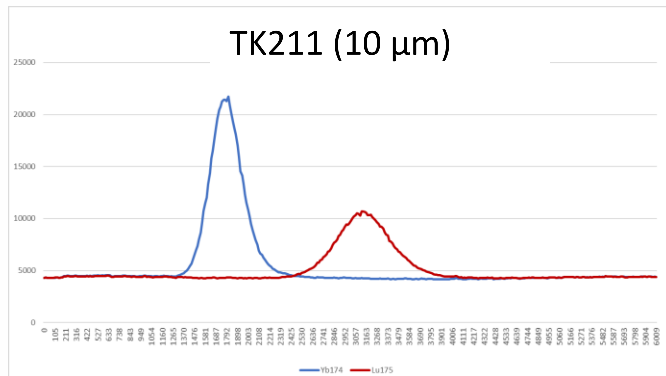
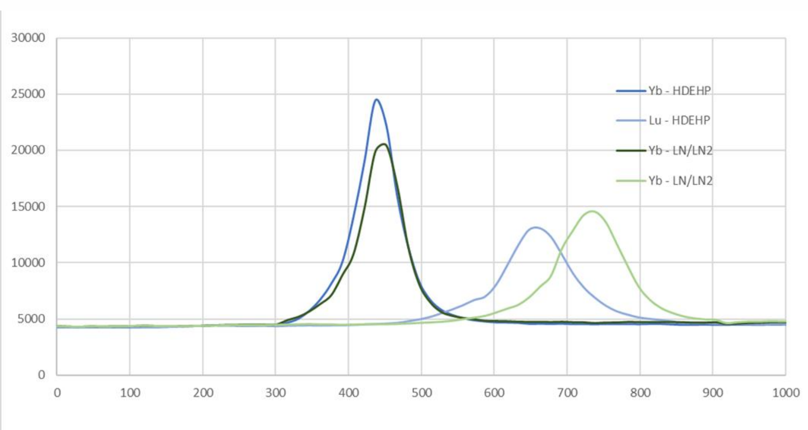
- TK211 and TK212
  - 10µm resin beads for improved lanthanide separation
  - On-bead mix of different extractants for improved selectivity





Comparison (run under identical, non-optimum conditions):



- Increased Lu/Yb selectivity by using extractant mix of suitable ratio
- Increased radiolysis stability via alcohols

• DGA based resin for facilitated LN elution

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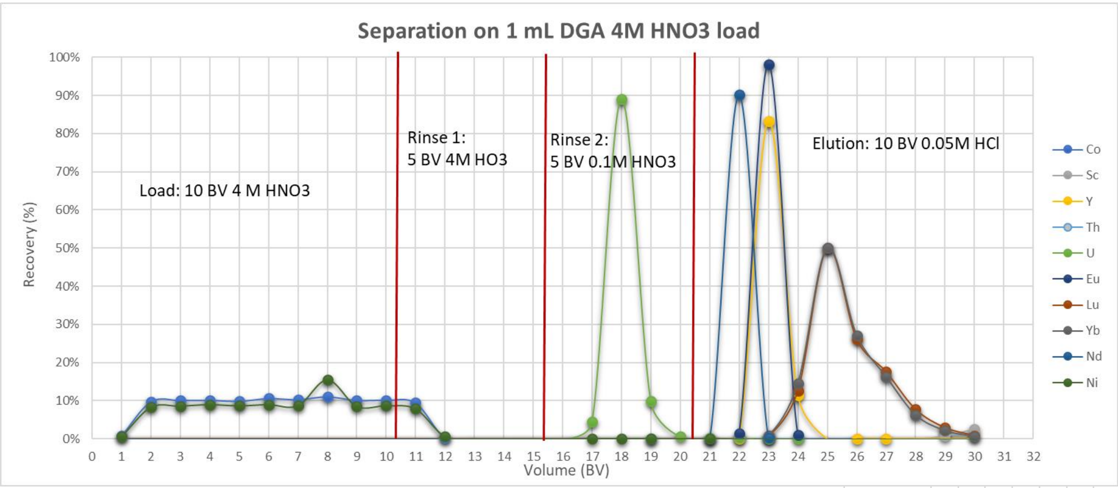
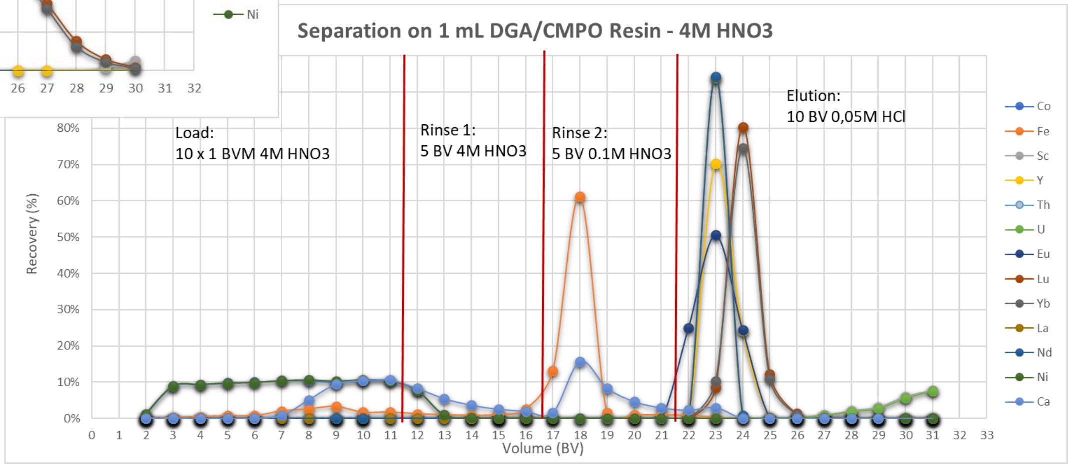
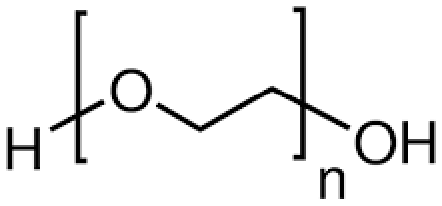




- DGA shows excellent retention of REEs but especially heavy REE as Lu difficult to elute in 0.05M HCl
- Modification of DGA (TK221) Resin allows for faster Lu elution

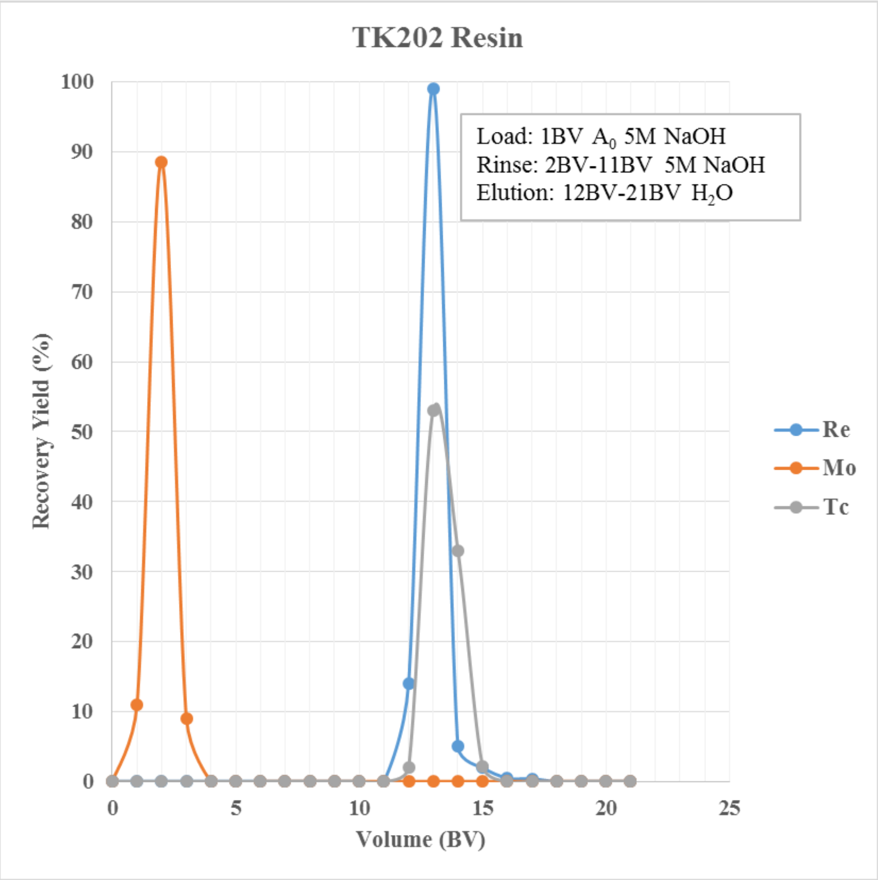
Beta testing: TK202 Resin

- Based on Polyethylene Glycol (PEG) grafted on inert support



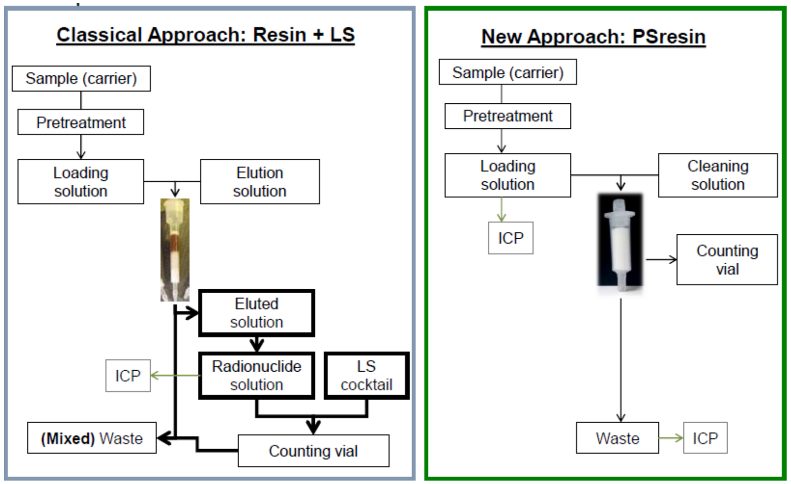
- Tc retention from high NaOH (preferably 5M NaOH)
- Tc retention increased by Mo
- Separation from high masses of Mo
- Elution with water
- Potential uses:
  - Radiopharmacy => direct Tc-99 production by irradiation of Mo targets
  - Decommissioning => Tc determination in decommissioning samples after sample fusion

TK202 Resin – Elution curves



- Tests show Re-Tc have similar behaviour in tested conditions
- Clean separation of Re-Tc and recovery in 5BV H2O
- Tests at Polatom with real samples (Mo targets):
- « Addition to the ^{99m}Tc solution even up to 3g Mo/gTK202 resin does not deteriorate distribution of 99mTc between the resin and 5M NaOH in equilibrium »
- « ^{99m}Tc recovery from the column containing 100mg TK202 resin reached 96% »

TK TcScint



- Scintillating Resins (PSm)
- « TK ElScint » range of products
- First: « TK TcScint »
- Developped by Uni Barcelona
- Plastic scintillator beads impregnated with selective extractants
- Direct measurement of cartridges after loading on LS counter
- Environmental monitoring => Tc-99 by LSC
- Chemical yield preferably Re/ICP-MS in effluents

Some other on-going projects

- SE Resin
  - Se-72/As-72 generator, Se-79
- n.c.a. Lu-177 separation
- Ac separation
- At separation (TK400,…)
- Functionalised polymers & silicates,…
  - e.g. DO-DGA, DE-DGA, macrocycles,…
- Improvement of radiolysis stability
- Ra separation (TK100/1, CAs)
- Cs/Rb separation (TK300)
- Impregnated scintillating beads
  – TK TcScint => Uni Barcelona
- Range of PAN based Resins
  - Decontamination of (large volumes) effluents
  - Variety of inorganic compounds embedded in organic matrix
  - Radionuclides, heavy metals,…
- Extractive discs
- Rapid tests
  - Test sticks => Uni Southampton
  - DGA Sheets (2D TLC)
  - Spin coated discs
- DGT (Diffusive Gradients in Thin Films) => 'bio-availability'
- Microfluidics

Thank you for your attention!

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