TrisKem International

Overview over some newly developed extraction chromatographic resins and their application in the production and quality control of radioisotopes for diagnosis and therapy

Steffen Happel
French-Czech « Barrande» Nuclear Research Workshop
25/04/19

TRISKEM
Expertise in Separation Chemistry

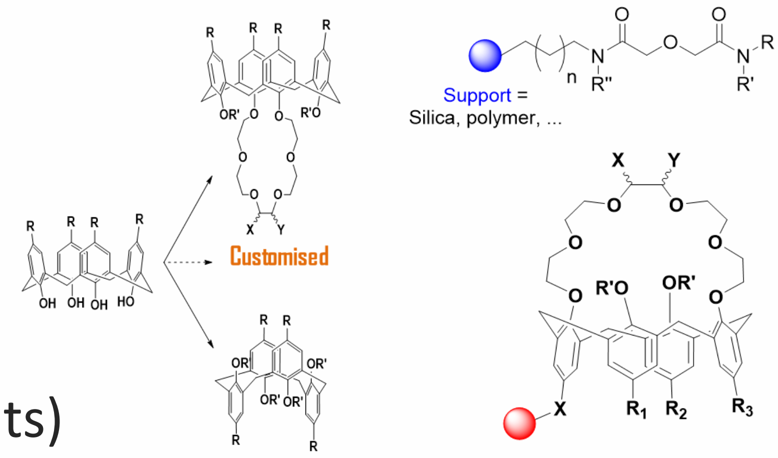
TrisKem International

- Based in Rennes (France)
- Independent company since 02/07
  - Formerly part of Eichrom Europe
  - Sales into 70 countries
- Development and production of selective resins
  - Mainly extraction chromatographic resins
  - PAN embedded inorganic compounds => **CVUT**
    - Production upscale planed (multi t) => effluent decontamination
  - Functionalized polymers and silicates
- Use in a variety of domains
- Staff : 22
  - incl. 9 R&D & TS group => strong focus on R&D

R&D TrisKem International

- Development of new materials and applications
- R&D and TechSupport group:
  - 3 RadChem PhD, 2 OrgChem PhD,

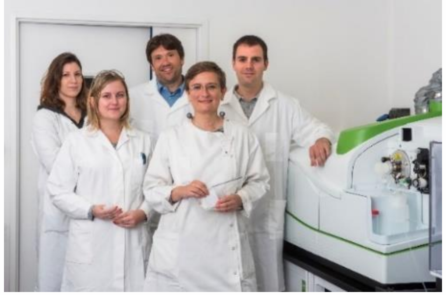
    1 Engineer and 3 Technicians
- Two R&D labs
  - Synthesis Lab (new resins and extractants)
    - Incl. grafted resins (silica or polymers), macrocycles,…
  - Application Lab
    - Preparation of extraction chromatographic resins
    - Resin characterisation and method development => ICP-MS…



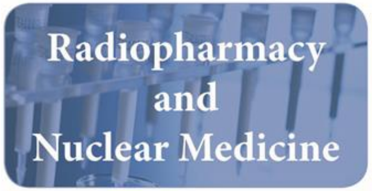
- Supported by BPIFrance
  - ➢ CARAT (Pb-212), LU177, CLIPS2020

R&D TrisKem International

- R&D labs
  - Equipment: Nexion 350 with TruFAST, IC, TOC, TGA, IR, automatic dessiccator, benchtop NMR (43 MHz), surface area and pore size volume analyzer, size and shape analyser, pycnometer
- Acces to production lab
  - Production equipment (incl. four 20 L reactors)
  - Packing equipment (columns/cartridges)
- Customized resins /solutions and contract R&D
- Very interested in R&D cooperations
  - Co-operations with universities, national labs, research centers…
  - Participation in calls for grants
  - New separation materials and applications & automatization

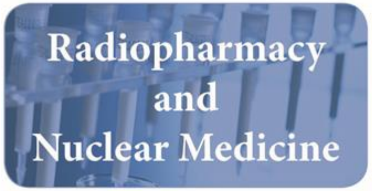


Domains and applications

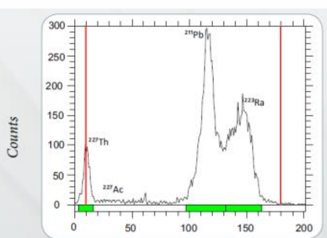


- Radiopharmacy/Nuclear Medicine
  - Radionuclide production
    - Characterization of resins (Dw, elution studies)
    - "Cold" development of separation methods (ICP-MS)
    - Cooperation with cyclotrons & reactors (NL, RN producers, universities…)
    - Cooperation with equipment manufacturers
    - Separation of radionuclides from irradiated targets
      - » Diagnostics: Zr-89, Cu-64, Ga-68, Ge-68, Ti-44/5, Sc-43/4, Tc-99m…
        - ZR Resin, CU Resin, TK200, TBP, TK400, TK201, TK202,…
      - » Therapy: Pb-212, Ac-225, Ra-223, Lu-177, Cu-67, Sc-47…
        - TK400, TK200, TBP, CU Resin, TK211/2…

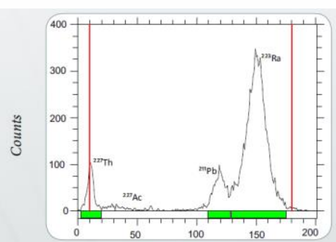
Domains and applications



- Radiopharmacy/nuclear medicine
  - Purification of generator eluates
  - Decontamination of contaminated effluents
  - Quality control
    - Cartridge based methods (alphas in Mo,…)
    - **DGA sheets** (functionalized TLC, Ra-223, Ga-68, Pb-212,….) => developed and produced by **CVUT**
      - » TLC scanner or radiometer/LSC after cutting
      - » 2D TLC under development (with Subatech) => use in decommissioning

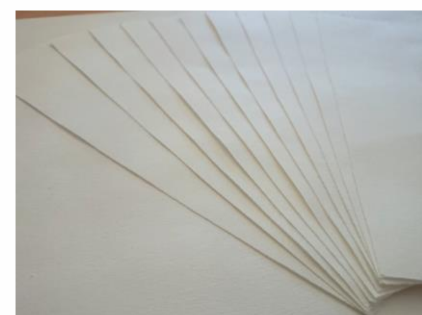


Radiochromatogram measured immediately after separaton. Low abundant radiatons of ^{227}Ac were not detected.



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.



Extraction chromatography

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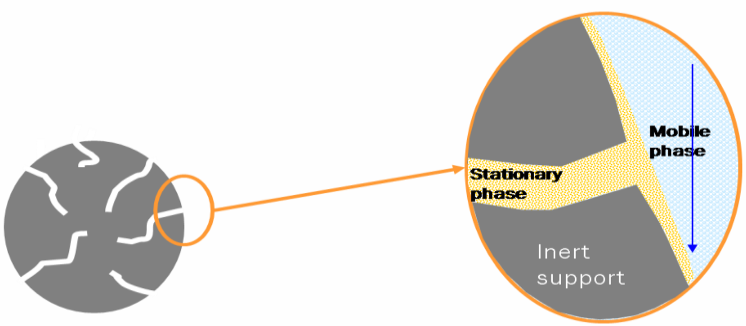
Organic extractant impregnated onto inert support

- Distribution between two non-miscible phases
- Wide choice of different extractants/selectivities
  - Crown-ethers, amines, phosphonates, oximes,….
  - Pure extractants, synergetic mixtures, solid extractants in diluents
- Selectivity for analyte/product & no or very low selectivity for target/matrix

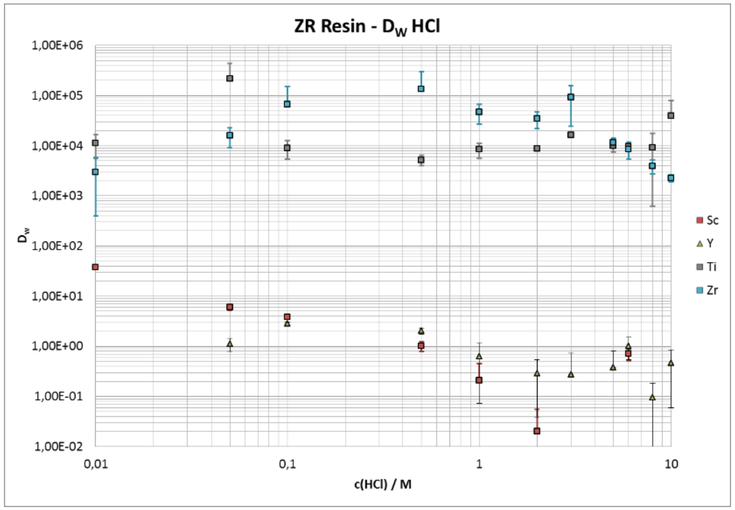
  => small columns and volumes
- Bleeding => may need to be adressed

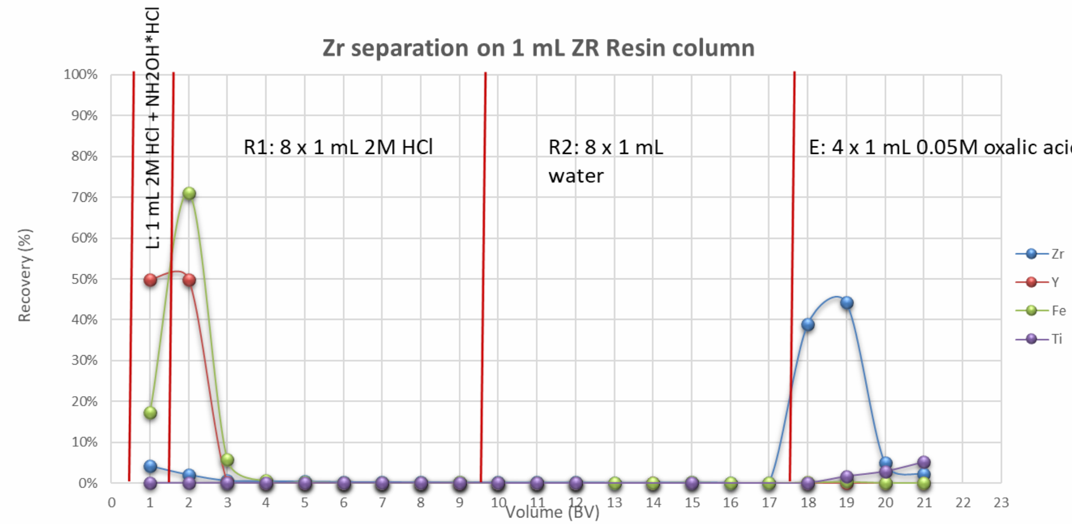


ZR Resin

- Original scope: Hydroxamate based resin
    - Zr-89 production via (p,n) reaction from ^{nat}Y targets
    - Ready to use
    - No activation
    - Facile Zr elution (avoid 1M oxalic acid)
- Other application developed
    - Ti separation from Sc
    - Ge separation from Ga
    - Ga separation from Zn

Zr-89 separation from Y

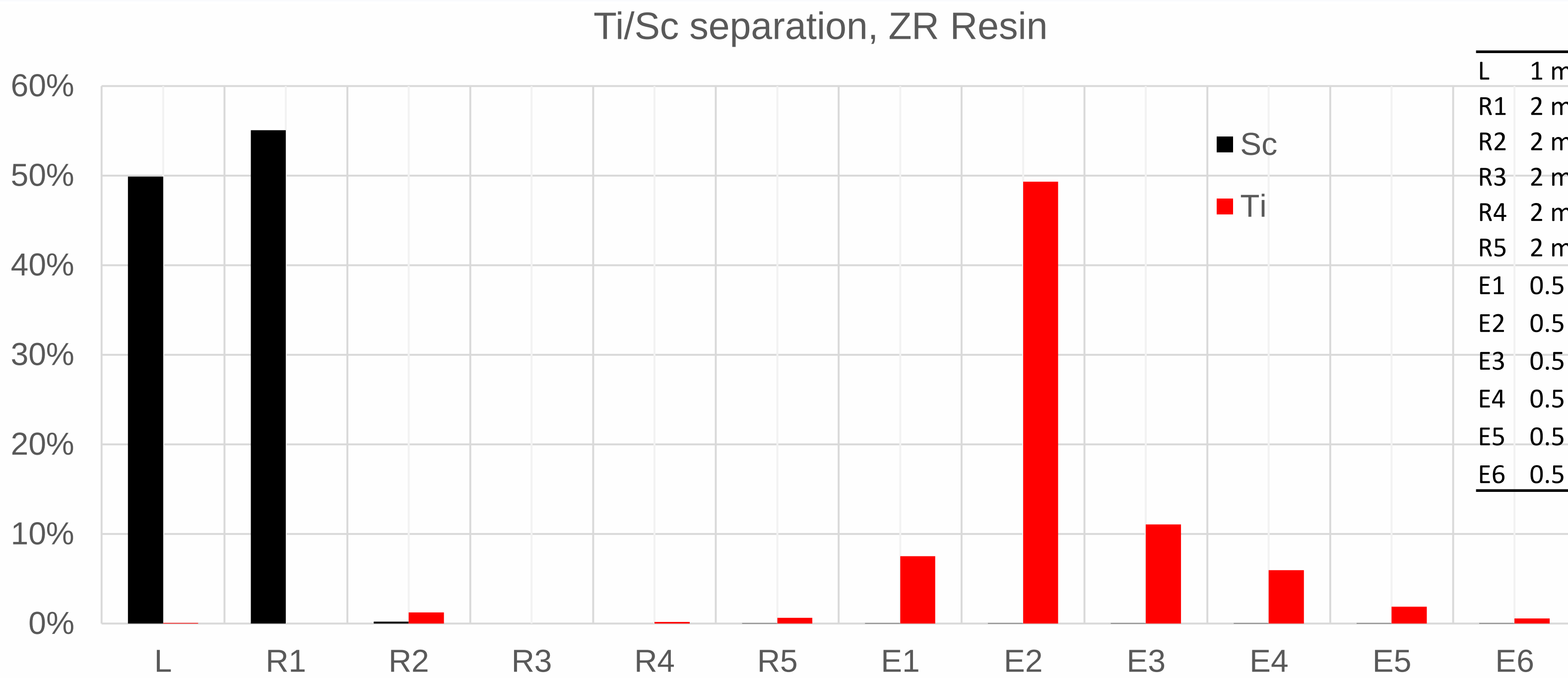




- Obtain data on selectivity
- Elution studies for method development
- Load from 2 – 6M HCl
- Rinsing as described by Holland
- Clean Y and Fe removal

- Quantitative Zr elution in 1.5 - 2 mL ≥ 0.05M oxalic acid
- Compatible with commercial systems
  - Taddeo, Pinctada, AiO, EZAG
- ➢ TBP Resin => Zr-89 chloride (Graves et al.)

Ti-Sc Separation (Ti-44/5)



L	1 mL	ME 10 M HCl
R1	2 mL	10 M HCL
R2	2 mL	10 M HCL
R3	2 mL	10 M HCL
R4	2 mL	10 M HCL
R5	2 mL	10 M HCL
E1	0.5 mL	0.1 M citric acid
E2	0.5 mL	0.1 M citric acid
E3	0.5 mL	0.1 M citric acid
E4	0.5 mL	0.1 M citric acid
E5	0.5 mL	0.1 M citric acid
E6	0.5 mL	0.1 M citric acid

- Ti retained from (high) HCl, Sc not retained
- Ti elution with 0.1M citric, >0.2M oxalic acid, 0.1M H_2O_2
- Publication Malinconico et al. use of 1M oxalic acid

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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*

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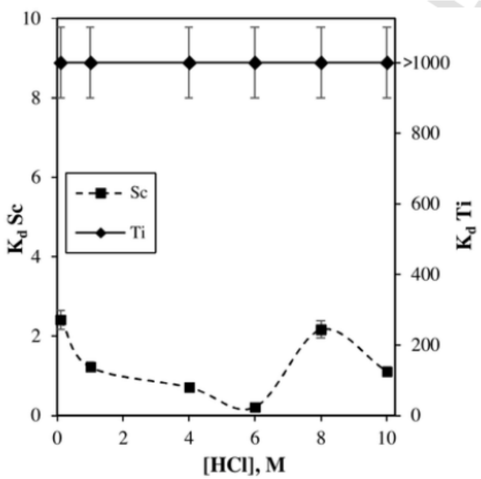


Fig. 3. HCl concentration dependency of K_d for $^{44}Ti/^{46}Sc$ on ZR hydroxamate resin.

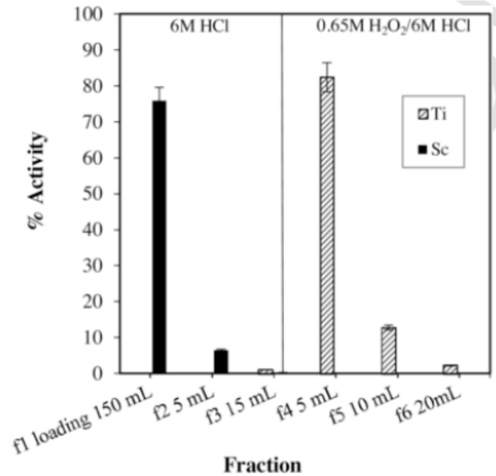


Fig. 5. $^{44}Ti/^{46}Sc$ elution profile using ZR hydroxamate resin with a load of 4 g of scandium.

- **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

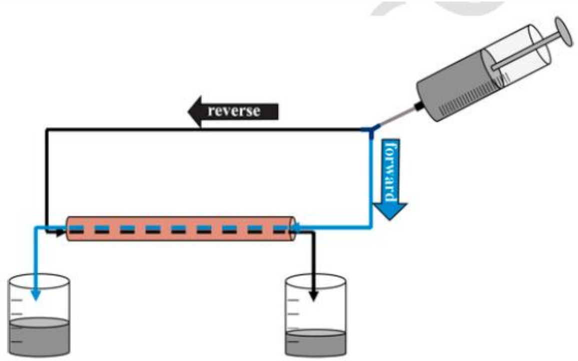


Fig. 1. Schematic concept of a forward/reverse flow radionuclide generator.

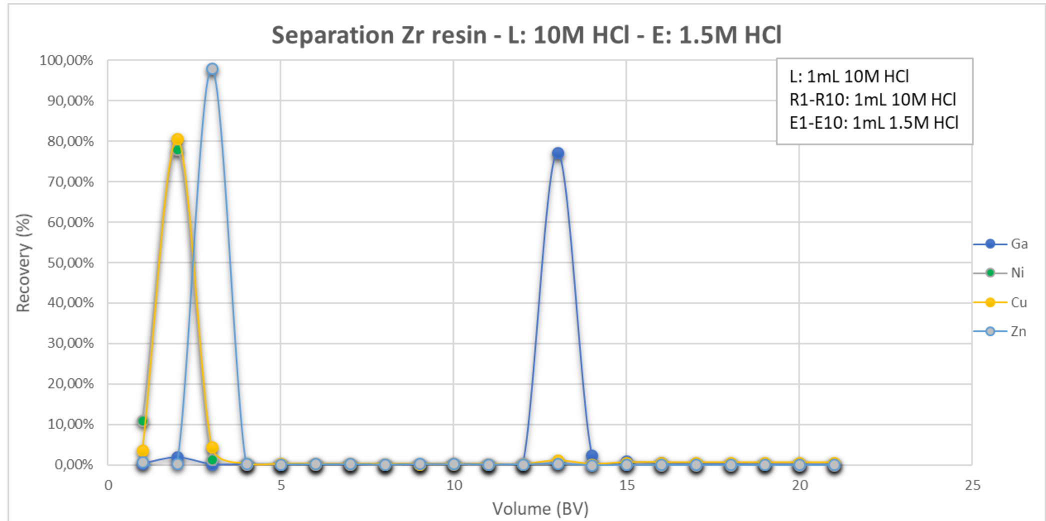
- Direct (1 mL ZR Resin) and reverse elution (2 mL ZR Resin)
- 65 column volumes tested up until publication
- High Sc yields, max. Ti-44 breakthrough: 4.1^{E}-4%
- Obtained Sc gave labelling yields > 94%
- Generator just been set-up at BNL

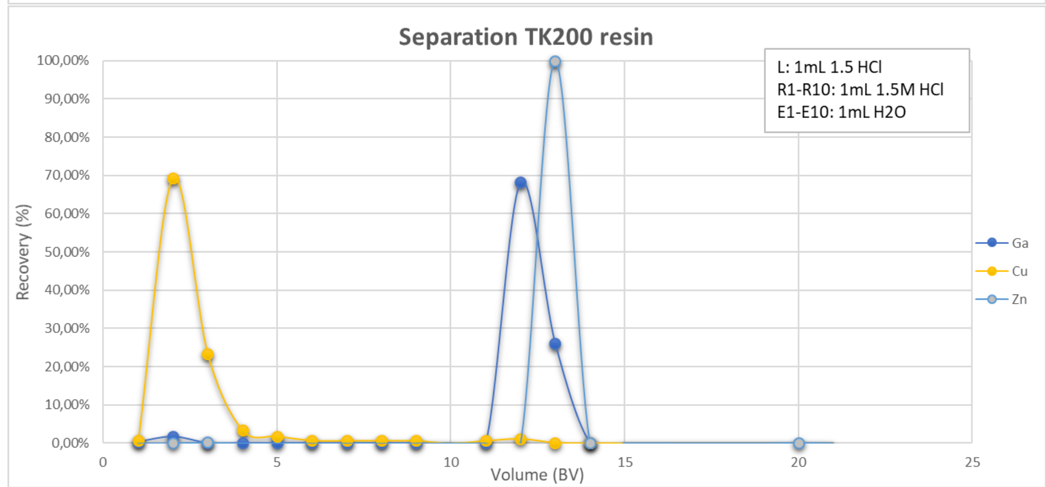
Ga-67/8 separation from Zn targets

- ZR Resin + TK200 Resin
- 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
- Load on TK200, elution in water
- For solid targets: single cartridge method (TK400) possible

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

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





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%

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]

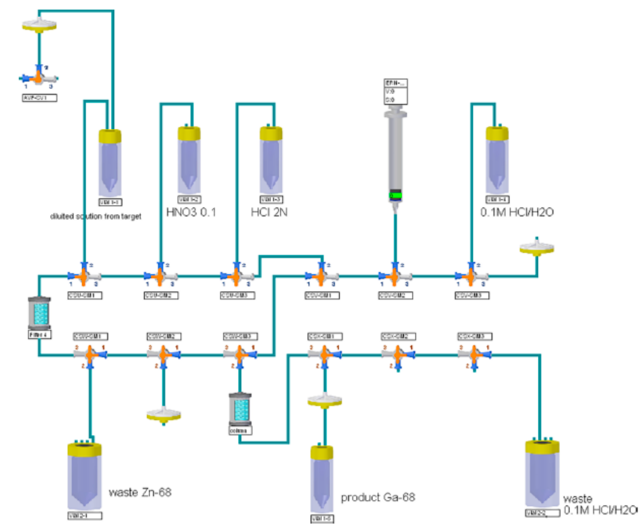
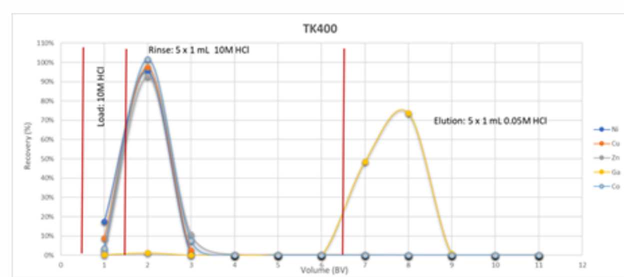
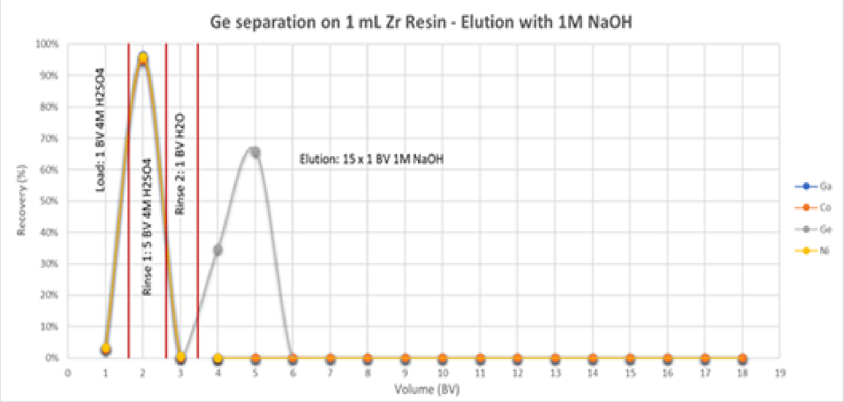


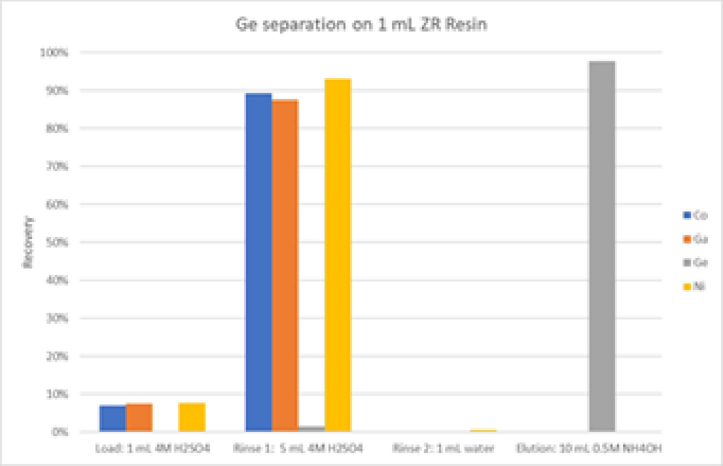
Fig. 4. Schematic diagram of the separation process (Modular Lab, Eckert & Ziegler, Berlin).

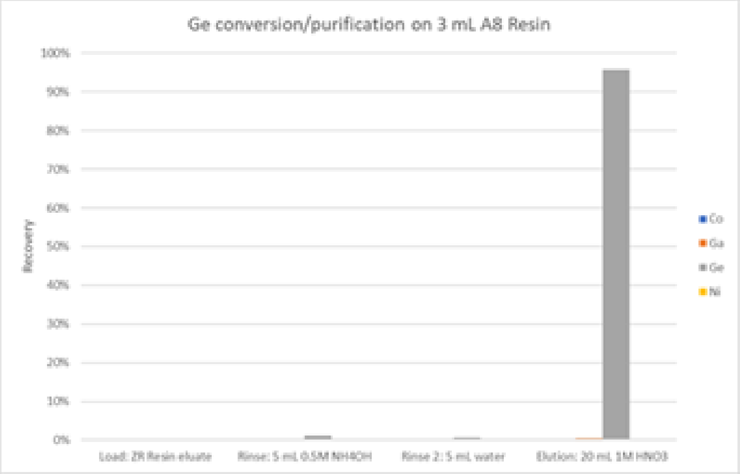


Ge-68 separation from Ga/Ni or Ga/Co

- Ge separation from target material on ZR Resin
  - Loading from HNO_3, H_2SO_4 or HCl
- Most efficient elution under alkaline conditions
  - ➢ Elute may be loaded onto e.g. SnO_2 after acidification
  - ➢ Conversion via AIX => needs elution in NH_4OH
  - AIX : further purification and elution in acid
  - Tests on real samples planed for July

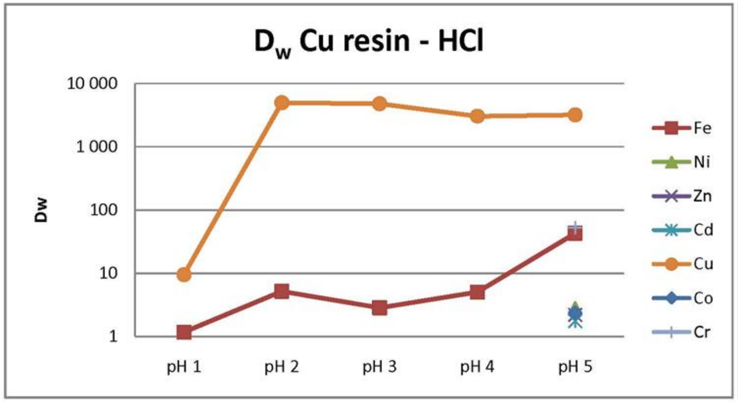


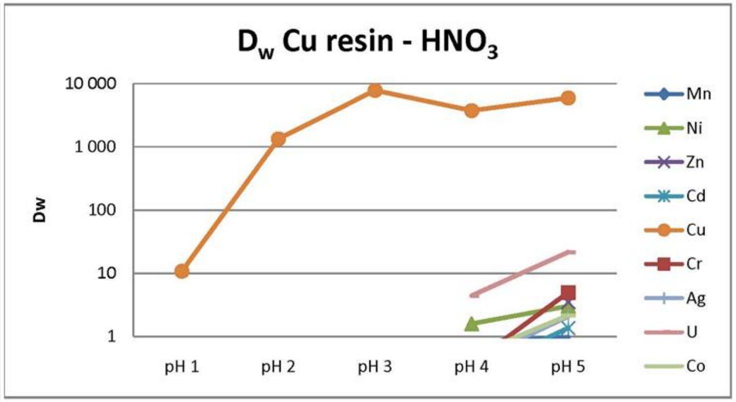




CU Resin

- Oxime based resin
- High selectivity for Cu => especially with respect to Zn and Ni





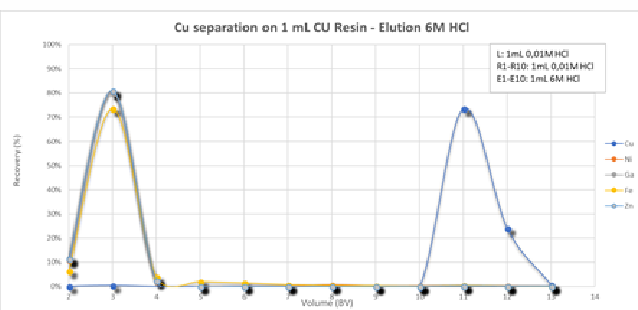
- Load from pH >2
  - Very suitable for liquid targets
  - Solid Zn targets (=> Cu-67 e.g. De Graffenreid et al >10g Zn targets, Pupillo, Haddad et al.)
  - Not ideal for solid Ni targets
- Elution in high acid (2 – 8M HCl)
  - Evaporation or conversion via AIX/TK201

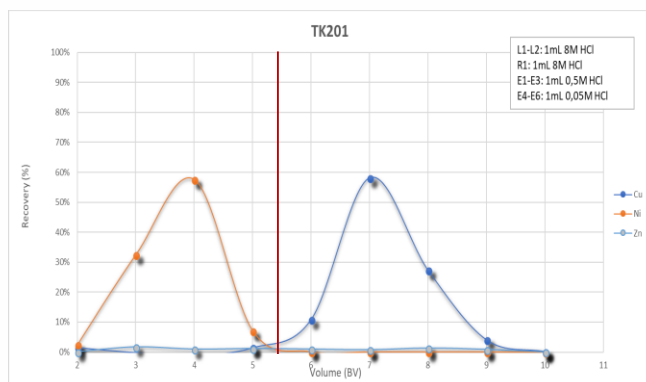
Cu-64 separation from solid targets

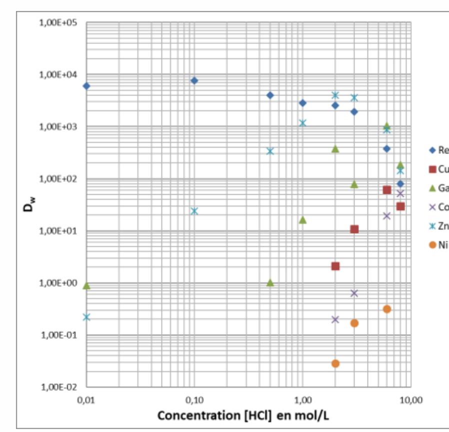
- Cu-64 from Ni-64 separation usually via AIX
  - Problem: shrinking/swelling of AIX & large elution volumes
- Use of TK201 instead

➢ Working on direct Cu separation

➢ Main focus on rapid method for Cu-64 from solid Ni targets:
  - TK201 Resin to convert from high HCl to dilute HCl for load onto CU Resin
  - Improvement of Ga/Co removal via CU Resin
  - Use of TK201 for final conversion







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

Cu Resin

- Dissolve irradiated (86.4 µA for 0.79 d) ^{nat}Zn target (13.70 g) in trace metal grade conc. HCl
- Evaporated to dryness and reconstitute into milliQ water (91.5 mL) to give a 312 mg $ZnCl_2$/mL solution
- Ensure pH ≥ 2 with pH paper
- Added ~60.6 mL (18.9 g $ZnCl_2$) to Cu Resin column (2.40 g)
- Quantitative transfer with 2 x 20 mL H_20→ into load bottle
- Rinsed with pH 2 HCl (80 mL)
- Recover radiocopper with 2 x 20 mL 6 M HCl
- Evaporate 6 M HCl to dryness

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

n.c.a. Lu-177 separation

- Separation of Lu-177 from bulk Yb-176
  - Challenge: very similar chemistry and large targets

  => generally large columns & slow separation
- Generally most accepted: chromatographic separation (CEX/HIBA & ExChrom)
- On-going optimisation on ExChrom resin route
  - Mixed extractant systems (LN/LN2/LN3) – synergy?
  - Use of radical scavenger to increase radiolysis stability
  - Optimisation of inert support and separation conditions
  - Sequential separation (e.g. direct LN2 eluate loading onto LN)
- L-CEX type of Resin under development for HIBA work
- Looking for additional options (electrochemistry?)

• Resin/separation optimisation work

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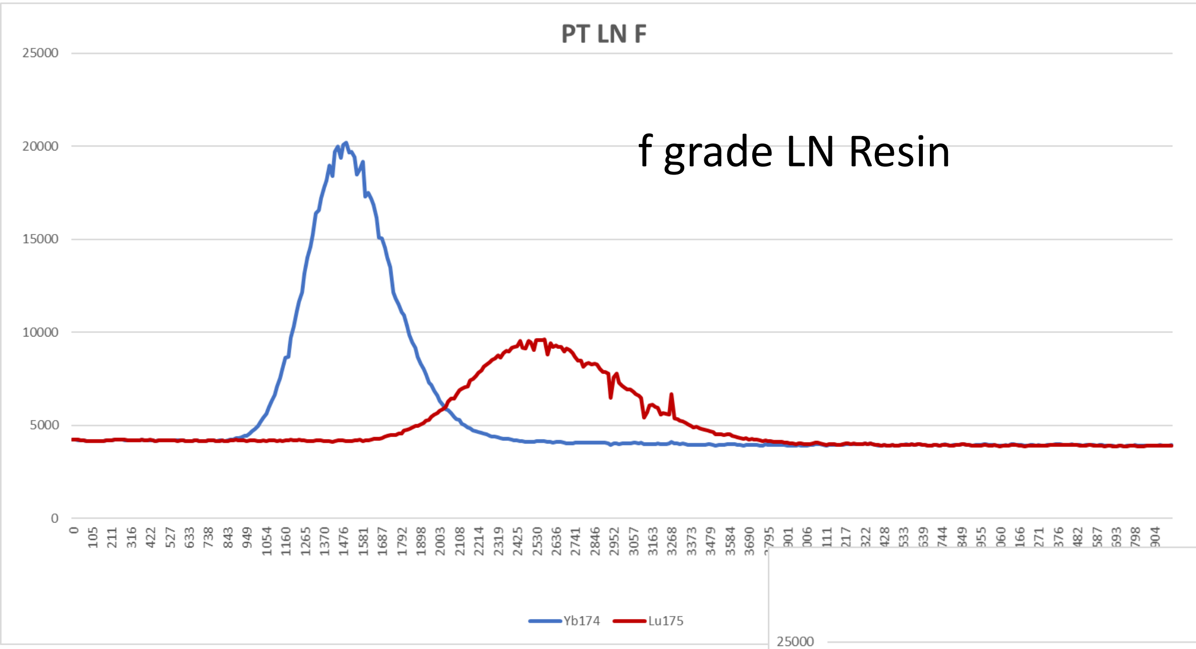
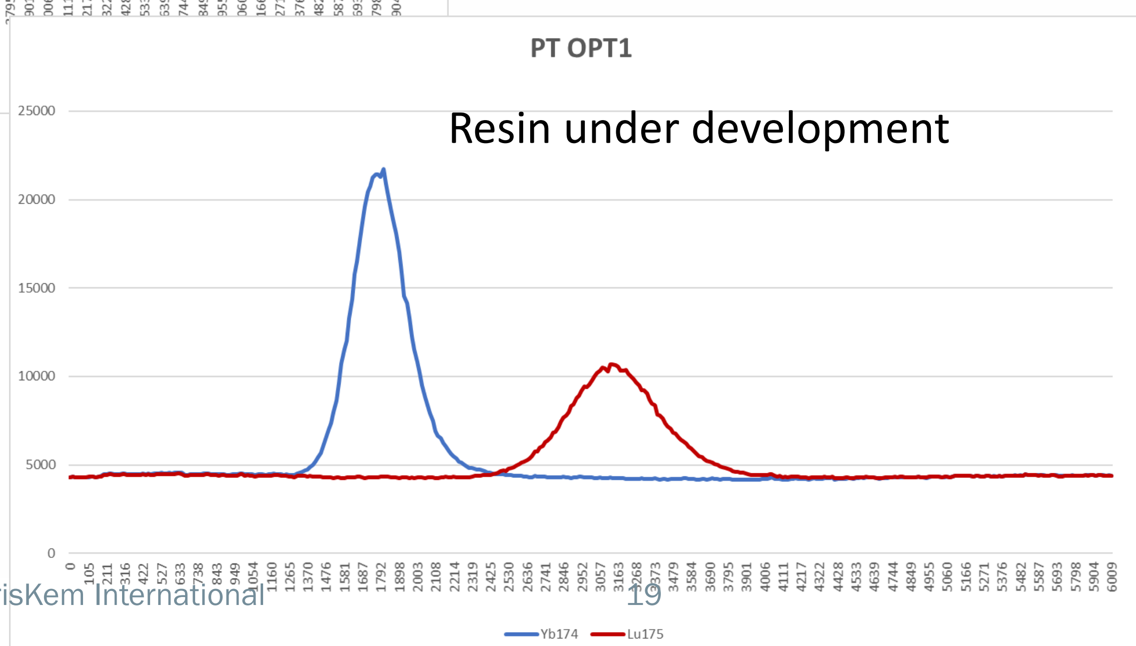
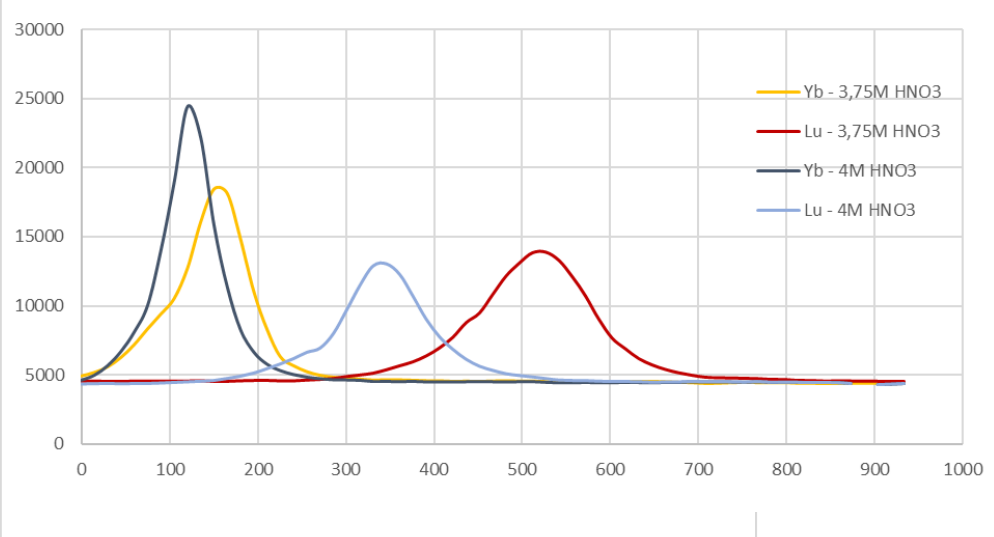


Comparison (run under identical, non-optimum conditions):

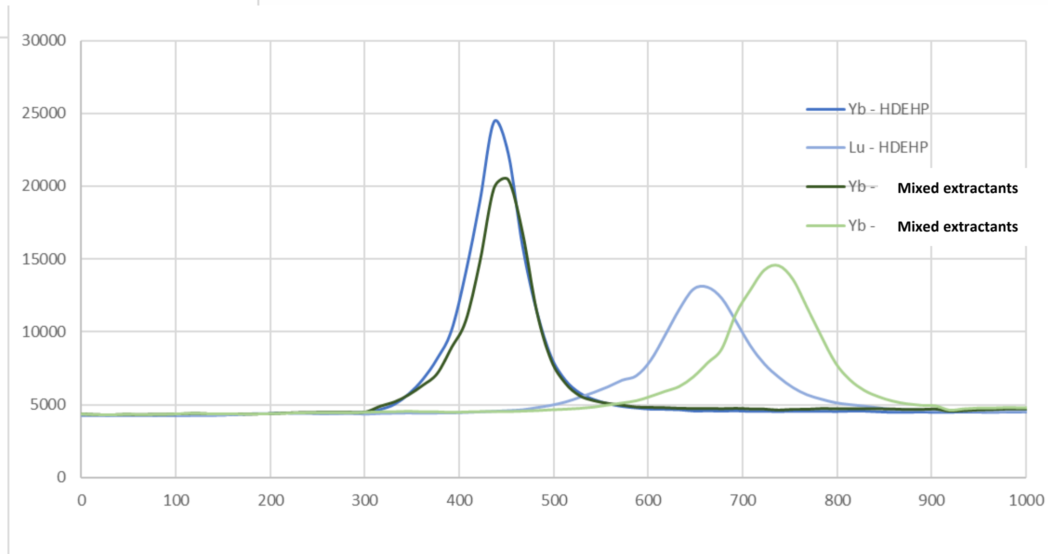
- Standard f grade resin (smallest grade available) vs
- New resin under development



Resin/separation optimisation work



- At lower acid concentrations:
- Lower overlap but larger elution volumes
- Possibility to speed up Lu elution with higher HNO_3 after Yb removal



- Mixed extractants seem to show better separation than pure HDEHP
- Less overlap
- Larger 'distance' between peaks
- Currently under evaluation

Other on-going projects

- Tc separation from Mo
  - TK201 & TK202
- SE Resin
  - Se-72/As-72 generator, Se-79
- Sc separation from Ca
- Cu-64 from solid targets
- Ac-225 separation
- At separation (TK400,…)
- Functionalised polymers & silicates,…
  - e.g. DO-DGA, DE-DGA, macrocycles,…
- Ra separation
- Improvement of radio stability
- Cs & Rb separation
- Range of PAN based Resins
  - Decontamination of effluents
  - Variety of inorganic compounds embedded in organic matrix
- Rapid tests
  - Test sticks => Uni Southampton
  - DGA Sheets (2D TLC)
  - Extractive discs
- Scintillating beads (UB):
  - TK TcScint
- DGT (Diffusive Gradients in Thin Films)
  - Passive sampling/'bio-availability'

Thank you for your attention!

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