
# TrisKem International

## Application of extraction chromatography in the purification and QC of radiometals for use in Nuclear Medicine and Radiopharmacy

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CSC 2023 VANCOUVER JUNE 4-8 | #CSC2023

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
- Main product line: extraction chromatographic resins
- Staff : 20
- R&D, QC and TechSupport group:
  - 4 RadChem PhD, 3 Technicians
- R&D: Development of new resins, techniques and applications
- Several domains

# Research interests - Radiopharmacy

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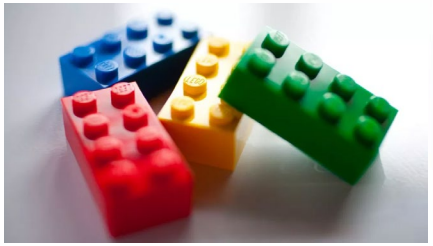
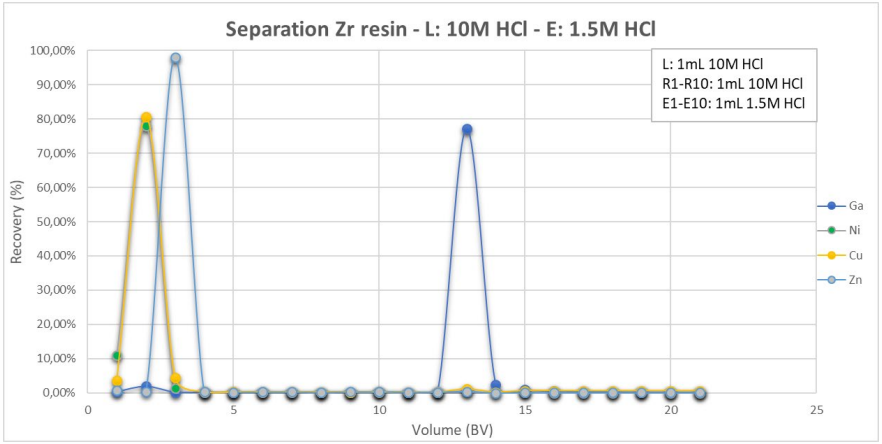
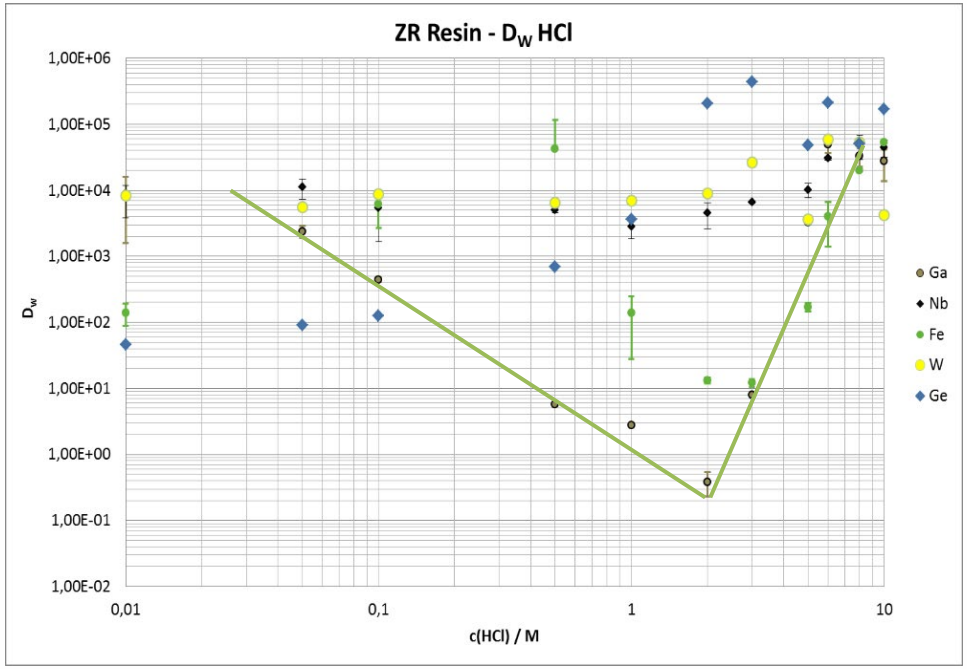
- Purification of radiometals for use in diagnostics and therapy
  - Mainly: separation of radionuclides from irradiated targets
    - Diagnostics: Zr-89, Cu-64, Ga-68, Ge-68, Ti-44/5, Tc-99m, Sc-43/4…
    - Therapy: Ac-225, Pb-212, Lu-177, Tb-161, Cu-67, Sn-117m, Sc-47…
  - Also: QC, valorization/recycling and waste/effluent treatment
  - Resin characterization and method development done ‘cold’
    - Cooperation with cyclotrons & reactors, universities,…
  - Choice of right resin(s):
    - Rapid separations, high purity of products
    - Radiolysis stability
    - No selectivity for target material, high selectivity for product
    - Elution under ‘soft‘ conditions in small volume => labelling/injection
    - Facile automatization e.g. cassettes / no evaporation steps
  - Combining several resins can facilitate the separation
    - Conversion (high acid to dilute acid)
    - Removal of impurities upfront



# 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*]

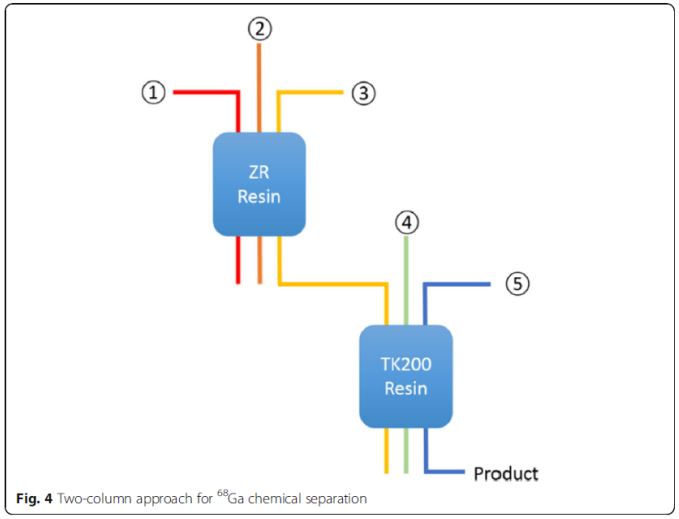



**Fig. 4** Two-column approach for $^{68}$Ga chemical separation

**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)

- Solid targets:
  - 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 flow 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

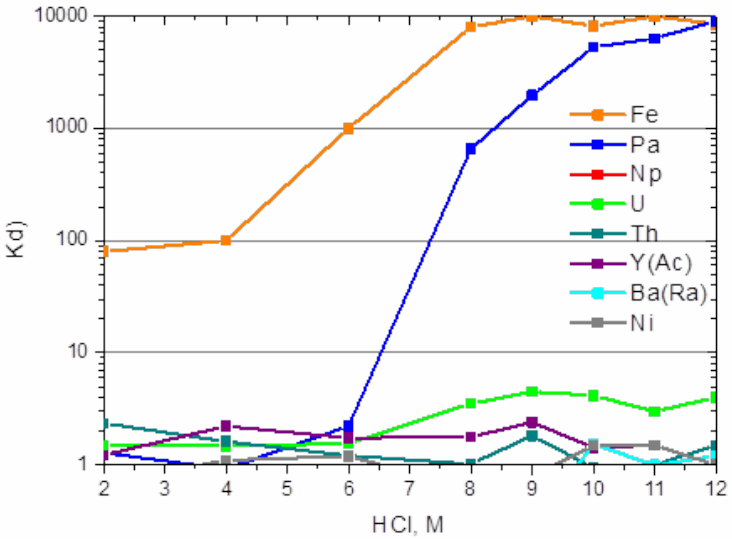
Demystifying solid targets: Simple and rapid distribution-scale production of [$^{68}$Ga]$GaCl_3$ and [$^{68}$Ga]Ga-PSMA-11

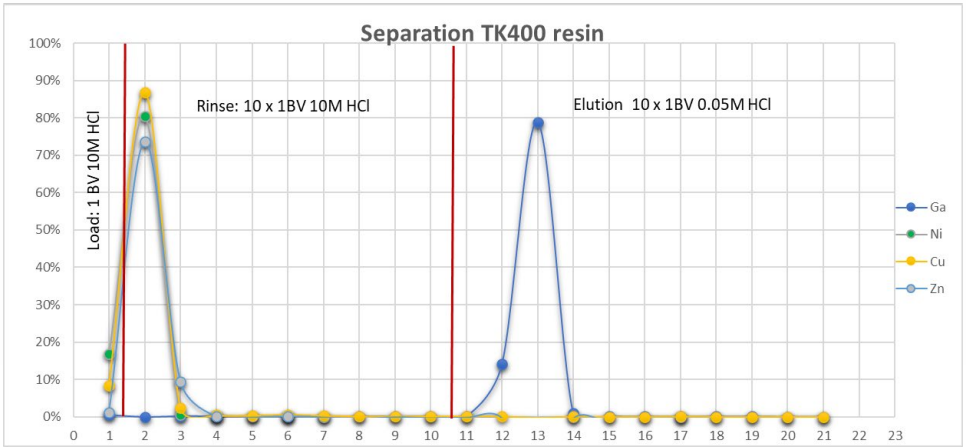
Johan Svedjehed, Martin Pärnaste, Katherine Gagnon *

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

# TK400 Resin

- Long chained alcohol – initial work by A. Knight et al.
- Retention only at high HCl concentration, elution in low HCl, water,…
- Main application: **Pa separation**
- Other applications:
  - Also retains Mo, Nb, **Fe**, **Ga**, Po
  - **Fe separation** (higher cap than TRU)
  - **Ga removal from Cu-67 & Fe, Nb removal from Zr**
  - **Ga separation from Zn at high HCl**
  - Nb separation from Zr possible (Nb-90)
  - Under further testing for At separation (elution…)
  - Bleeding => upcoming TK401 Resin




- Preferably Ga elution in 1.5 – 2M HCl => Fe remains retained on TK400
- Ga elution onto TK200

# Cu-61/4 separation on TK201

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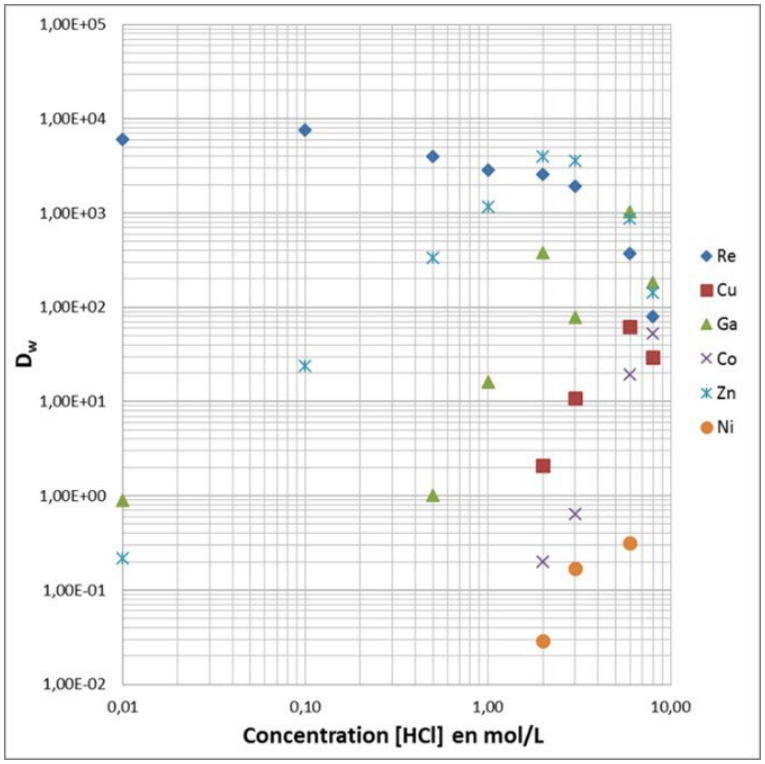
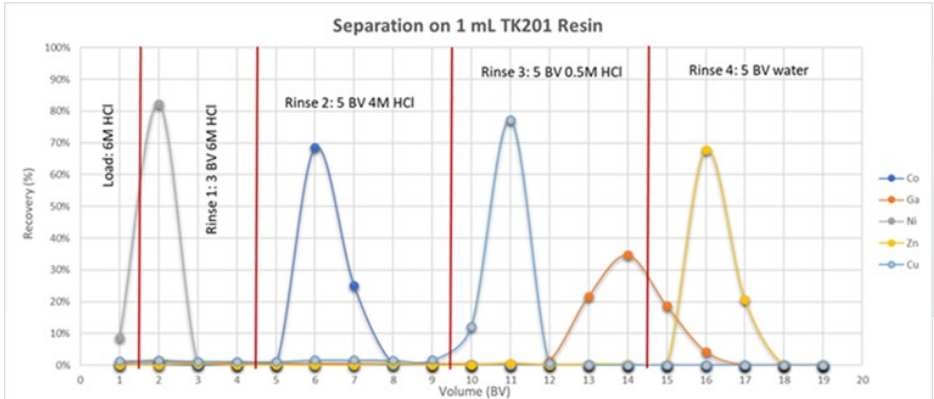
- Cu-61/4 separation from solid Ni targets
  - Ni targets dissolved in high HCl
    - CU Resin generally not used
  - Typically separation via anion exchange
    - Elevated elution volumes
  - Use of TK201 instead (sharper elution)
    - Originally for Tc separation
    - No selectivity for Ni, good Cu retention, Zn very well retained
  - Load and rinse at 6M HCl
    - Ni removal and recovery/recycling
  - Co elution with 4 – 5M HCl
  - First tests: Cu elution with 0.5M HCl
    - Zn remains retained
    - Ga and Fe separation

    ⇒ Eluate too acidic - requires further treatment => requires improvement



# Cu-61/4 separation on TK201

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- Improvement:
  - Use of TBP (or TK400) upfront for Fe/Ga removal
    - allows for Cu elution in 0.05M HCl => suitable for labeling
    - Zn remains retained
  - Problem: TK201 'acid sponge' => eluate higher than 0.05M HCl
  - Gagnon et al. use of NaCl/HCl for better pH control of eluate

- TK201 also used with CU Resin (and TK400) for Cu-67 separation from Zn targets
  - Conversion from 6M HCl to 0.05M HCl and Zn removal
- Currently being tested for Co separation (2x TK201) from Ni targets and for Zn separation

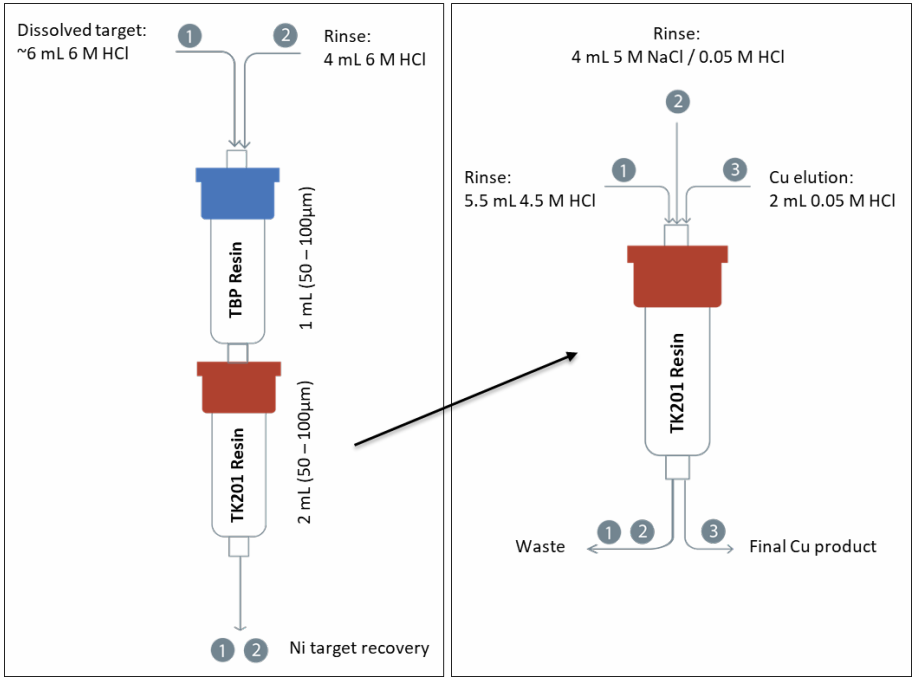
Svedjehed et al. EJNMMI Radiopharmacy and Chemistry (2020) 5:21
https://doi.org/10.1186/s41181-020-00108-7

EJNMMI Radiopharmacy and Chemistry

RESEARCH ARTICLE Open Access

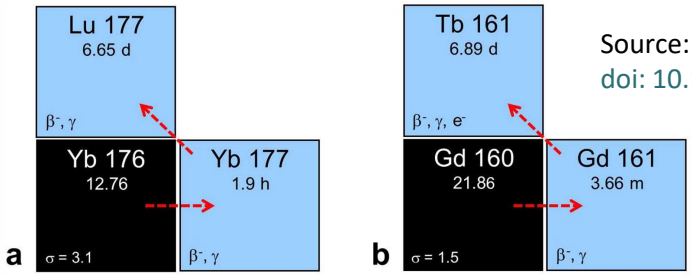
Automated, cassette-based isolation and formulation of high-purity [$^{61}$Cu]$CuCl_2$ from solid Ni targets

Johan Svedjehed[1], Christopher J. Kutyreff[2], Jonathan W. Engle[2,3] and Katherine Gagnon[1*]

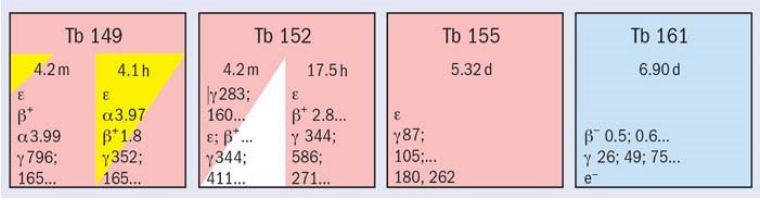


# Tb-161 separation

- nca Lu-177 more frequently used but strong interest in nca Tb-161
- Part of the 'Swiss knife of nuclear medicine' => Tb isotopes




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/

  - Typically irradiation of several hundreds of mg (or more)
  - Work on upscale on-going (incl. recycling and decontamination of effluents) => originally 0.5 - 1g targets / now: >1g for Tb-161 and >5 – 10g for Lu-177
- Separation via TK211/2/3 Resins
  - Mixture of extractants (HDEHP, HEH[EHP], Cyanex 272, Cyanex 572)
  - Inert support containing aromatic groups + higher capacity for extractant
  - Long-chained alcohol as radical scavanger
  - 30µm particles => smaller (10 – 15µm) possible but high pressure drop…

# Tb separation from 1000 mg Gd targets

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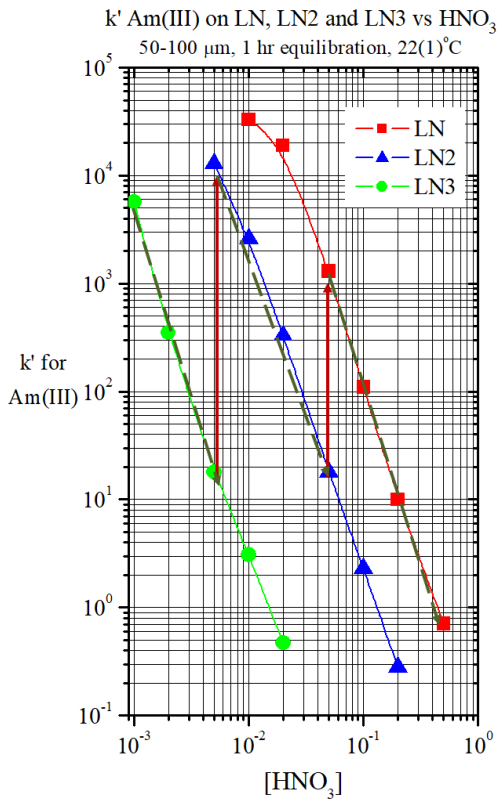
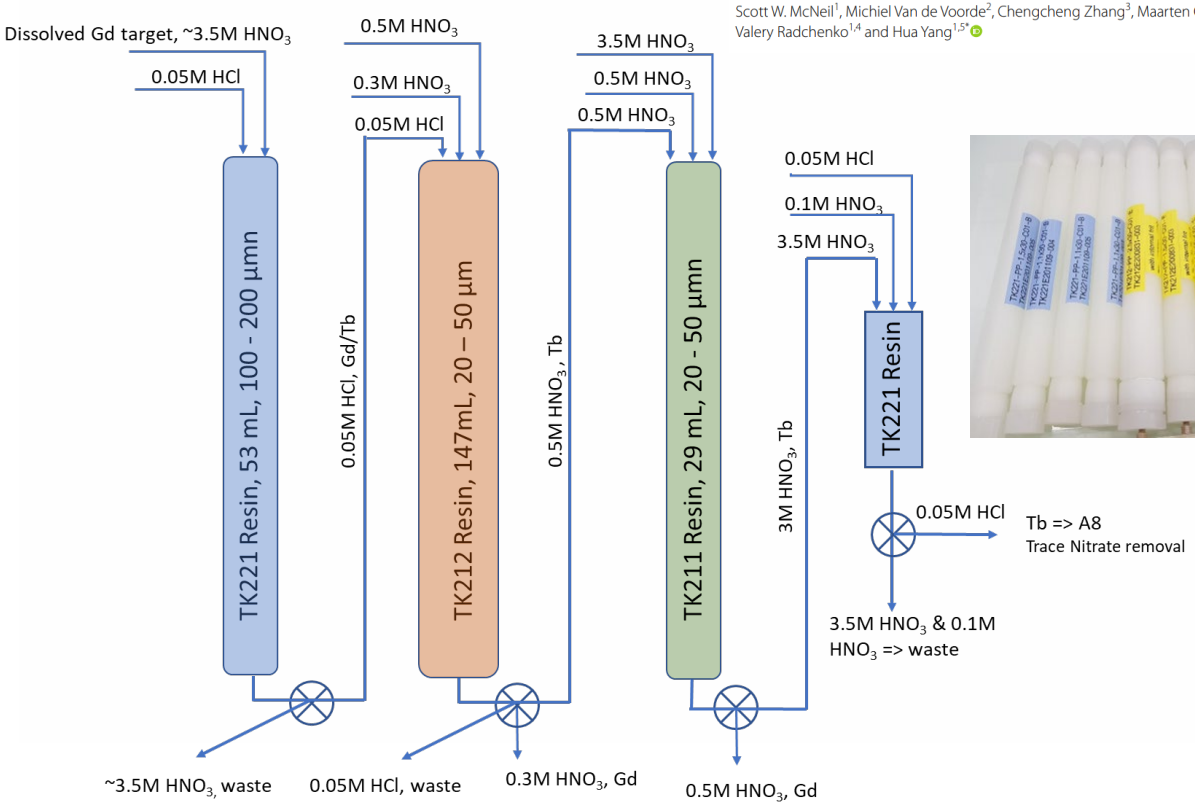
- 500 – 1000 mg Gd in cold work, hot 200 – 300 mg Gd targets
- Irradiated target typically dissolved in >3M $HNO_3$ => Conversion via TK221 Resin
- **Sequential separation** on TK212/TK211
- Final conversion to dilute HCl on TK221 + trace nitrate removal on AIX
- Mainly Tb-161, also Tb-155



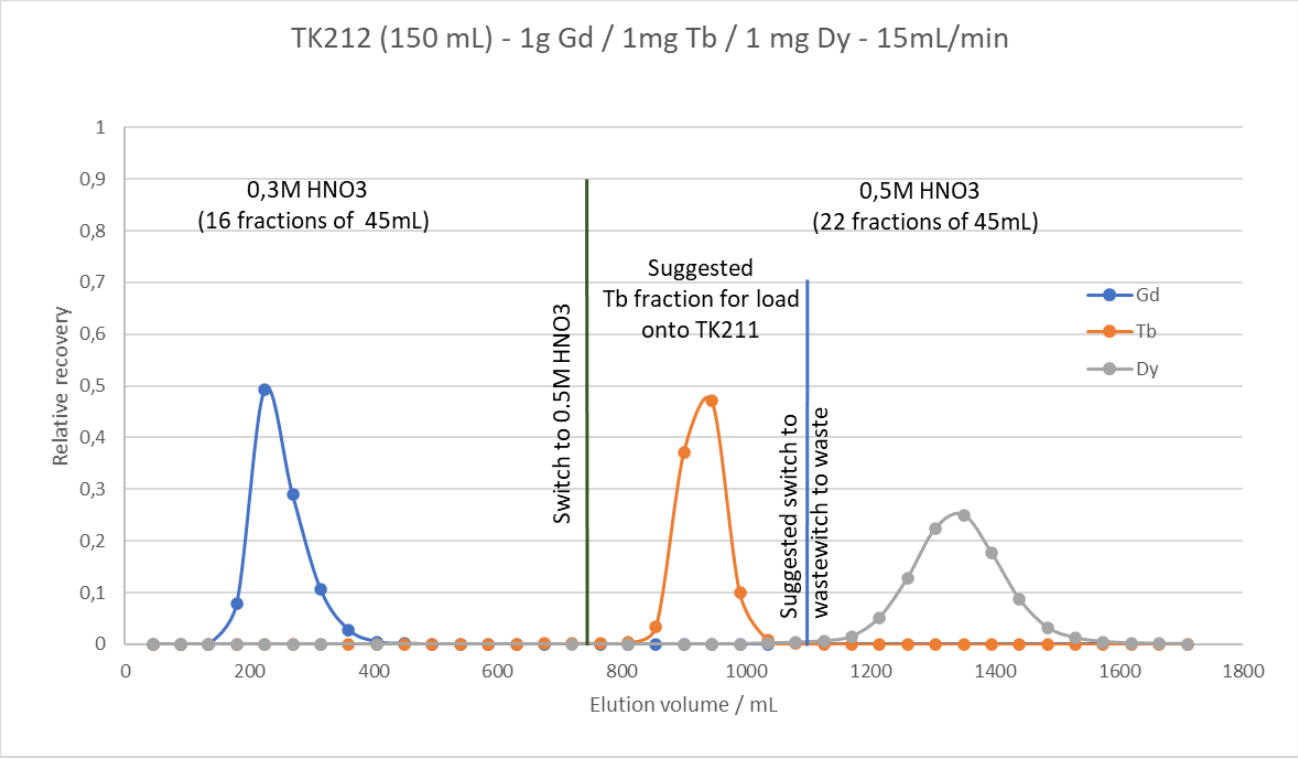

A simple and automated method for $^{161}Tb$ purification and ICP-MS analysis of $^{161}Tb$

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



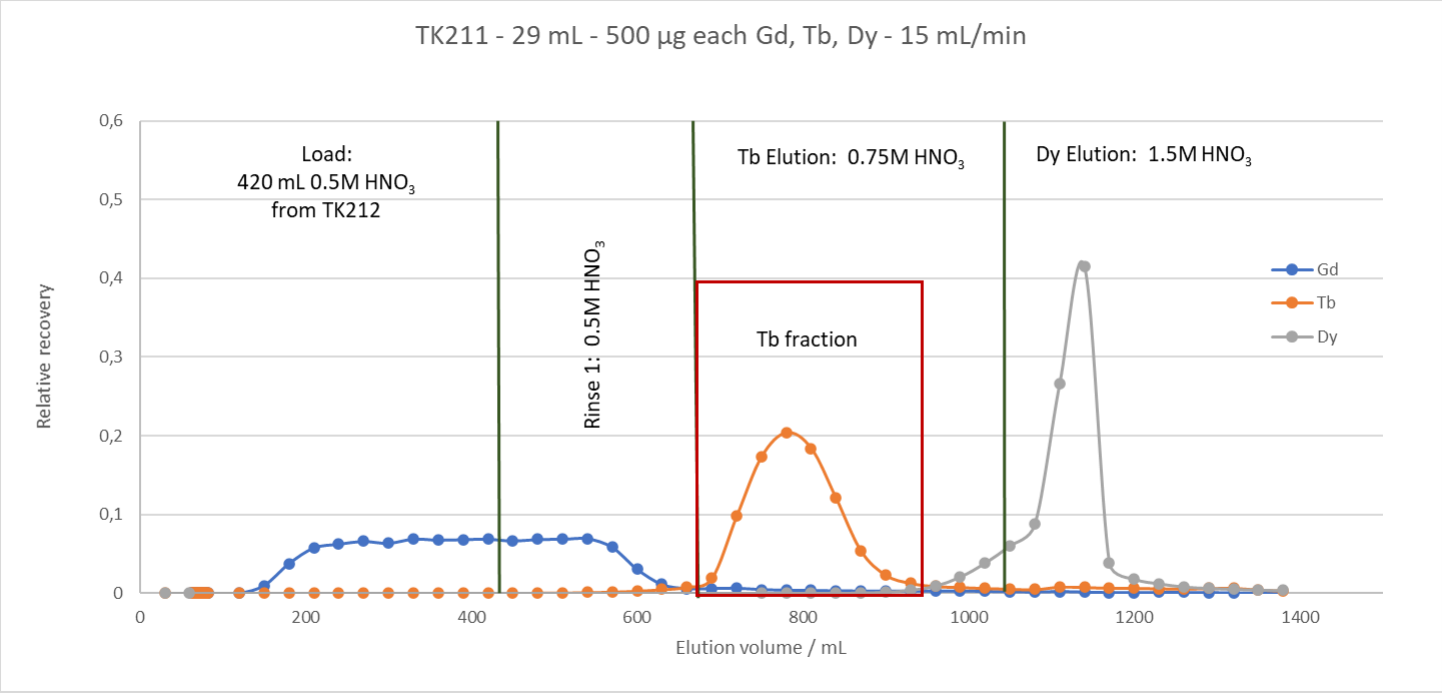
# Tb separation from 1000 mg Gd targets

- Initial separation on TK212 – 147 mL column (30cm x 2.5cm)
- Flow rate ~15 mL/min
- Gd recovery => very expensive & difficult to find
- Tb separation from Gd and Dy – ideally using online detection
- Fine purification on TK211 (29 mL)




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

# Tb purification on TK211



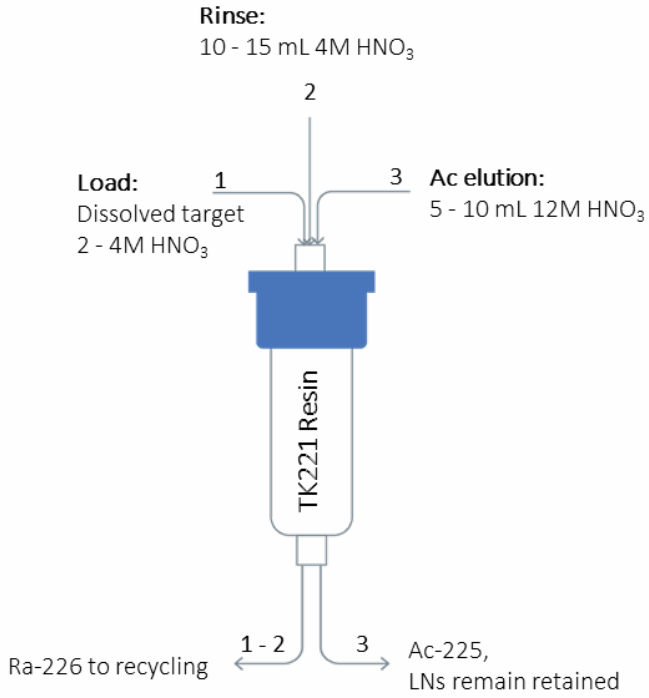

- Direct load of Tb fraction from TK212 onto TK211 (29 mL – 30cm x 1.1cm)
- Flow rate ~15 mL/min
- Gd breakthrough during load & rinse with 0.5M $HNO_3$ (alternatively HCl)
- Tb elution (Dy sufficiently well removed before) preferably in **>3M $HNO_3$**
- Conversion to dilute HCl via TK221, A8 for nitrate removal
- **Option: LN3 cartridge for Dy removal from Tb before use (e.g. after long shipment)**

# Ac-225 separation

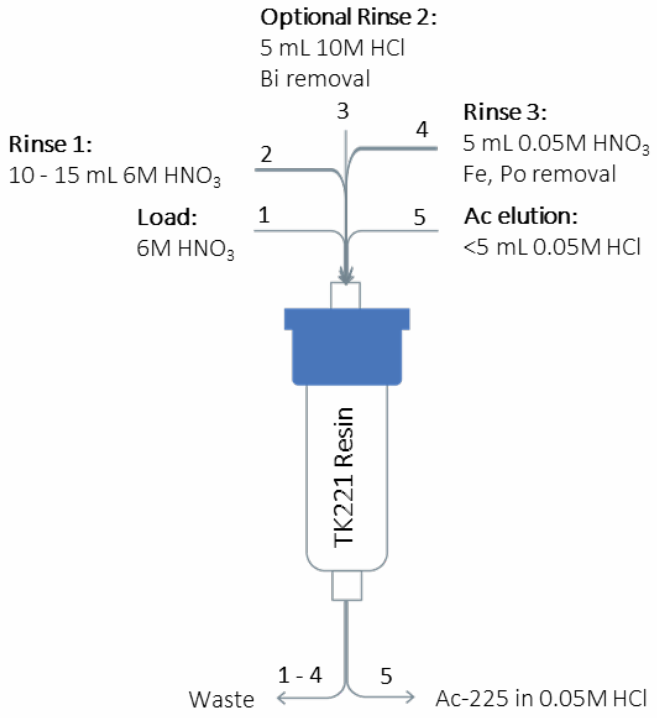
- Ac-225 separation chemistry well established
- Currently typically DGA (mainly B) is used fore Ac/Ra separation
  - Open questions:
    - Imperfect La/Ac separation (suggested: additional separation on LN)
    - Radiolysis stability sufficient? => limited stability of DGA
- On-going tests:
  - Use of TK221 (TO-DGA / phosphine oxide) or TK222 (TEH-DGA / phosphine oxide) => TK221 shows higher La retention than DGAs
  - Focus on La/Ac separation
  - Sharp Ac elution => for TK221/2 only in dilute HCl
  - Improved radiolysis stability?
  - Resalting possible? Ac nitrate => Ac chloride
  - Ac data et al: publication under preparation

# Ac-225 separation – method under optimisation

- Two TK221 cartridges for removal of impurities incl. La
- Two additional, optional Pb removal steps (TK102 and TK101)

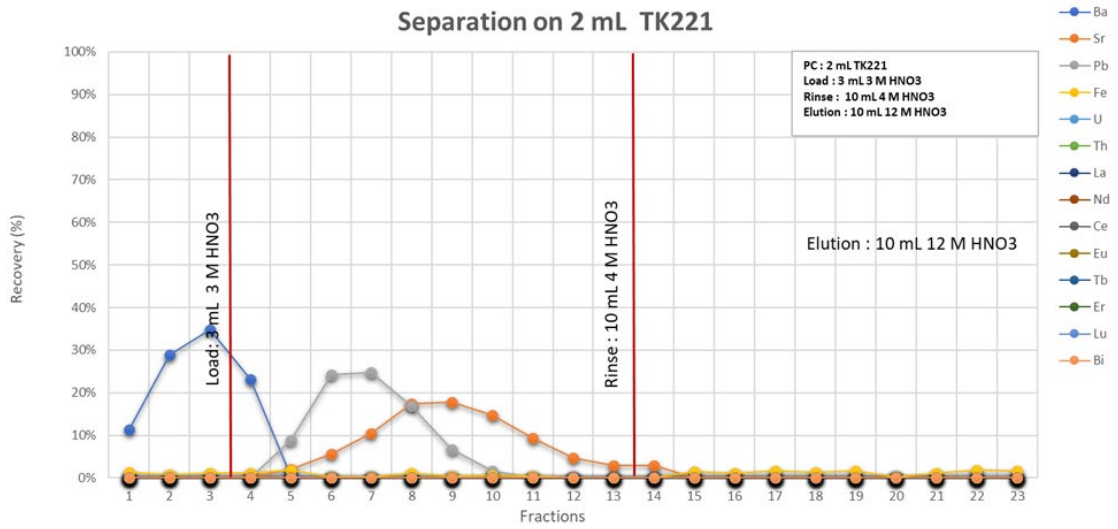


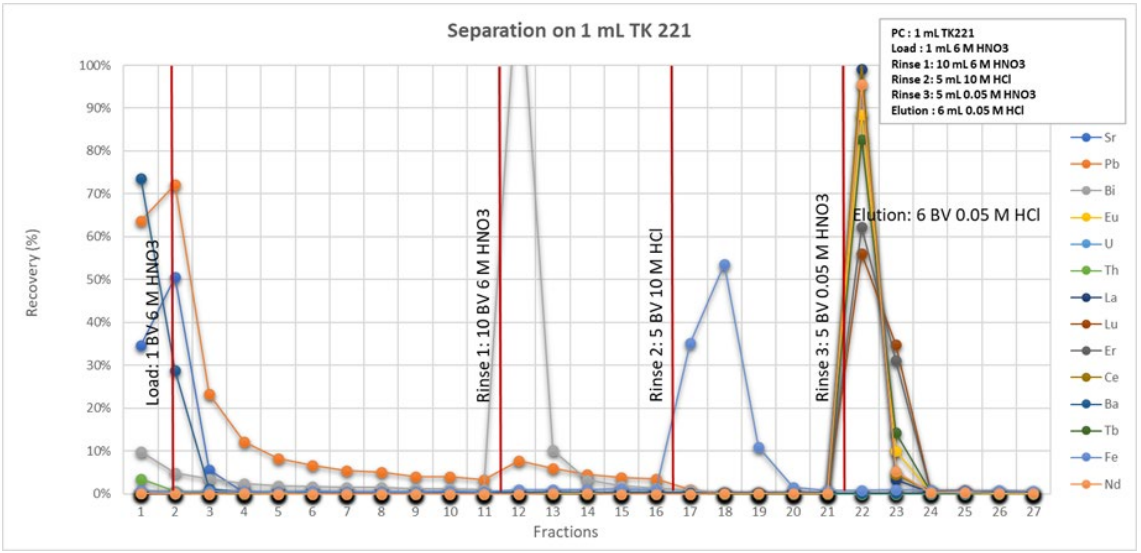

Step 1 TK221:
Target dissolved in 2 – 4M $HNO_3$
Ra, Ba, Pb, Sr,… removal with 4M $HNO_3$
Ac elution in ~12M $HNO_3$ (LNs retained)




Step 2 TK221:
2x diluted eluate from first TK221
Rinse with 6M $HNO_3$ and optional rinses with:
10M HCl => Bi removal and
0.05M $HNO_3$ (Fe, Po removal)
Ac elution in 0.05M HCl

# TK221 Resin – Ac separation – step one

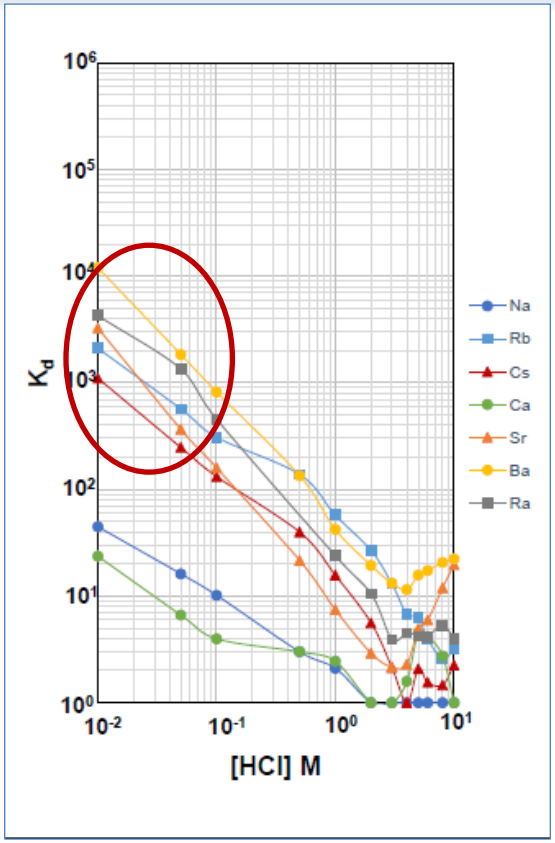


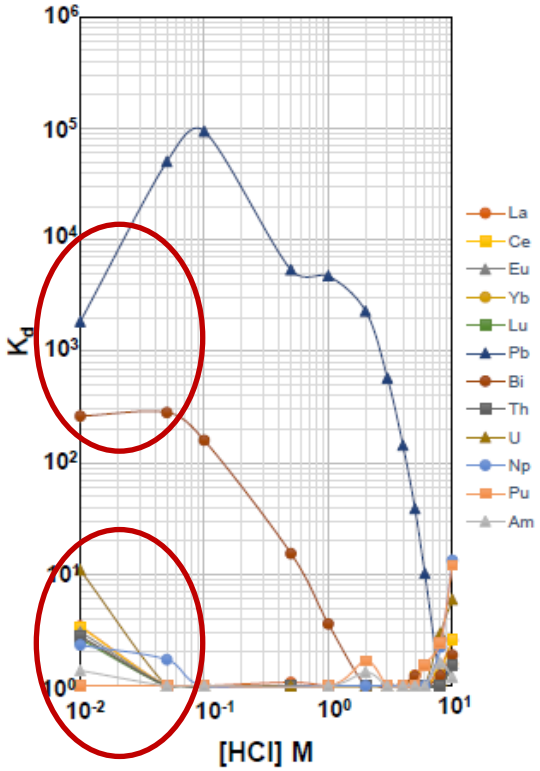



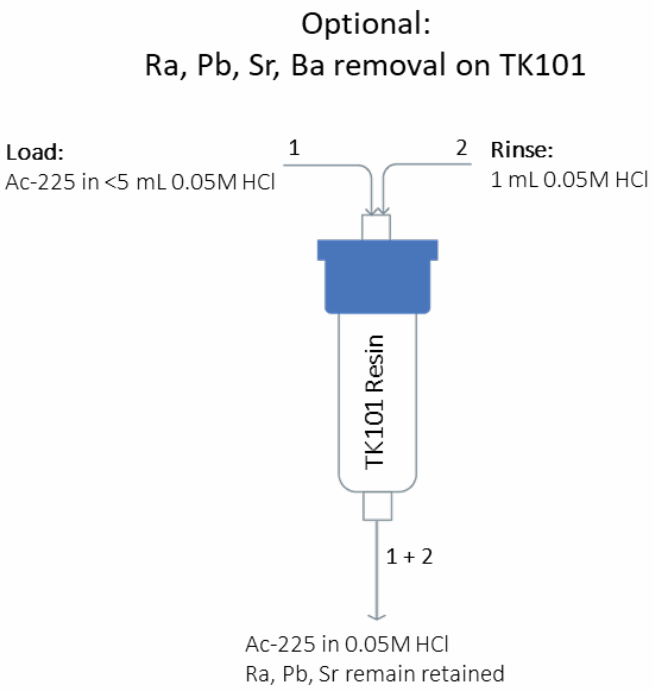

- In case LN need to be removed
- Two step procedure

- First Ac / LN separation
- First TK221
  - Load from elevated $HNO_3$
  - Ac elution in very high $HNO_3$
  - LNs, U, Th retained
  - Particular attention to Pb/Sr
    - Elution in 4M $HNO_3$
- Second TK221
  - Dilute x2 => load
  - Bi removal 10M HCl
  - Fe removal in 0.05M $HNO_3$
  - Ac elution in 0.05M HCl
  - Important: Lanthanides need to be removed upfront (1st TK221)
  - Additional purification on TK101 possible (Ra, Ba, Pb, Sr)

# Optional: TK101 purification step




Data courtesy of B. Russel (NPL)

Optional Pb, Bi, Ra, Sr,… removal step (TK101)
Pass Ac fraction (0.05M HCl) through TK101
Ac passes - Ra, Pb, Sr, Bi,… retained

# Ra purification / recycling

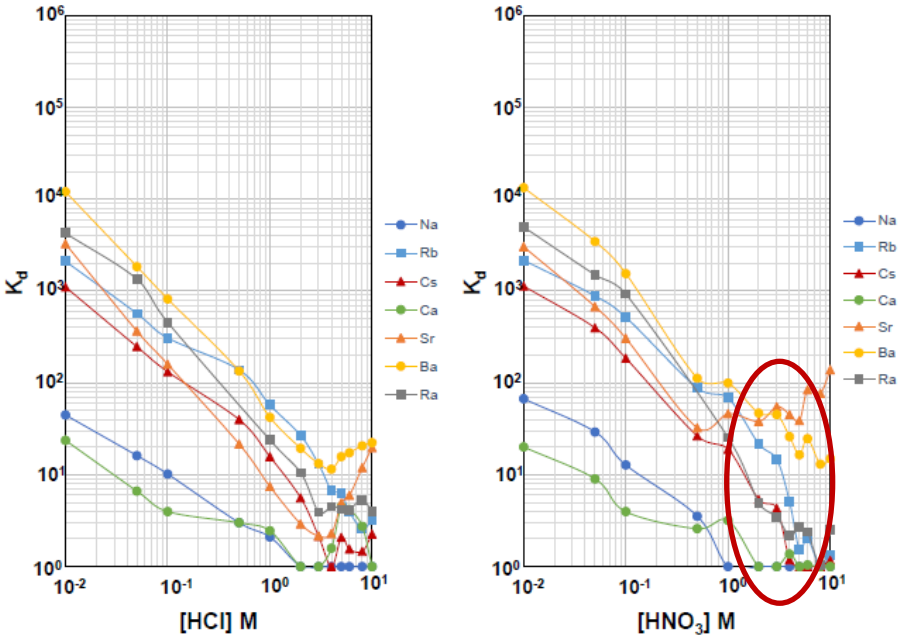
- In case Ra needs to be purified on-column (e.g. dissolved Ra needles) => Use of TK101 for Ra retention / purification
  - Test against Chelex, CEX, TK100
- TK101 => similar to TK100 but ionic liquid replaces HDEHP
  - Both based on same crownether as SR Resin
  - TK100 developed for Sr and Pb uptake also between pH ~2 and 7 (DGT)

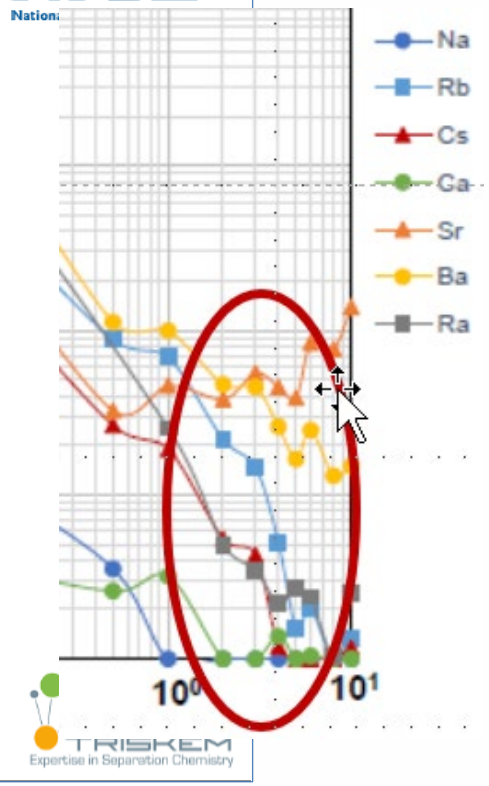
    $\Rightarrow$ Wagner et al. TK100 discs

    $\Rightarrow$ Retains wide range of elements
  - Replacing HDEHP by ionic liquid (=> TK101 Resin) allows for retention of Pb, Sr, Ba, Ra,… from pH ~2 – 7 without extensive extraction of other elements

# TK101 - Radium

## TK101 Group 1 and 2

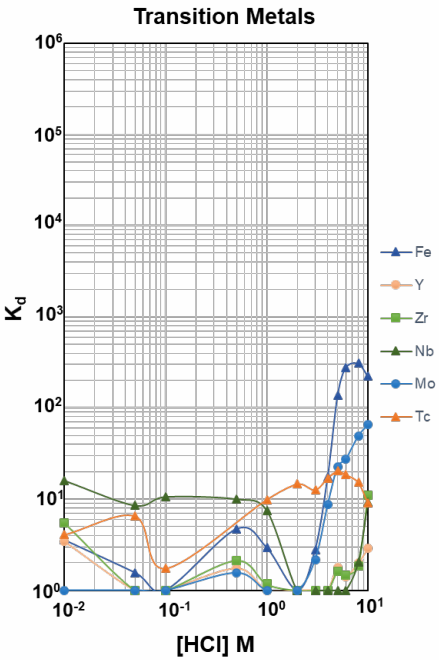


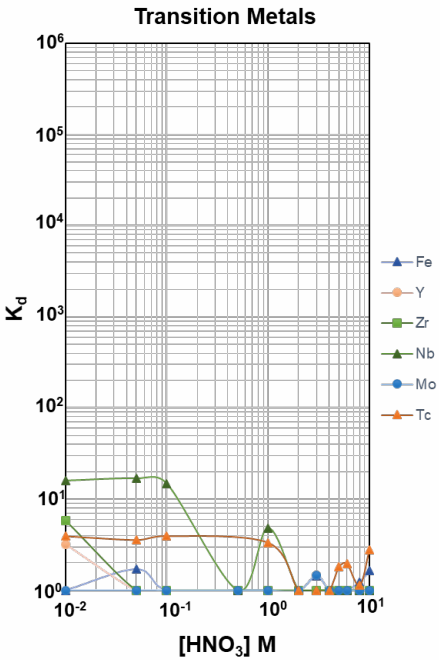




Data provided by
Russel et al. (NPL)

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

# TK101 Resin

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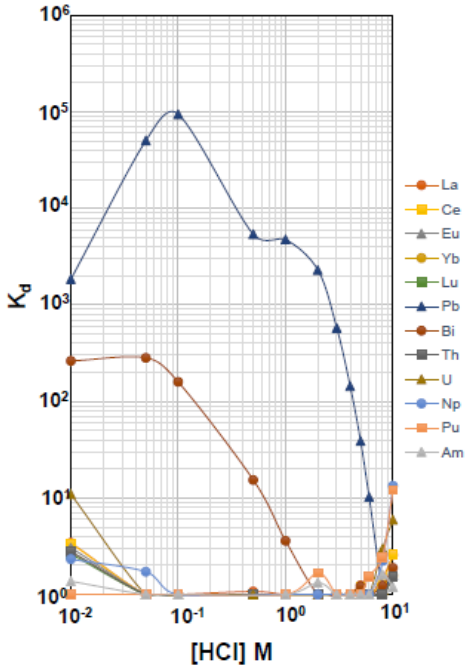
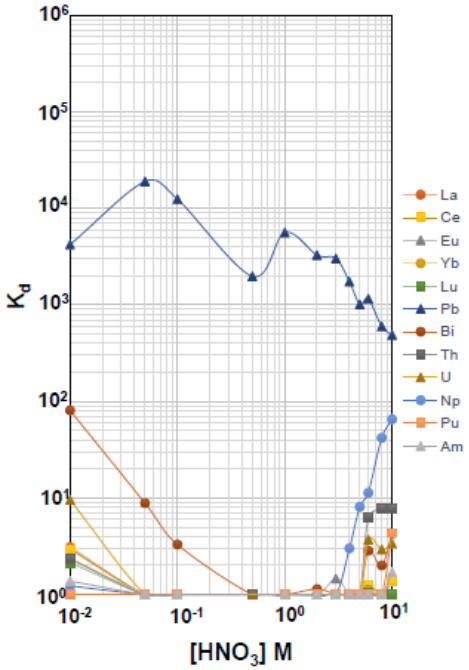
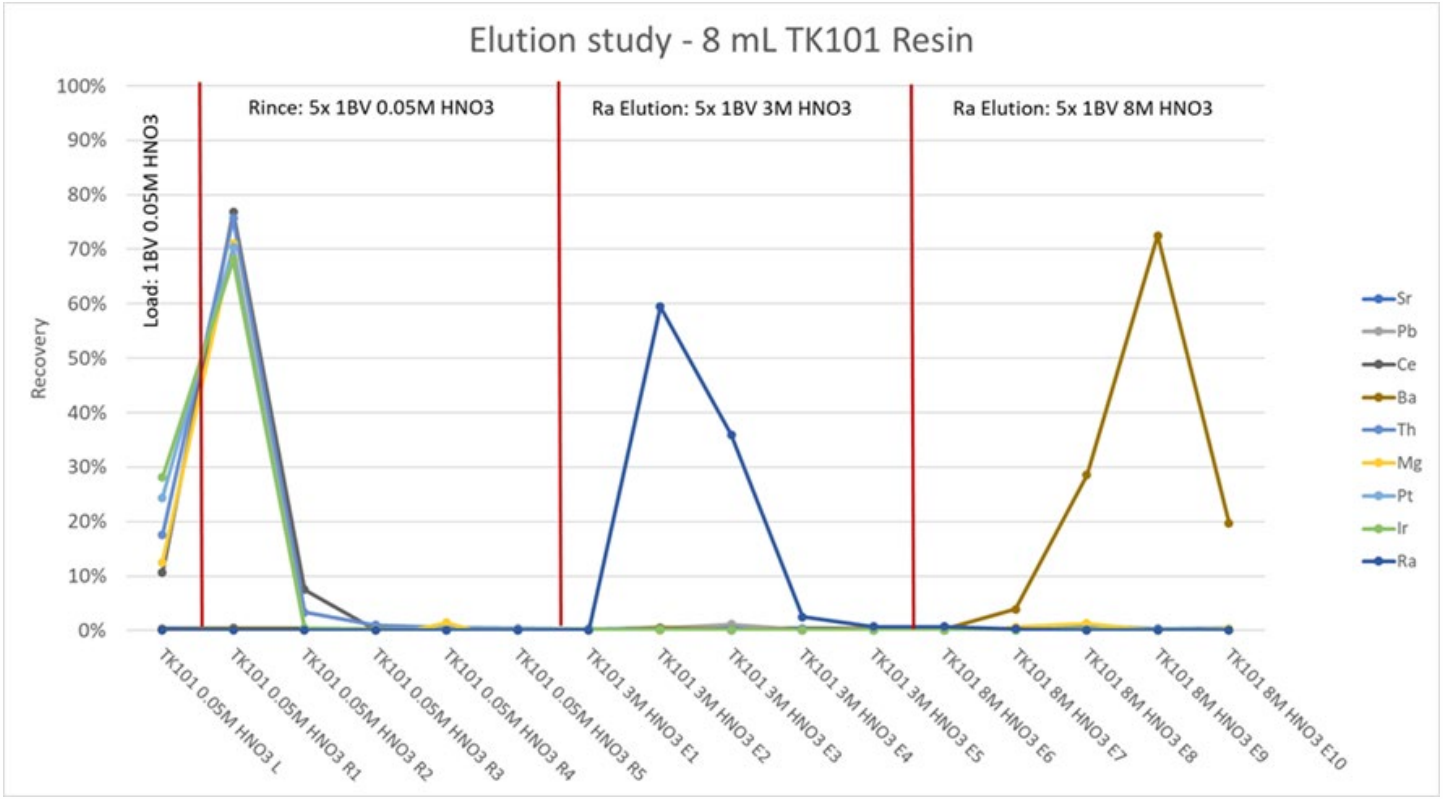



- No / extremely low selectivity for TM, Th/U, Ac
- Very strong Pb retention => elution in high HCl or citrate

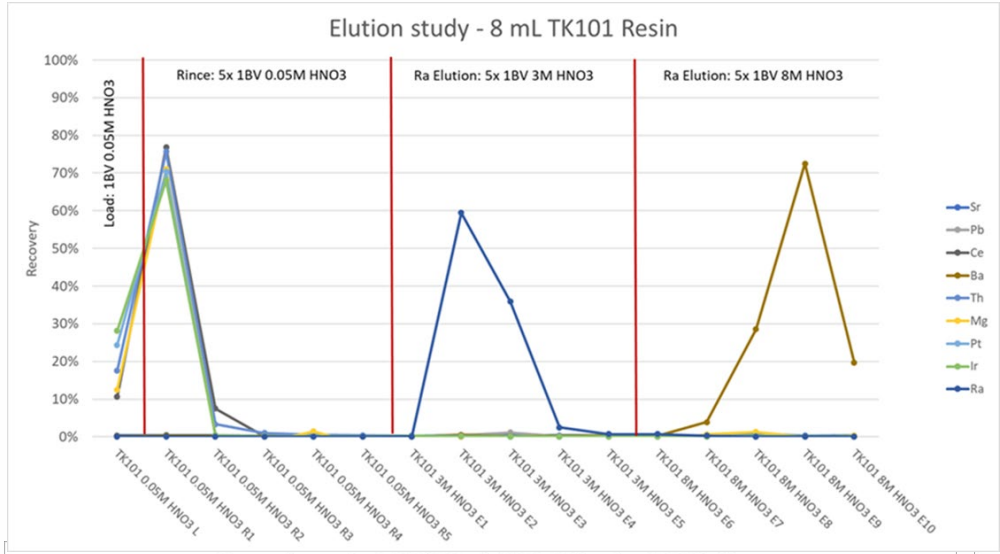
# Ra separation on TK101



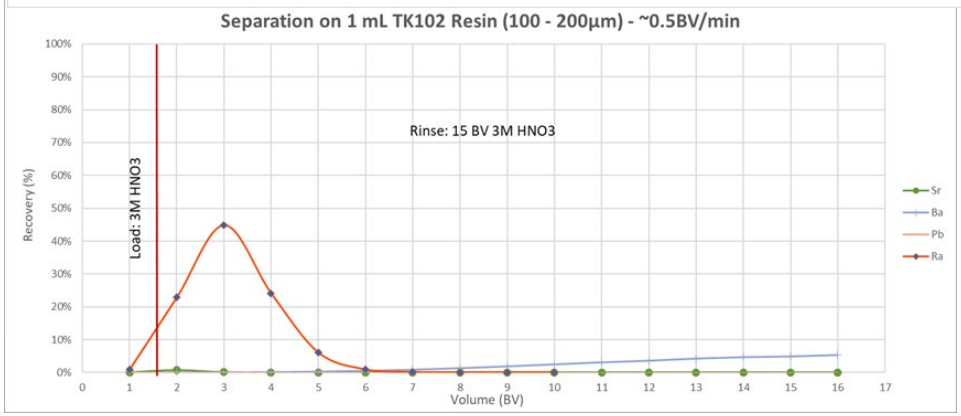

- Good Ra separation when loading from dilute $HNO_3$/HCl
- When eluting Ra in 3M $HNO_3$, Ba, Pb, Sr remain retained
- No retention of U, Th, Pt, Ir,…
- Ra eluted in 3M $HNO_3$
- Tl and Ba eluted in 8M $HNO_3$

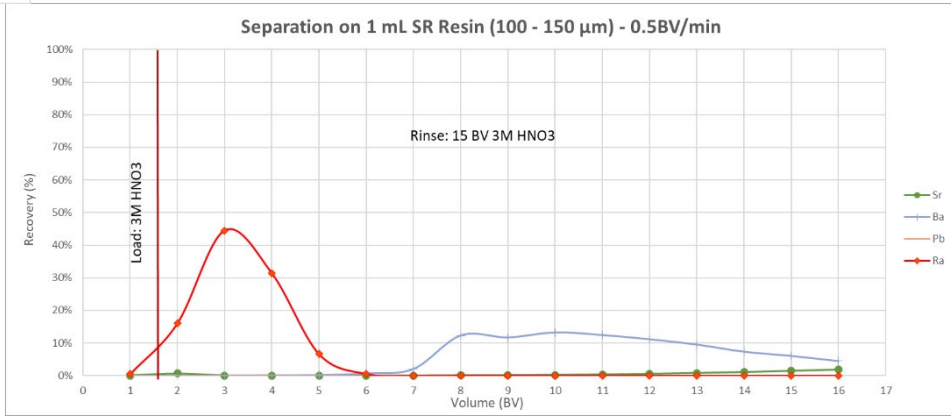
# Ra purification

- Work on crown-ether based resin for Ra ongoing
  - Aim: Ra retention from acidic/high $NO_3^-$ matrices, high capacity
- In-between: work on TK101 and TK102…



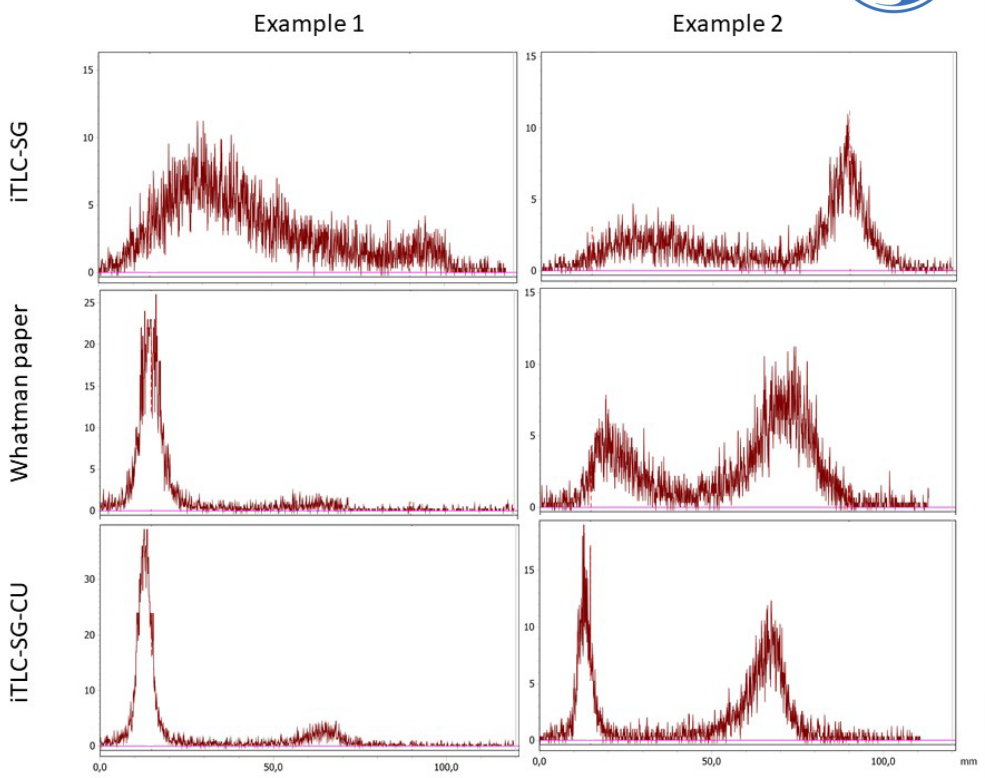

- Ra separation from matrix (e.g. Pt/Ir) and Ba
  - Ra retention and purification at 0.05M $HNO_3$
  - Ra elution in 3M $HNO_3$
  - Pb, Sr, Ba remain retained
- Might require additional TK102 for Ba removal



# CU Sheets

- Poster presented at Terachem 2022 (Svedjehed et al.)
- Other than for DGA Sheets not for radionuclidic purity
- 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
- Beta testing, commercialisation September 2023



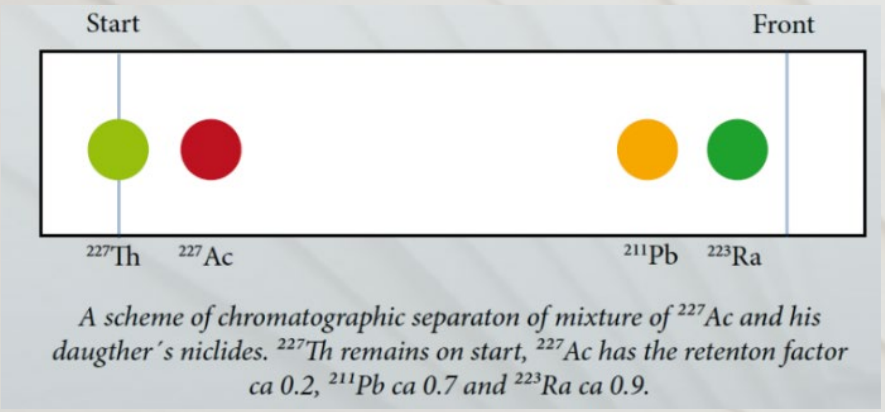

- Other systems under development/testing (TK101, ZR,…)

# DGA Sheets

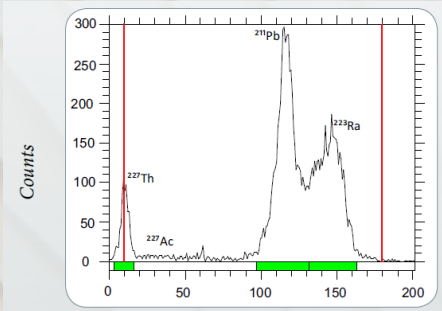
- TO-DGA (normal DGA) and TEH-DGA (branched DGA) impregnated TLC paper
  - Developed at CVUT (Kozempel et al.)
- QC of radionuclides and generator eluents

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

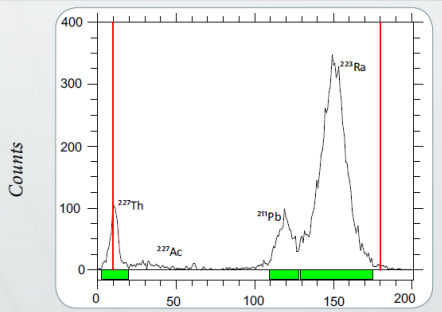
  - TLC scanner or radiometer/LSC or HPGe after cutting
- Run under acidic conditions => radionuclidic purity




*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.*

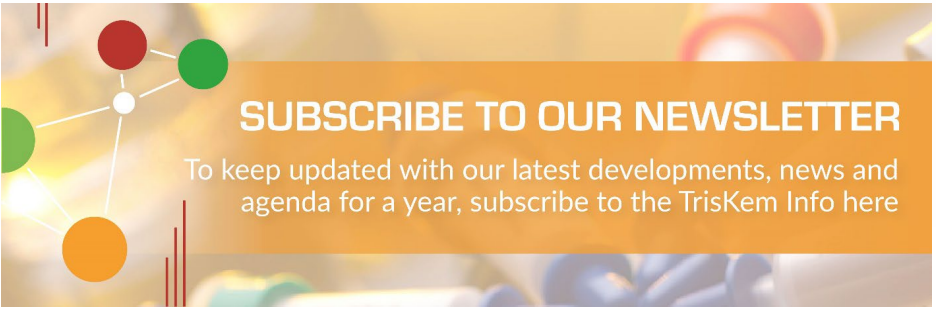
- More types of sheets under development (selectivities, geometry, support)
  - ZR, TK201,…
  - 2D TLC for radionuclide screening ?

# Research interests

- Upscale of radiolanthanide separations
- Ra Resins
- Radiometal purification
  - Sb, Pd, Hg, Mn, V, In, Sc, At…
- Improvement of radiolysis stability
- Separation of DTMs
  - Calixarene-based Cs/Rb Resins
  - Mo, Nb, Se, Sb,…
- RP RN in the environment
- In-field preconcentration
  - Impregnated membranes
  - Cartridges

- 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,…
- Rapid tests
  - Range of impregnated PSm resins
    - Uni Barcelona
  - Impregnated membranes
  - Range of 'Test sticks'
    - NPL, JCU
- Other 'geometries' & 'Non-resin' separation materials
- Microfluidics

# Thank you for your attention!

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