# Update on resins and methods for the purification and QC of radionuclides for use in diagnostics and therapy

2025 Australasian Cyclotron Users Group
Heidelberg (Australia)

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22/05/2025

2025 Australasian Cyclotron Users Group

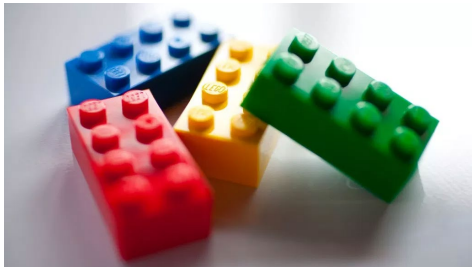
TRISKEM
Expertise in Separation Chemistry

# TrisKem International


- Based in Rennes (France)
- Independent company since 2007 (before part of Eichrom)
- Main product line: extraction chromatographic resins.
  - Also producing other separation materials
- Staff : 25
- R&D and TechSupport group:
  - 3 RadChem PhD, 2 Technicians (+ 1 PhD student and 1 master student)
- R&D: Development of new resins, techniques and applications
- Products used in several domains

# 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-61/4, Ga-68, Ge-68, Ti-44/5, Tc-99m, Sc-43/4…
    - Therapy: Ac-225, Lu-177, Tb-161, Cu-67, Pb-212, Sn-117m, Sc-47…
  - Requirements for resins:
    - No selectivity for target material, high selectivity for product
    - Elution under ‘soft‘ conditions in small volume => labelling/injection
    - Fast kinetics
    - Combining several resins can facilitate the separation
      - Conversion (high acid to dilute acid)
      - Removal of impurities upfront

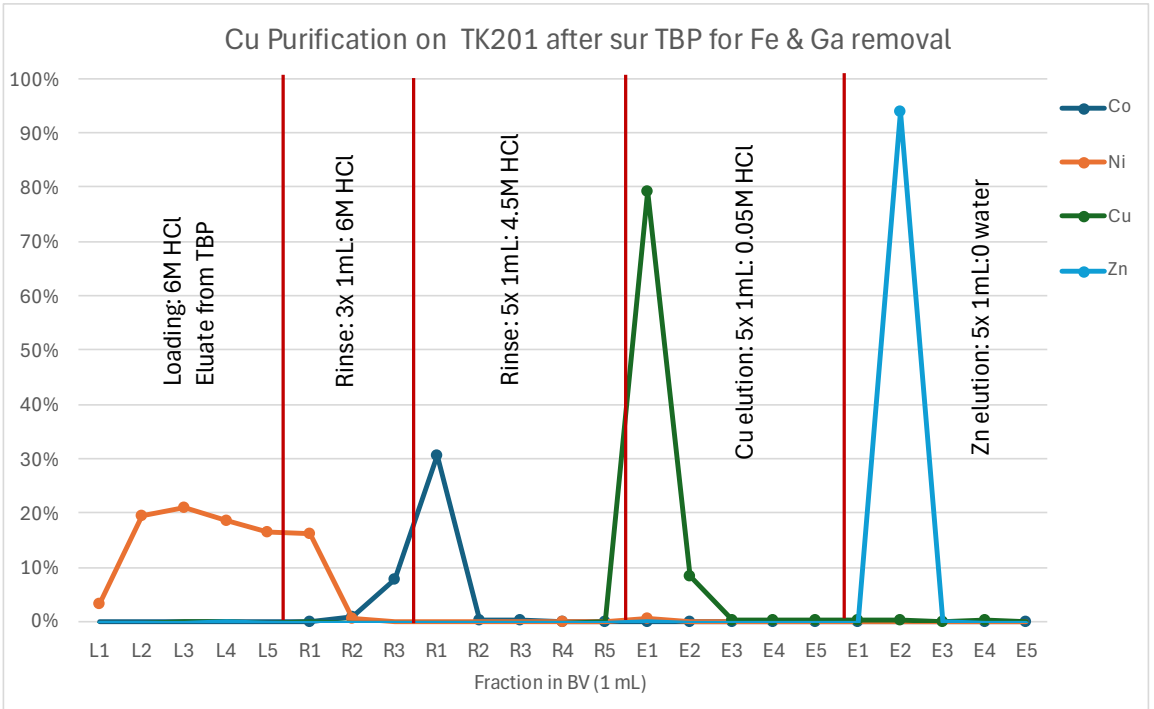



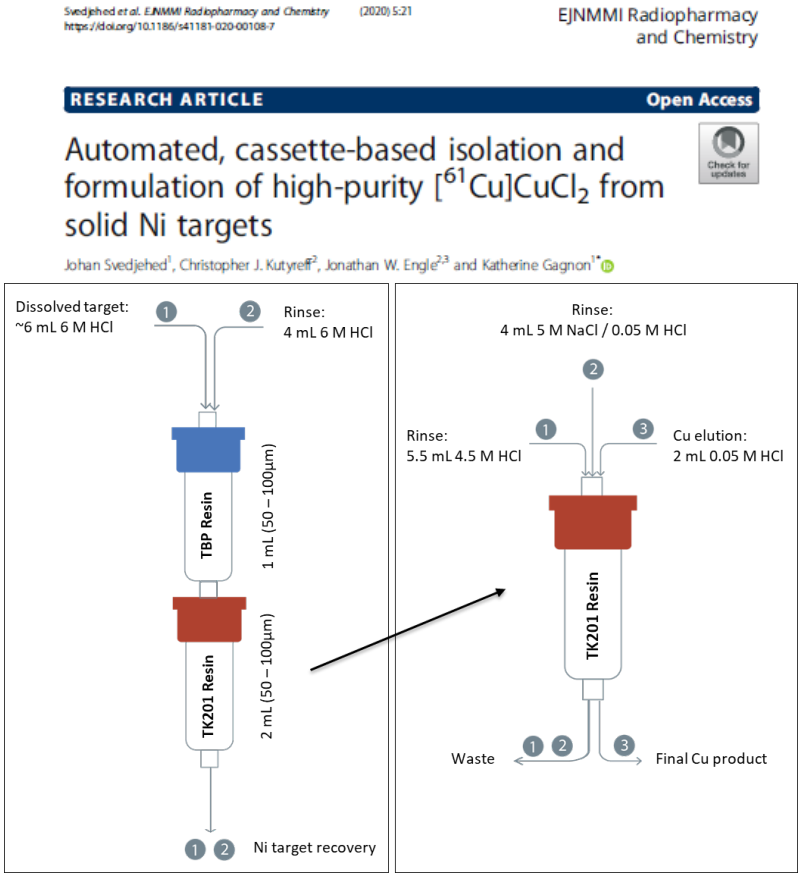
# Research interests - Radiopharmacy


- Quality control
  - Cartridge based methods (e.g. Sr-90 in Y-90,…)
    - New option “TK-**El**Scint cartridges” (impregnated plastic scintillator beads)
  - **“Sheets”**
    - p.ex. DGA sheets (functionalized TLC for Ra-223, Ga-68, Pb-212,…. => CVUT Prague), CU iSheets,…
- Decontamination of effluents/waste (Ge-68, lanthanides, radioiodine,…)
- Radiolysis stability (polymer, radical scavengers,…)
- Determination of radionuclides (mainly used in therapy, generally Lu-177 and Ac-225) in environmental and bioassay samples

# Cu-61/4 separation on TK201

- Cu-61/4 separation from solid Ni targets
  - Target dissolution in high HCl => 6M HCl
  - TK201 retains Cu, Zn, Co, Fe, Ga at 6M HCl
    - Difficult to get a clean Cu fraction in dilute HCl
  - Run through TBP (or TK400) for Fe/Ga removal
  - Separation of remaining radionuclides on TK201
  - Preferably avoid water (risk of Zn co-elution)





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

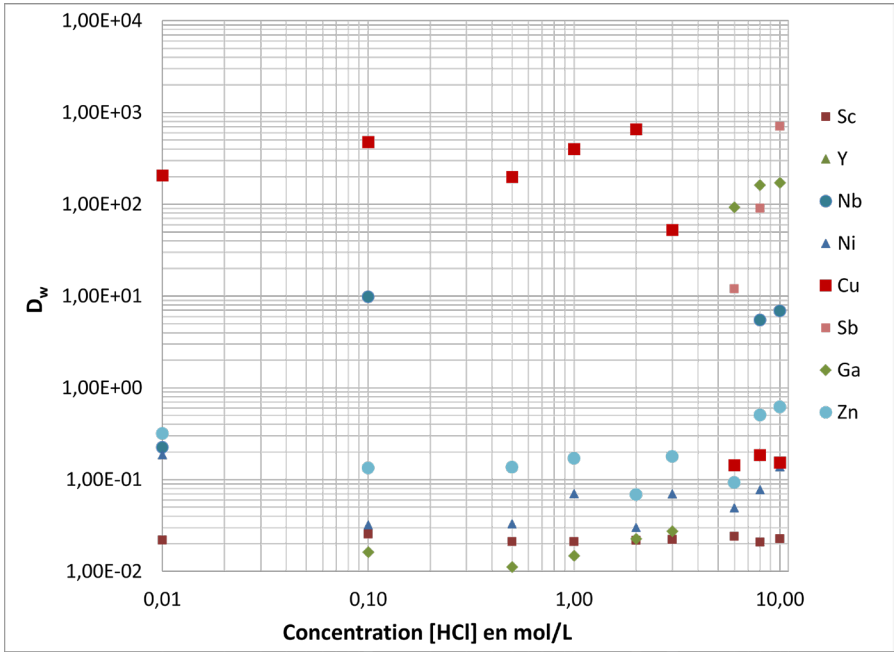
Johan Svedjehed[1], Christopher J. Kutyreff[2], Jonathan W. Engle[2,3] and Katherine Gagnon[1*]



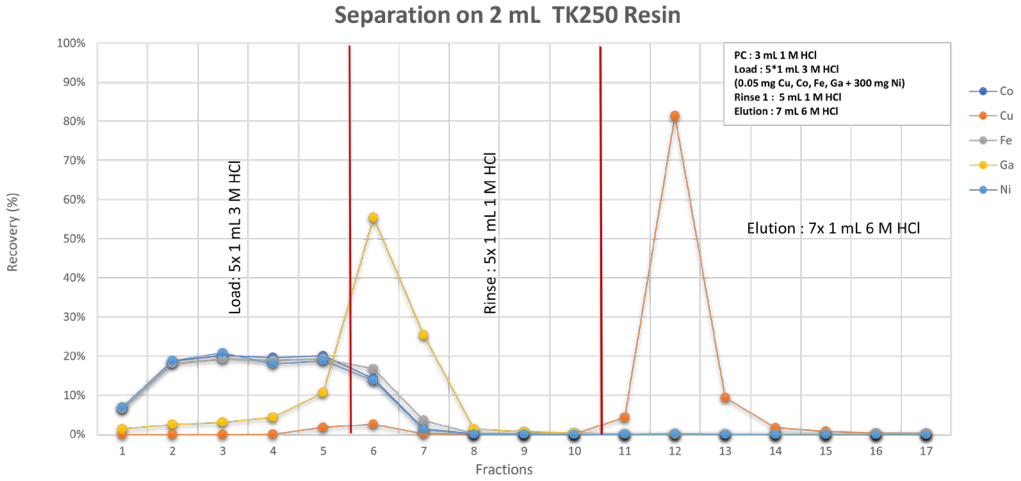
- Svedjehed et al. use of NaCl/HCl for better pH control of eluate
- Also being used for Zn separation
- Not applicable to solid Zn targets

# Upcoming: TK250 Resin

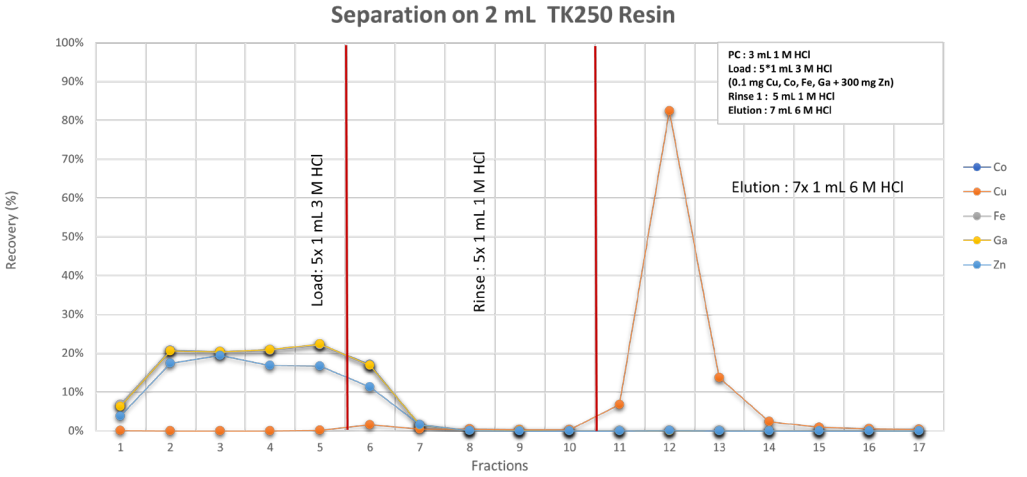
- CU Resin high selectivity for Cu over Zn but loading from pH >2 required
- Difficult to automize in case of solid Zn targets
- Upcoming TK250 Resin:
- Cu retention from low acid up to 3M HCl
- No selectivity for Ni **and Zn**
  - Tested up to 300mg each
- Cu elution in 6M HCl
- Rather low Cu capacaity (~0.13mg/g)




Dw values TK250 Resin, various éléments, HCl

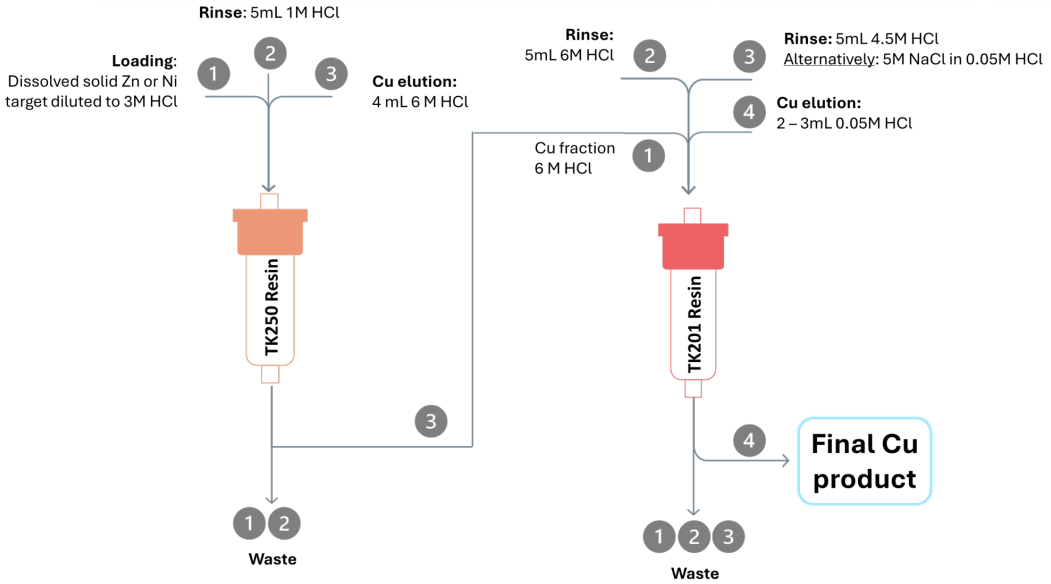



Cu separation from 300 mg Ni on 2mL TK250 Resin

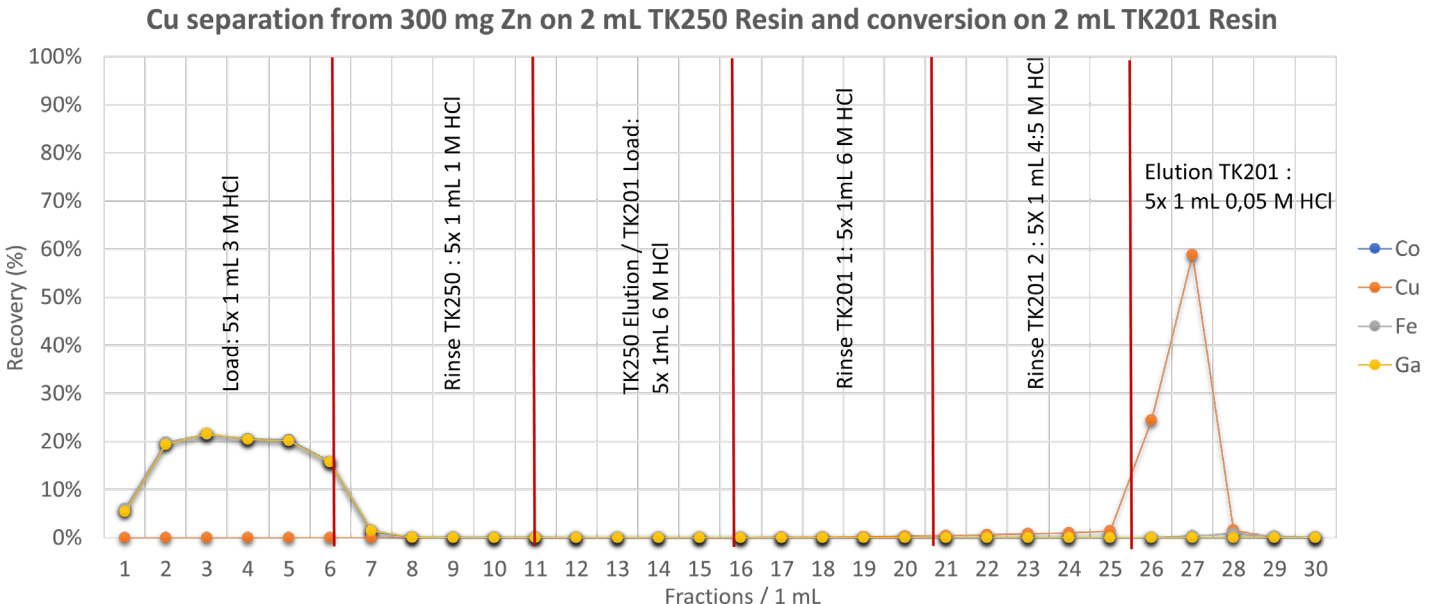



Cu separation from 300 mg Zn on 2mL TK250 Resin

# Upcoming: TK250 Resin




- $D_f$ typically >$10^3$ - $10^4$
- 6M HCl to low HCl on TK201 Resin
- Next steps:
  - Optimisation of resin composition
  - Upscale and stability testing
- Integration in sequential separation scheme for Cu and Ga from Zn targets e.g. with TBP Resin (for Ga)



# Zr-89 chloride via TBP and TK400

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

## [$^{89}$Zr]$ZrCl_4$ for direct radiolabeling of DOTA-based precursors☆

Serge K. Lyashchenko [a,b,*], Tuan Tran [a], Steffen Happel [c], Hijin Park [a], David Bauer [b], Kali Jones [b], Tullio V. Esposito [b], NagaVaraKishore Pillarsetty [b], Jason S. Lewis [a,b,d]

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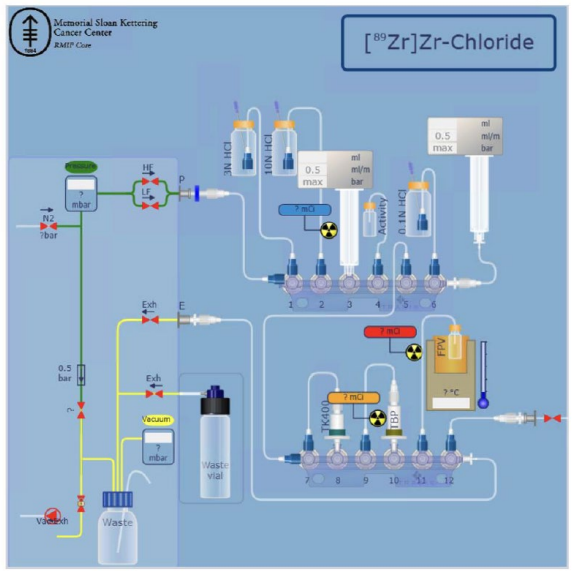



**Table 1.** Summary of Measured Iron Content in TBP-purified solutions.

| Purification Intervention | Measured Iron Content (ppm) | Source |
|---|---|---|
| No TK400, TBP only | 32.7–38.8 (n = 6) | Graves et al. |
| Single TK400, followed by TBP | 8 (n = 3) | This Study |
| Double TK400, followed TBP | < 1 (n = 3) | This study |

- Improvement of method published by Graves et al. (TBP only) => insufficient Fe removal
- Load and rinse on TBP Resin at ~10M HCl, elution in dilute HCl
- Use of 2xTK400 before TBP Resin for Fe removal
- Production of 11.1 – 14.4 GBq of [$^{89}$Zr]Zr-PSMA-617 and [$^{89}$Zr]Zr-PSMA-I&T
- Apparent specific activities of 11.1 - 14.4 MBq/µg
  - 2–3x more than before at industrial quantities.
- On-going:
  - Use of TK201 instead of TK400 for impurities removal (catch additional impurities? e.g. Cu)
  - Alternative methods for Zr oxalate conversion to Zr chloride (avoiding QMA)

**Table 2.** Summary of Radionuclide Purity Measurements in [$^{89}$Zr]$ZrCl_4$ Solution.

| Batch | [$^{89}$Zr]$ZrCl_4$ - Batch 1 | [$^{89}$Zr]$ZrCl_4$ - Batch 2 | [$^{89}$Zr]$ZrCl_4$ - Batch 3 | [$^{89}$Zr]$ZrCl_4$ - Batch 4 |
|---|---|---|---|---|
| Radionuclidic Purity | ≥99.9% | ≥99.9% | ≥99.9% | ≥99.9% |
| % of $^{88}$Zr | $6.9\times10^{-10}$% | $2.9\times10^{-10}$% | $4.7\times10^{-9}$% | $1.2\times10^{-8}$% |
| % of $^{88}$Y | $3.6\times10^{-10}$% | $2.0\times10^{-10}$% | $2.2\times10^{-9}$% | $5.1\times10^{-9}$% |

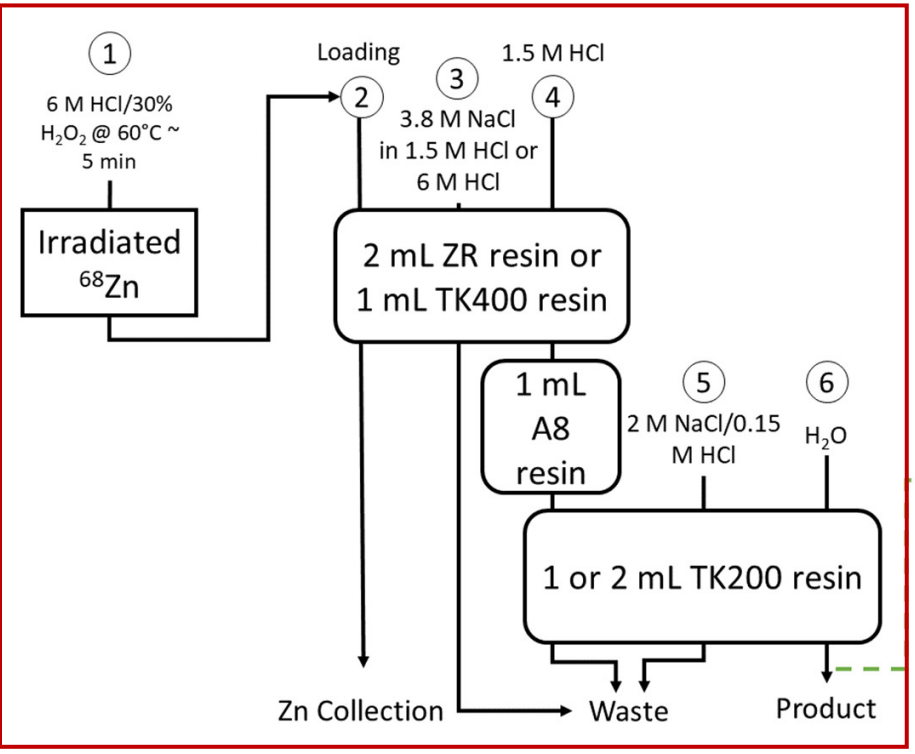
# Ga separation on TK400 Resin

TK400 Resin => use for Ga solid Zn targets (alternative to ZR Resin)

- Ga retention on TK400 from high HCl, elution in low HCl
- No Zn retention
- Faster kinetics than ZR Resin

W. Tieu et al. use of single TK400 cartridge for solid Zn targets (purity lower than ZR/TK200)

Svedjehed et al. use of TK400/A8/TK200 (all 1mL) for solid Zn targets




On-going:

- Use of TK201 instead of TK200 (idea by Bryce Nelson)
  - Potentially better Zn removal
- Improvement of TK400 Resin / Ga yields (Svedjehed: ~80%)

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*

# At-211 separation

- Requests for cartridge based separation of At from Bi targets in $HNO_3$. Resin approach already used by Burns et al. (3-octanone)
- Eriksen et al. showed At separation from Bi possible in $HNO_3$ via LLX using Octanol (=> TK400 Resin)
- Tereshatov et al. tested several extraction chromatographic resins for At separation from Bi incl. TK400
- At elution via alcohol (removal of org. phase + At from resin)
- TK400 and three additional resins currently being tested ("TK401", "TK402", TK200) – standard and new support
- Elution via NaOH possible?
- Currently shipping samples
- Also working on resins for Rn-211/At-211 generator

ELSEVIER

Chemical Engineering Journal
Volume 464, 15 May 2023, 142742

Mechanism of astatine and bismuth sorption on extraction chromatography resins from nitric acid media

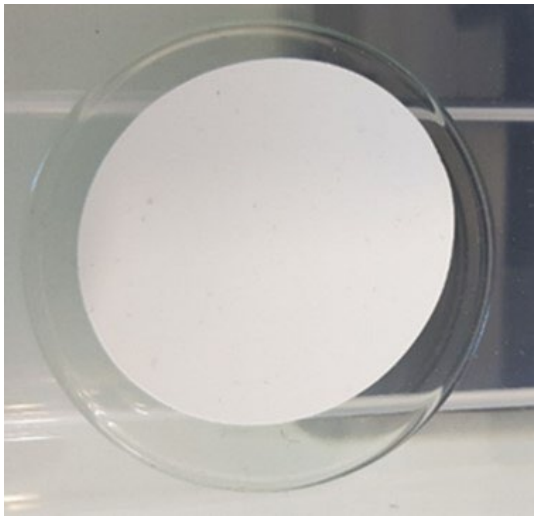
Evgeny E. Tereshatov [a], Jonathan D. Burns [b], Steven J. Schultz [a c],

# Under development: range of impregnated membrane filters

Upcoming: impregnated membrane filters ('Discs')

Several Discs under development and beta testing:

- ➢TK100, TK201, CU , GA, TK101…
- ➢25mm and 47mm diameter



First Disc in range: **TK-GrossAlpha Disc**

=> Alpha measurements

pH 1 - 2, typically up to 100mL samples

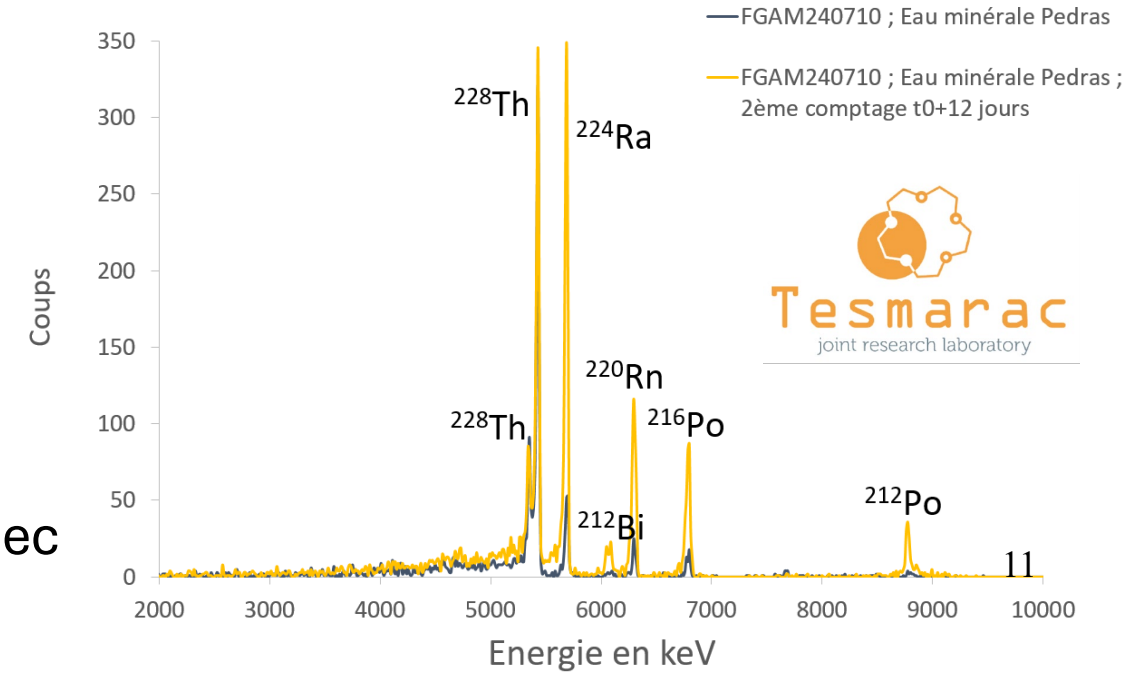
Filtration (1 – 10mL/min)

High retention of alpa emitters

- Mainly retained on the surface
- Suprisingly good resolution

Discs glued on steel support => alpha spec

Presence of Th or Ra in QC samples?



# DGA Sheets/iSheets

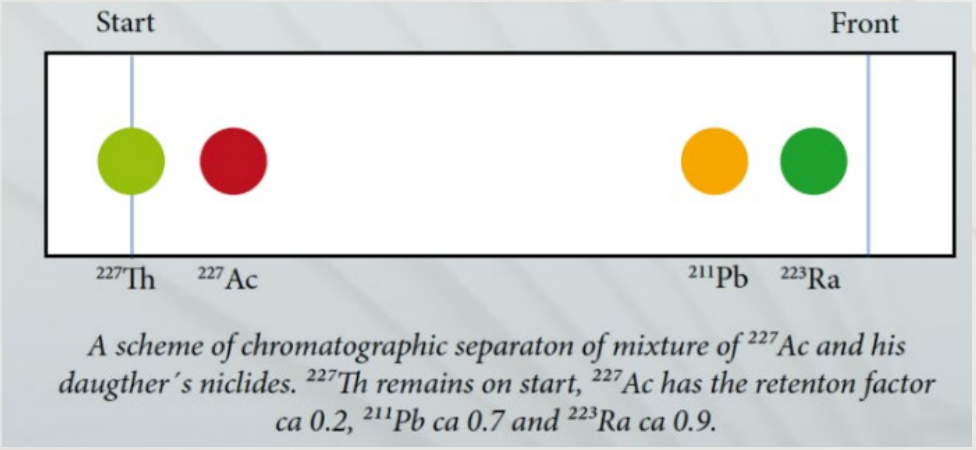
TO-DGA (normal DGA) and TEH-DGA (branched DGA) impregnated TLC paper

- Developed at CVUT (Kozempel et al.)

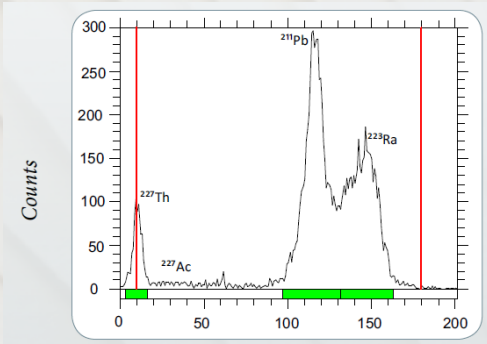
QC of radionuclides and generator eluents (p.ex. Ra-223, Ac-225/Bi-213, Pb-212, Ge-68/Ga-68 ...)

- TLC scanner or radiometer/LSC or HPGe after cutting

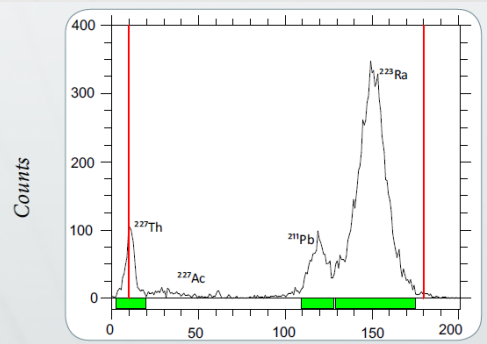
Run under acidic conditions => radionuclidic purity




*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.*

- Now also available based on iTLC support (faster development, higher DGA load)

=> **DGA iSheets (iSheets = based on iTLC paper)**

- 2D TLC for radionuclide screening?

# CU iSheets

Poster presented at Terachem 2022 (Svedjehed et al.)

QC of Cu radiolabeled peptides (labeled vs free Cu)

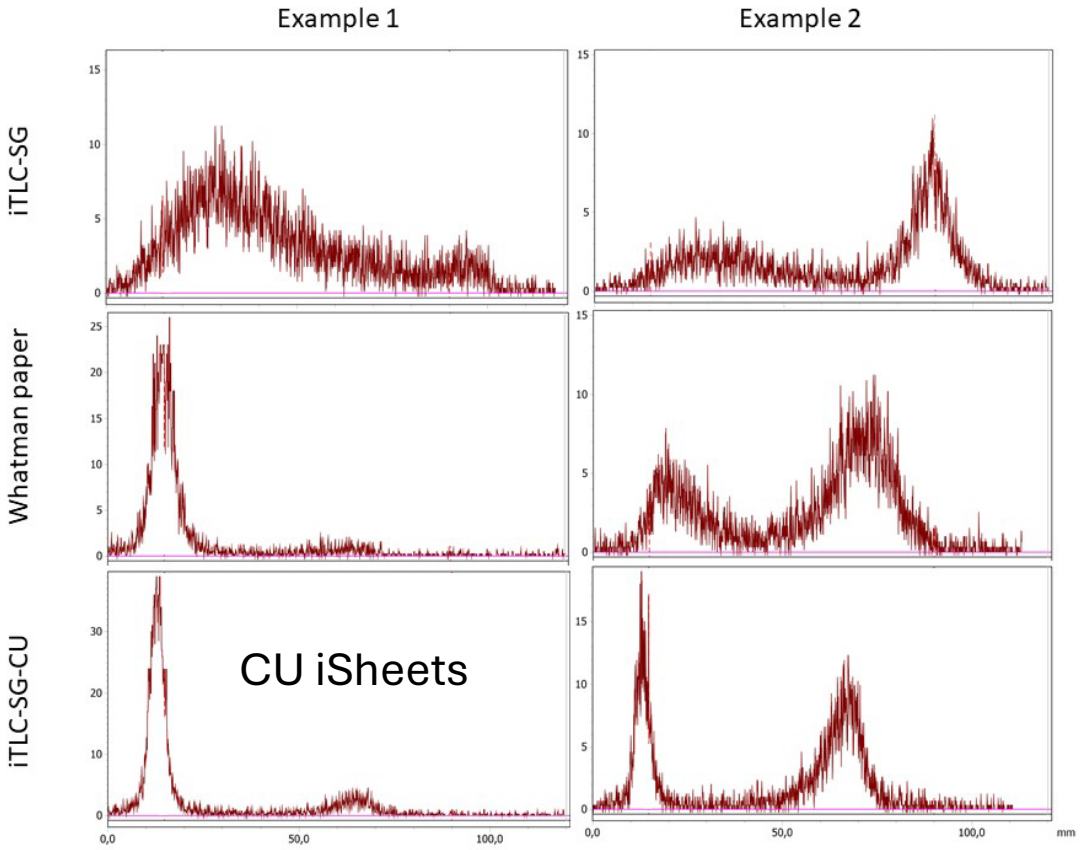
- Shown: [$^{61}$Cu]Cu-NOTA-octreotide

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
- Next: TK213 (Ac, Lu)

# Some other on-going projects

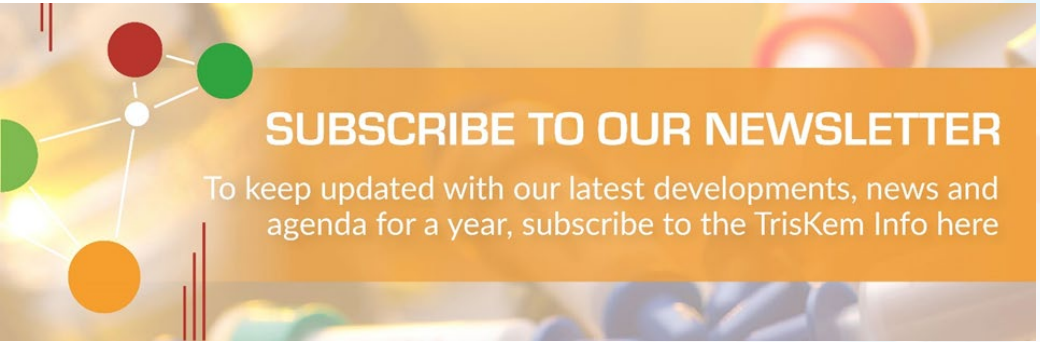
- Ac purification via TK221 (or TK222)
- Ra purification and recycling
  - TK101/TK102 (Ra/Ba separation)
  - Development of new Ra Resins
- Upscale of radiolanthanide separations (multi-gram):

  Lu-177 and Tb-161
- Tc-99 via cyclotron (TK202, C8 and AlOxA)
- Other radiometals
  - **Ge, Hg, Ag, Pd,…**
- Rapid QC
  - Discs, TK-**El**Scint cartridges (plastic scintillator beads based)
- Decontamination
  - Effluents and reaction wastes
  - I, Ge, Lu, O-18…
- Fate' of RN in the environment
  - Separation methods
  - Mainly longer lived RN (=> therapy)
    - Ac-225/7, Lu-177(m), radioiodine,…
  - Quantification
- Rn-211/At-211 generator
- Microfluidics
- Other 'geometries' &

  'Non-resin' separation materials
- Hydrometallurgy
- Analytical applications

# Thank you for your attention!

Interested in collaborations?
shappel@triskem.fr




TRISKEM
Expertise in Separation Chemistry

# TK202 Resin

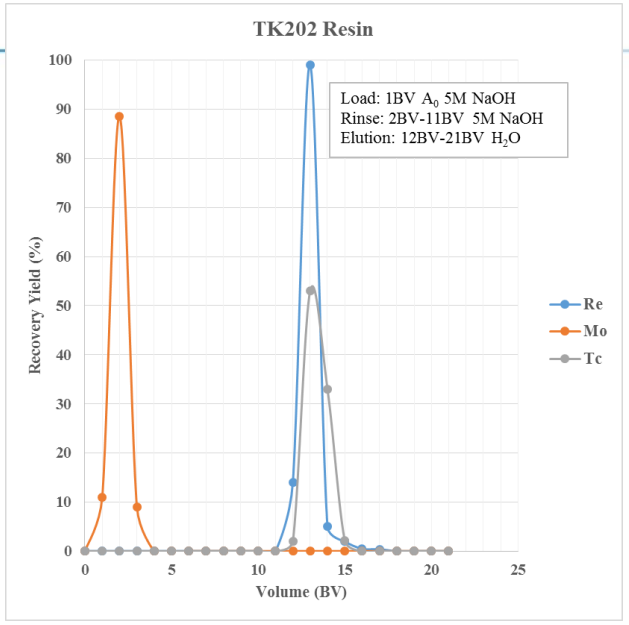
Tc retention from high NaOH (5 - 7M)

- Dissolved Mo targets
  - Increased Tc (Re) retention at higher Mo concentration
- Clean separation from other elements tested

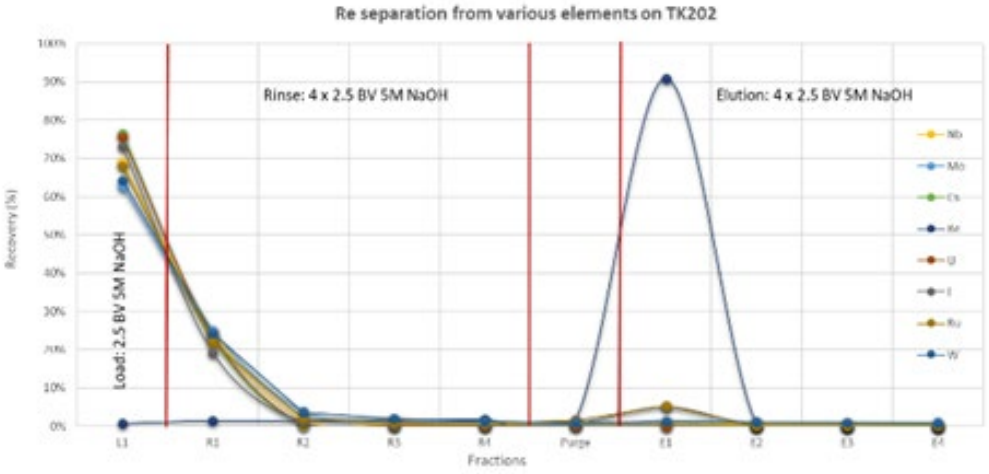
Re used as homologue

Elution in small volume of water

- Eluate will still alkaline and will contain Na
- Pass through CEX for ‘neutralisation’ and $Na^+$ removal and through
- aluminium oxide for trace Mo removal and recovery as 0.9% NaCl solution

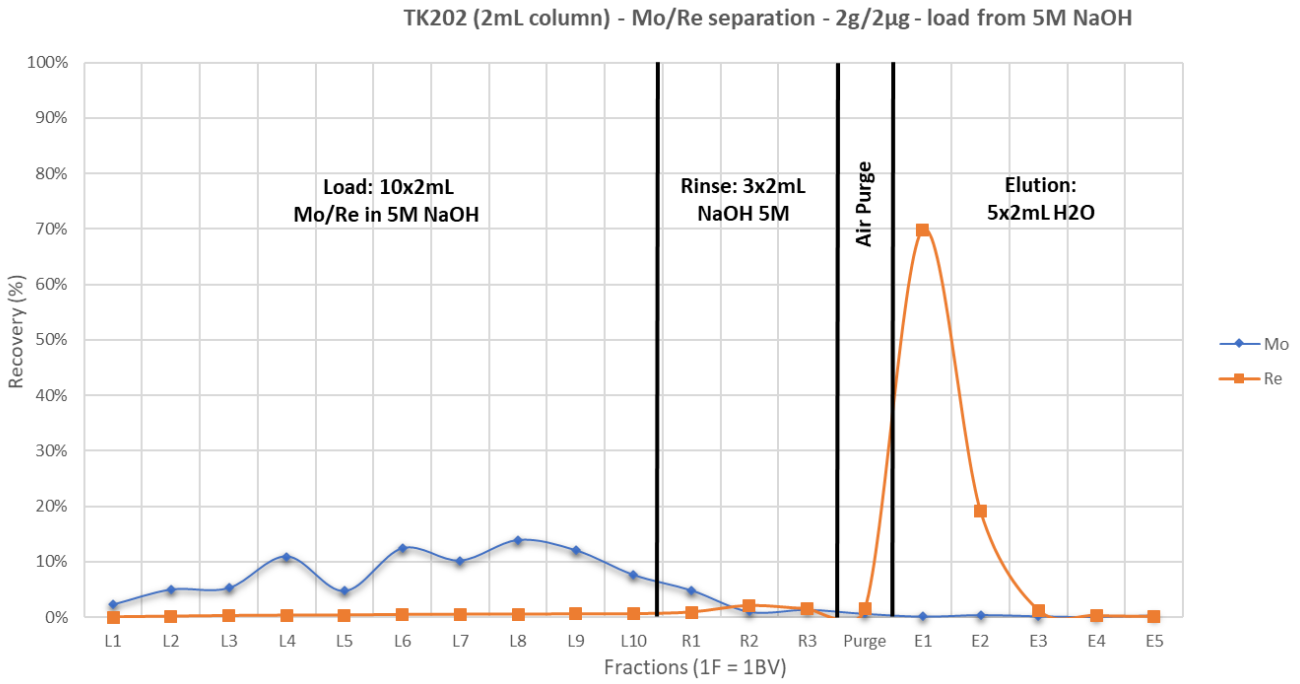



Re/Tc separation from Mo on TK202 Resin




Re separation from selected elements on 2 mL TK202 Resin cartridge, load and rinse at 1 BV/min, elution at 0.25 BV/min

# Tc-99m via cyclotron route

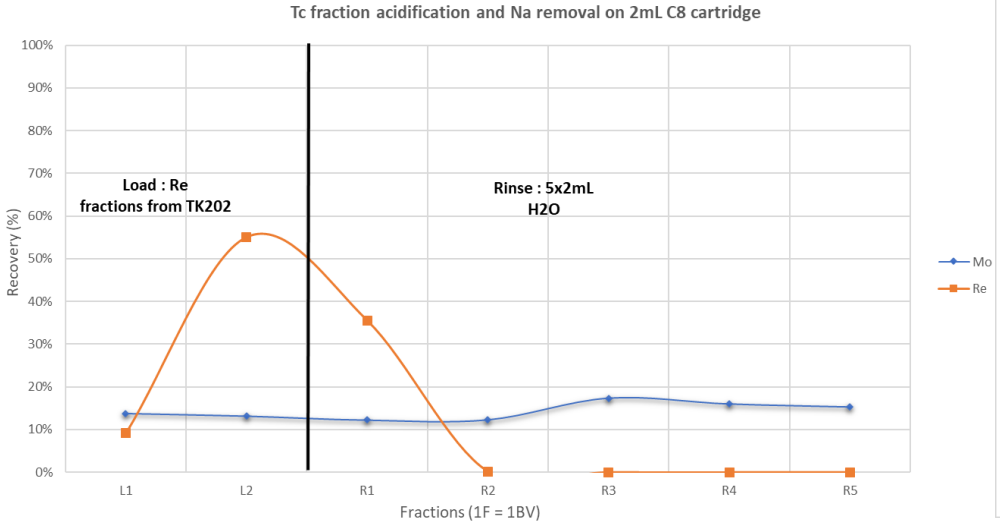


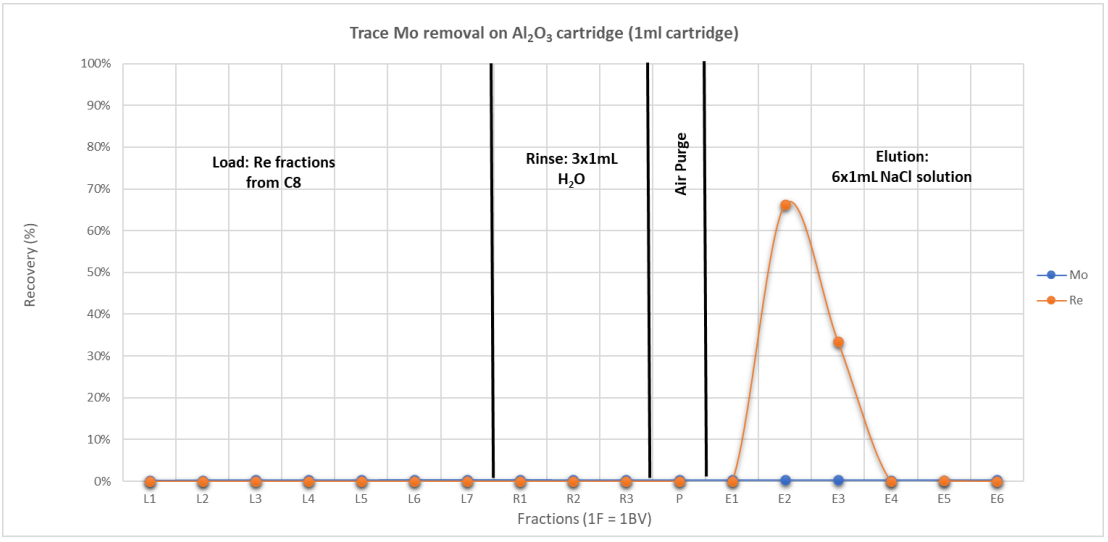

Tests performed cold with 2g Mo and 2 µg Re

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

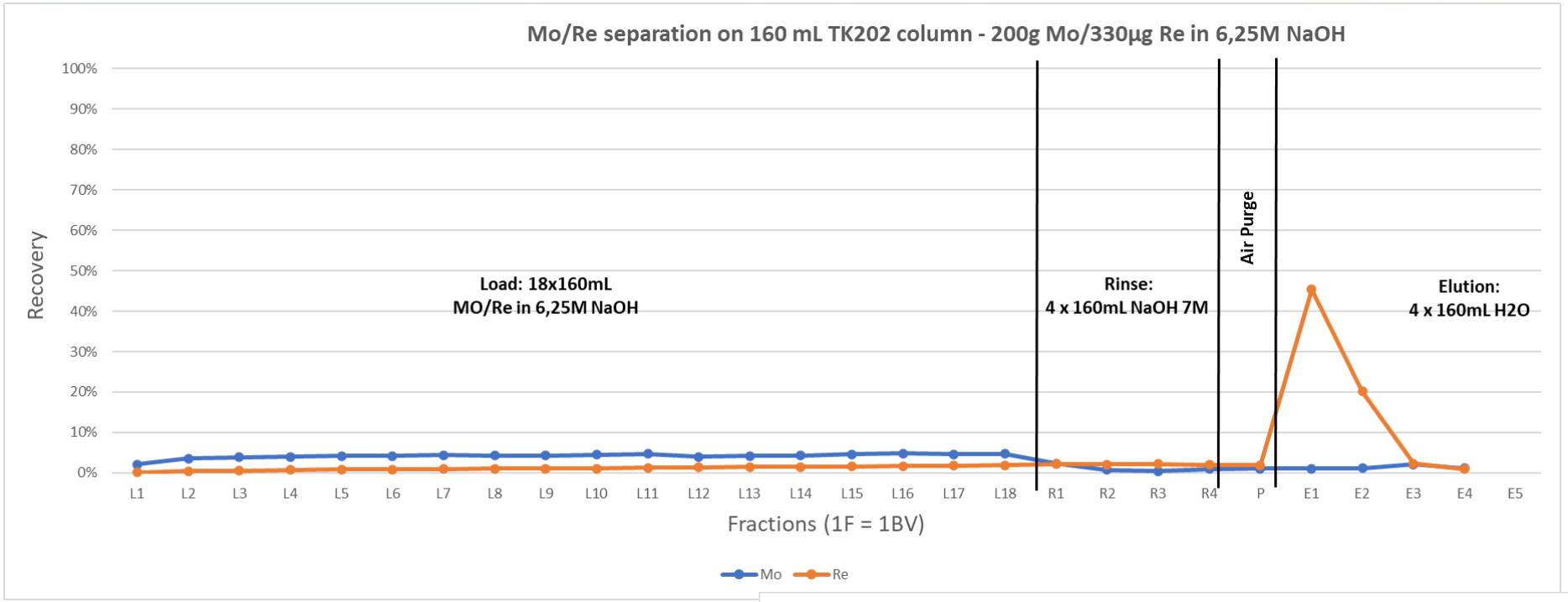
Method similar to Zeisler et al.

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



# Tc-99m from large Mo targets




Test with 200g Mo

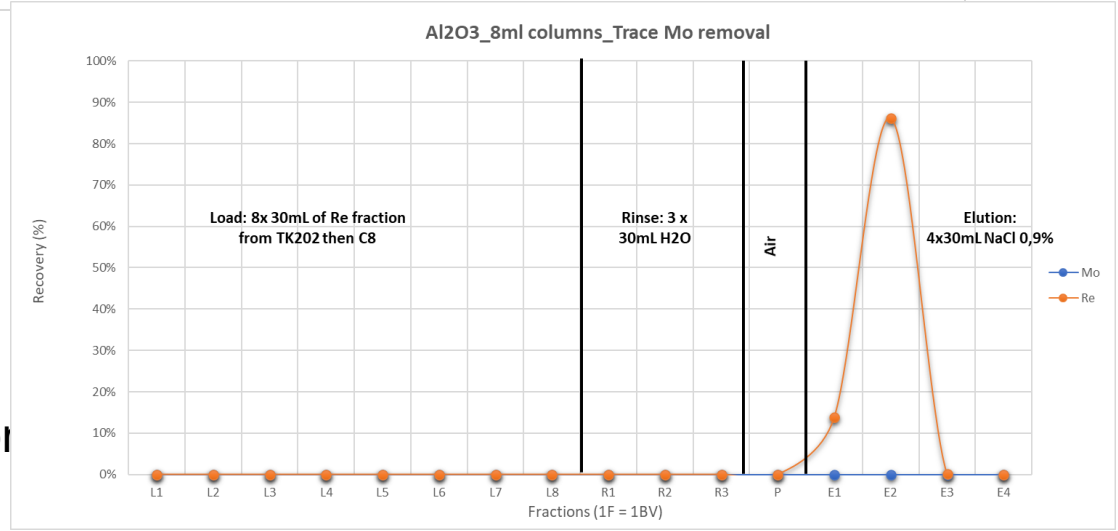
~160 mL TK202 column

Load from 6 - 7M NaOH - elution in water

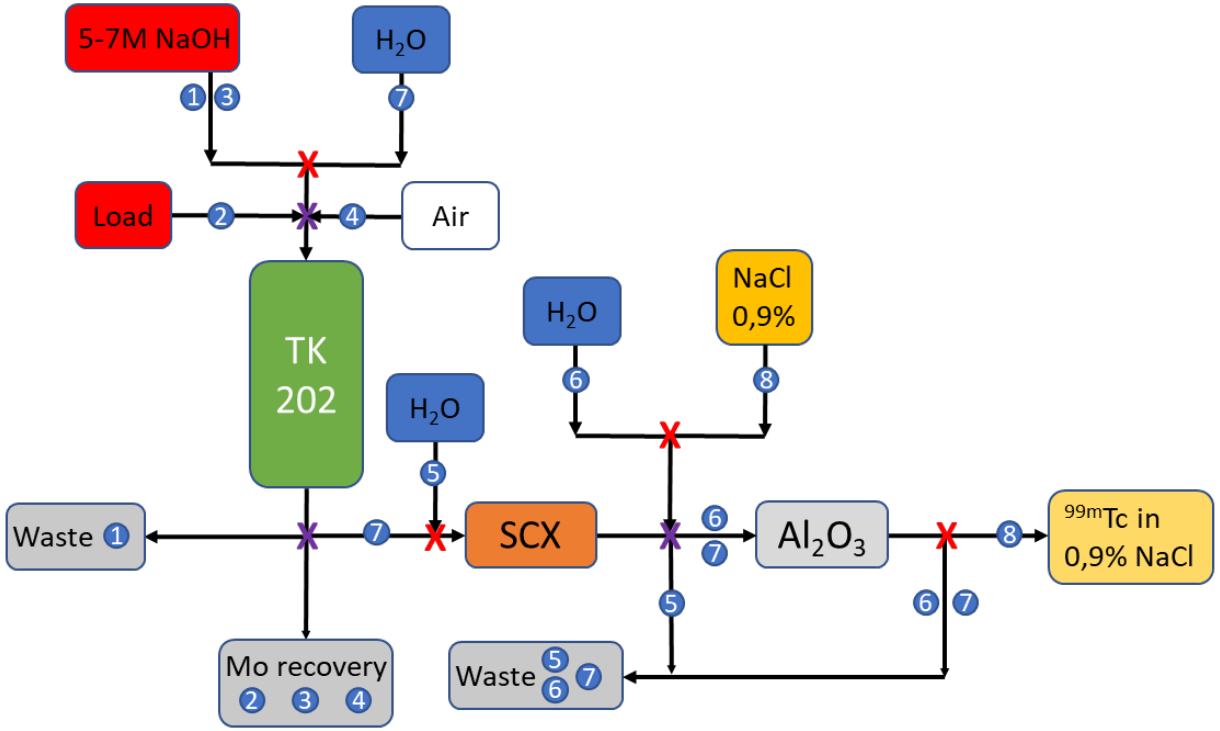
Pass through C8 cartridge for acidification and Na removal

Final concentration/conversion to 0.9% NaCl or

8 mL AlOxA cartridge



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




1. Pre-cond. TK202 – 5-7M NaOH ➔ alkaline waste
2. Load Mo/Tc on TK202 ➔ Mo recovery
3. Rinse TK202 – 5-7M NaOH ➔ Mo recovery
4. Purge TK202 – Air ➔ Mo recovery
5. Pre-cond. SCX – HCl then $H_2O$ ➔ Aq. waste
6. Pre-cond. $Al_2O_3$ – $H_2O$ ➔ Aq. waste
7. Elute Tc from TK202 on SCX and load on $Al_2O_3$ – $H_2O$
8. Elute Tc from $Al_2O_3$ – NaCl 0,9% ➔ Tc recovery

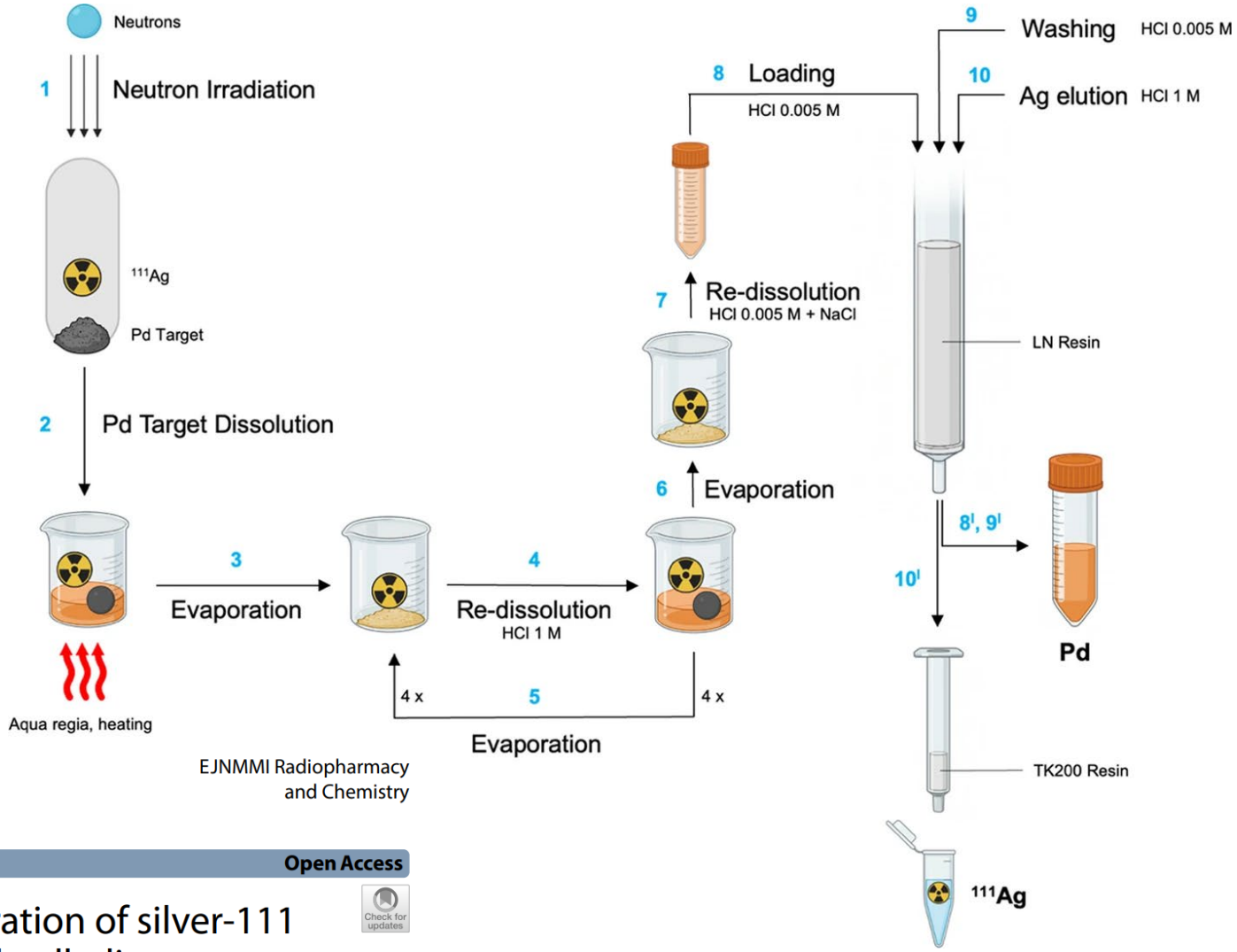
**TK202 : 35-75 or 75-150µm**
**X : 3-ways valve**
**X : 4-ways valve**
**SCX : Strong Cation Exchange**
**$Al_2O_3$ : Acidic Alumina**

**Developed with $ReO_4^-$ as $TcO_4^-$ surrogate**

**Re recovered on saline solution from alkaline**

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

# Ag-111 from Pd targets – LN/TK200




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

EJNMMI Radiopharmacy and Chemistry

**RESEARCH ARTICLE** **Open Access**

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

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