Using LN resin to purify terbium isotopes for use in nuclear medicine

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Triskem User Group
24th November 2020
vCARM ’20

Our Project

^{149}Tb α Alpha therapy	^{152}Tb β^+ PET imaging	^{155}Tb Electron capture SPECT imaging	^{161}Tb β^- Beta therapy

^{149}Tb	^{152}Tb	^{155}Tb	^{161}Tb
α	β^+	Electron capture	β^-
Alpha therapy	PET imaging	SPECT imaging	Beta therapy

^{149}Tb
α
Alpha therapy

^{152}Tb
β^+
PET imaging

^{155}Tb
Electron capture
SPECT imaging

^{161}Tb
β^-
Beta therapy

^{149}Tb	^{152}Tb	^{155}Tb	^{161}Tb
α	β^+	Electron capture	β^-
Alpha therapy	PET imaging	SPECT imaging	Beta therapy

Theranostic pair

=

Personalised medicine

How can we produced these isotopes?

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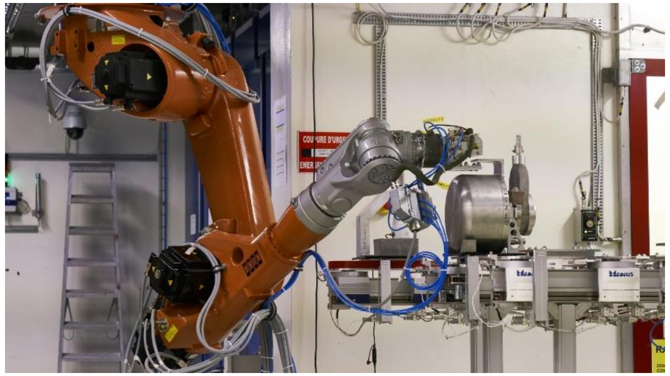

Synchrotron – proton-induced spallation

- $^{149,152,155}Tb$
- Mass separation
- Trace lanthanide impurities

How can we produced these isotopes?

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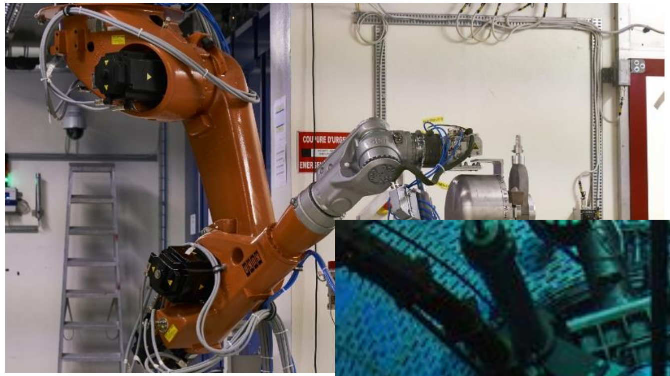
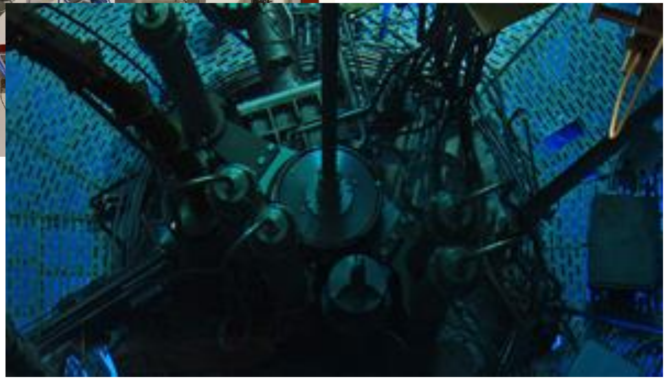
Nuclear reactor – neutron bombardment

- ^{161}Tb
- Bulk Gd, trace Dy impurities



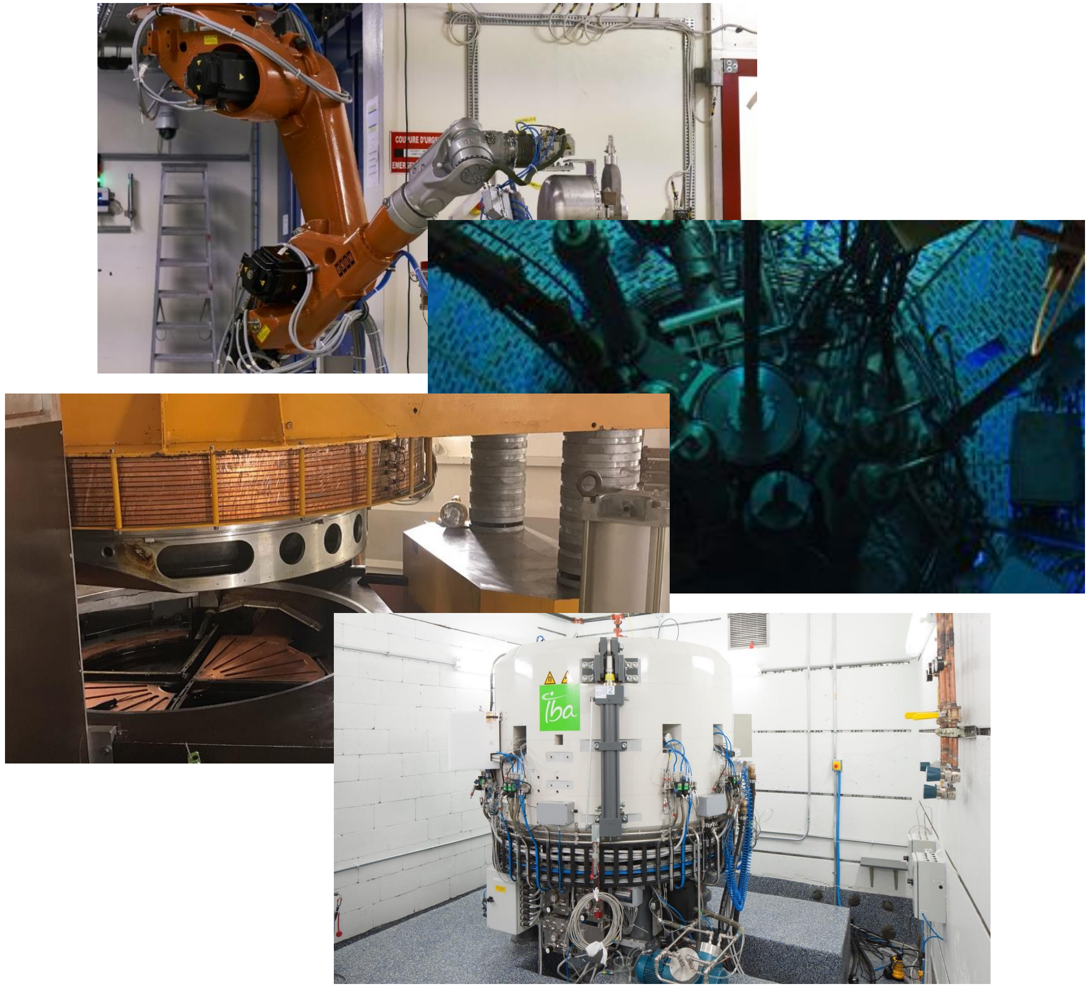


How can we produce these isotopes?

Synchrotron – proton-induced spallation
- $^{149,152,155}Tb$
- Mass separation
- Trace lanthanide impurities

Nuclear reactor – neutron bombardment
- ^{161}Tb
- Bulk Gd, trace Dy impurities

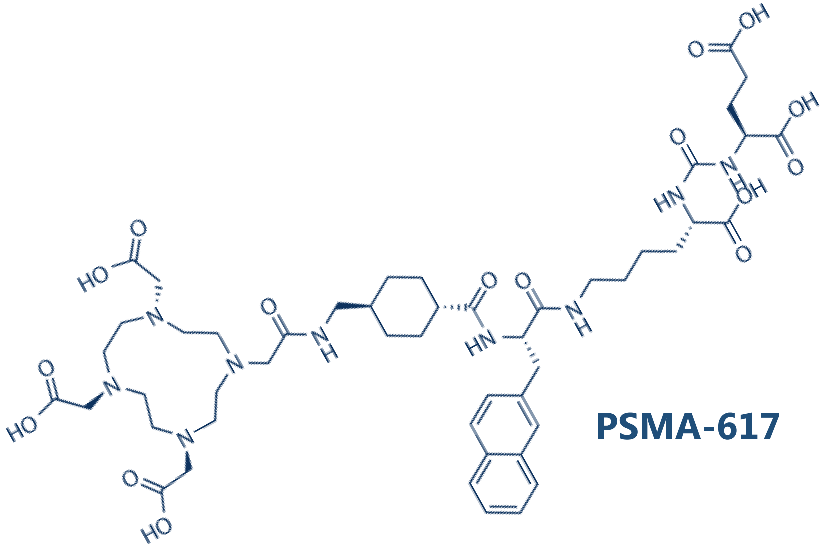
Cyclotron – light particle beams
- $^{152,155}Tb$
- Bulk Gd <u>or</u> Bulk Eu



Why is chemical separation needed?

- Maximising specific activity of radiopharmaceutical
- Maximising binding efficiency of ^{xxx}Tb to targeting molecule
- Minimising toxic side-effects from radioactive or stable impurities

- Minimising imaging interferences (SPECT/PET)



PSMA-617

Aim:
To isolate terbium from bulk or trace lanthanide impurities

57	58	59	60	61	62	63	64	65	66	67	68	69	70	71
La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Lanthanum	Cerium	Praseodymium	Neodymium	Promethium	Samarium	Europium	Gadolinium	Terbium	Dysprosium	Holmium	Erbium	Thulium	Ytterbium	Lutetium
138.905	140.116	140.908	144.243	144.913	150.36	151.964	157.25	158.925	162.500	164.930	167.259	168.934	173.055	174.967

Chemical properties of the lanthanide elements

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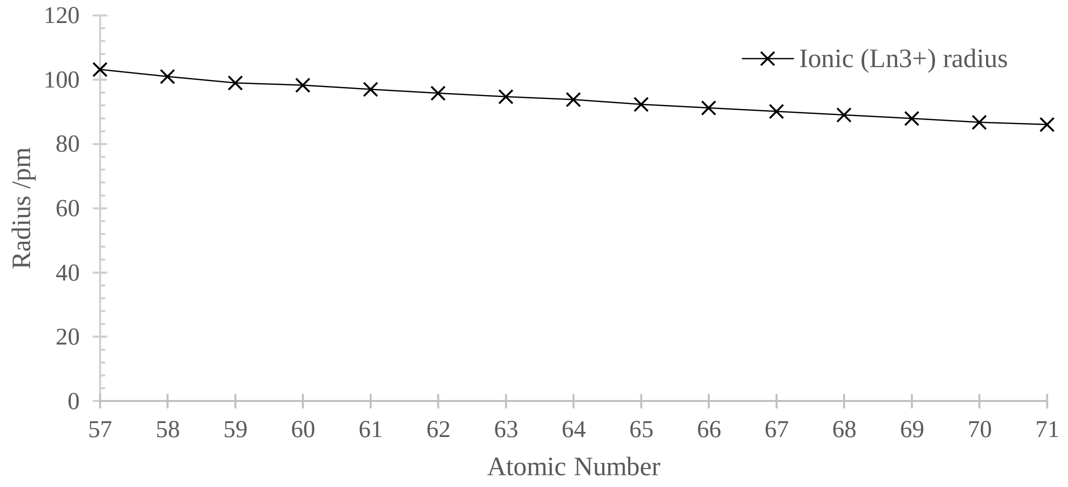
- Stable in III+ oxidation state in aqueous conditions (Ln^{3+})
- Slight variation in ionic radii with increasing atomic number
- Similar coordination numbers

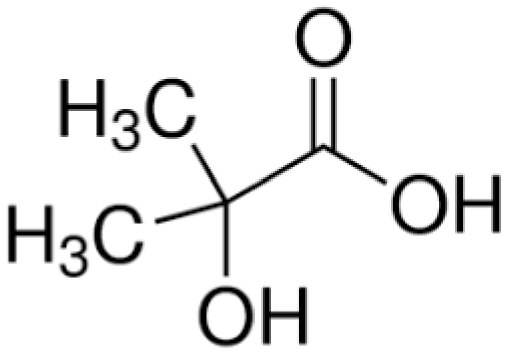
CHALLENGING TO SEPARATE NEIGHBOURING LANTHANIDES



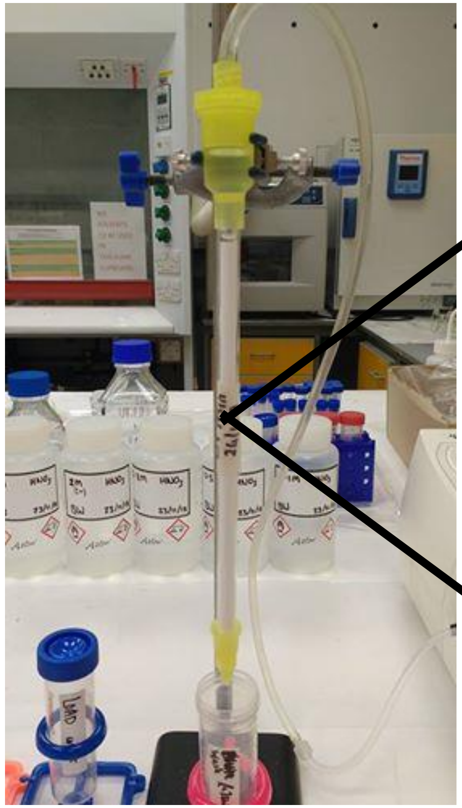
Commonly used lanthanide separation method

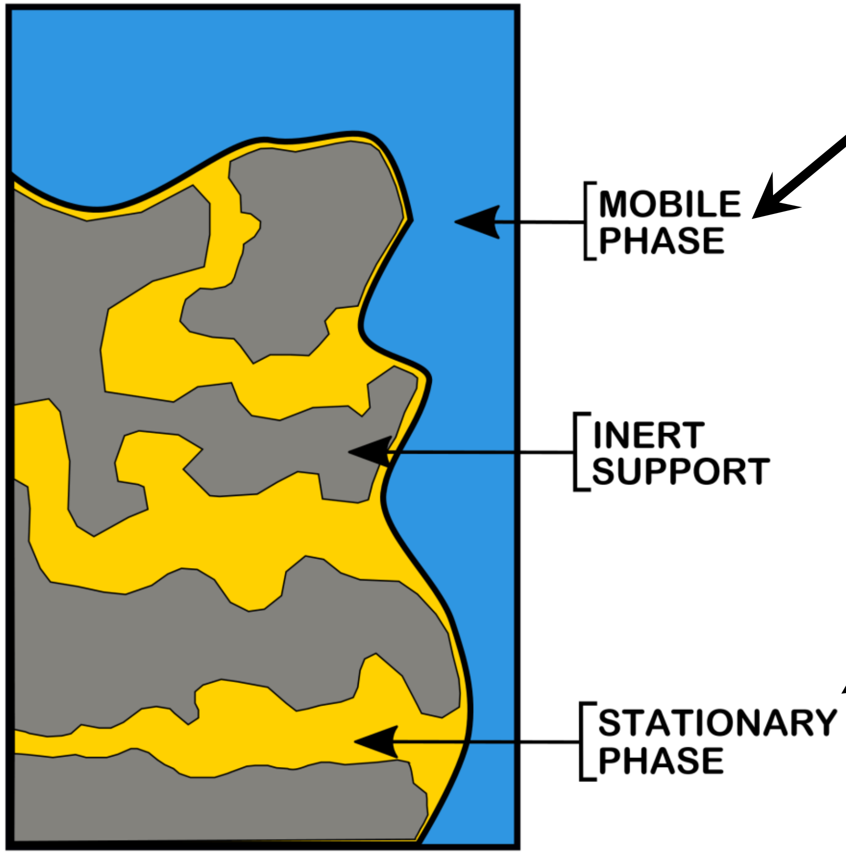
- Alpha-HIBA
- Cation exchange column

- Strict pH and concentration control
- High quality, expensive cation-exchange resins are required
- Requires an radiochemistry expertise



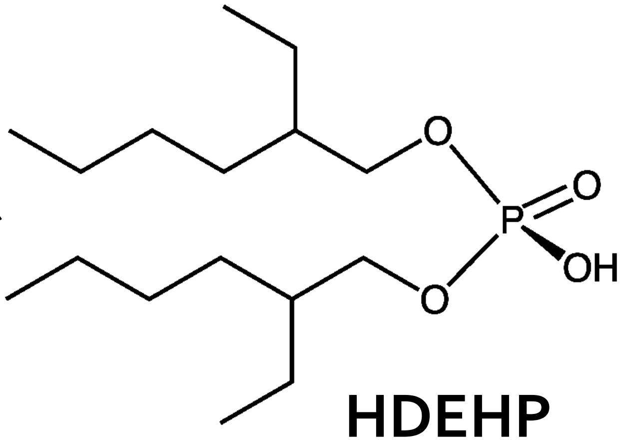
Alternative method – LN resin





EXTRACTION
CHROMATOGRAPHY

Nitric Acid,
HNO_3

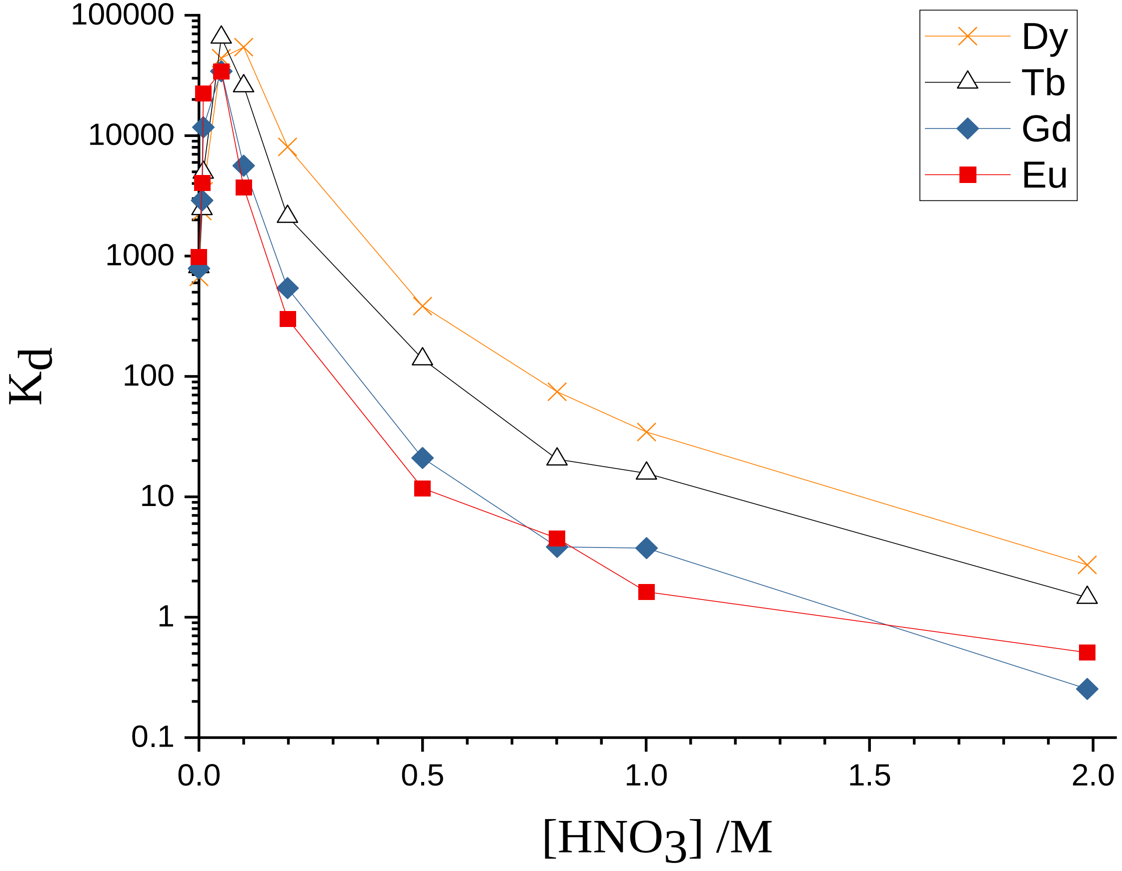


HDEHP

How do the different elements behave with LN resin?

- Batch separation
- K_d calculation

$$k_d = \left(\frac{(CPS)_0 - (CPS)_t}{(CPS)_t}\right) \times \left(\frac{V}{m}\right)$$



The initial 'semi-automated' approach

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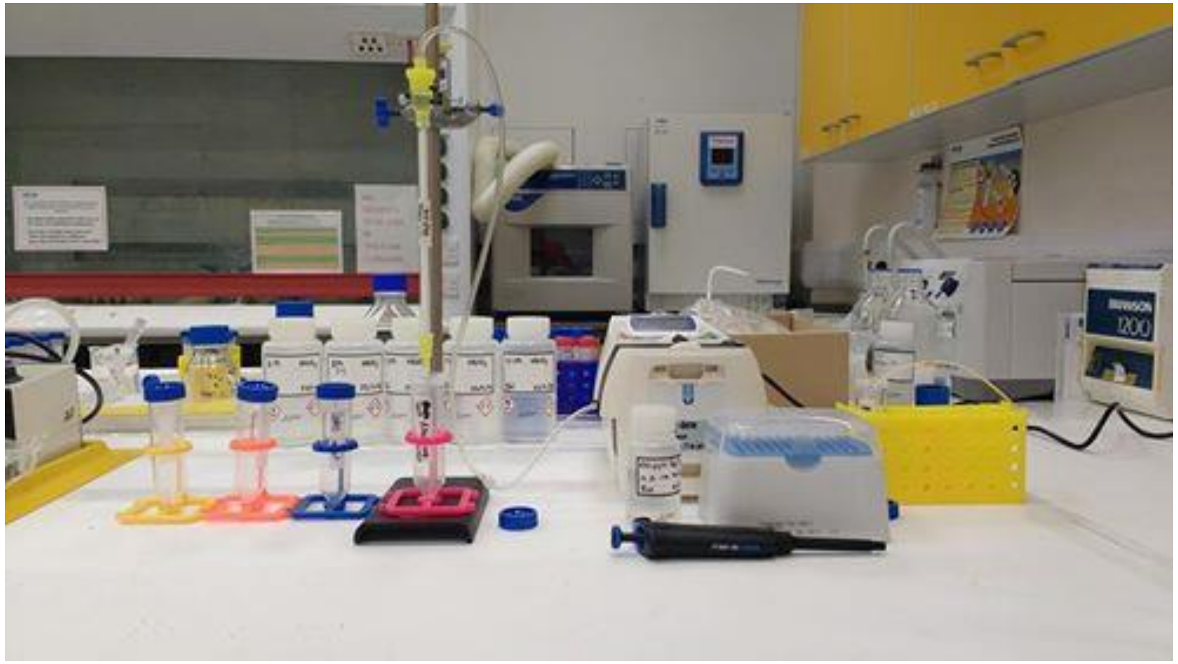
- 200 x 7 mm column (~7.7 mL, glass EconoColumn, BioRad)
- LN resin (50-100 µm)
- 1.0 mL/min flow rate

- Trace Eu/Gd/Tb/Dy
- Step-wise HNO_3 elution
- Collect 1 mL fractions



Column separation variables

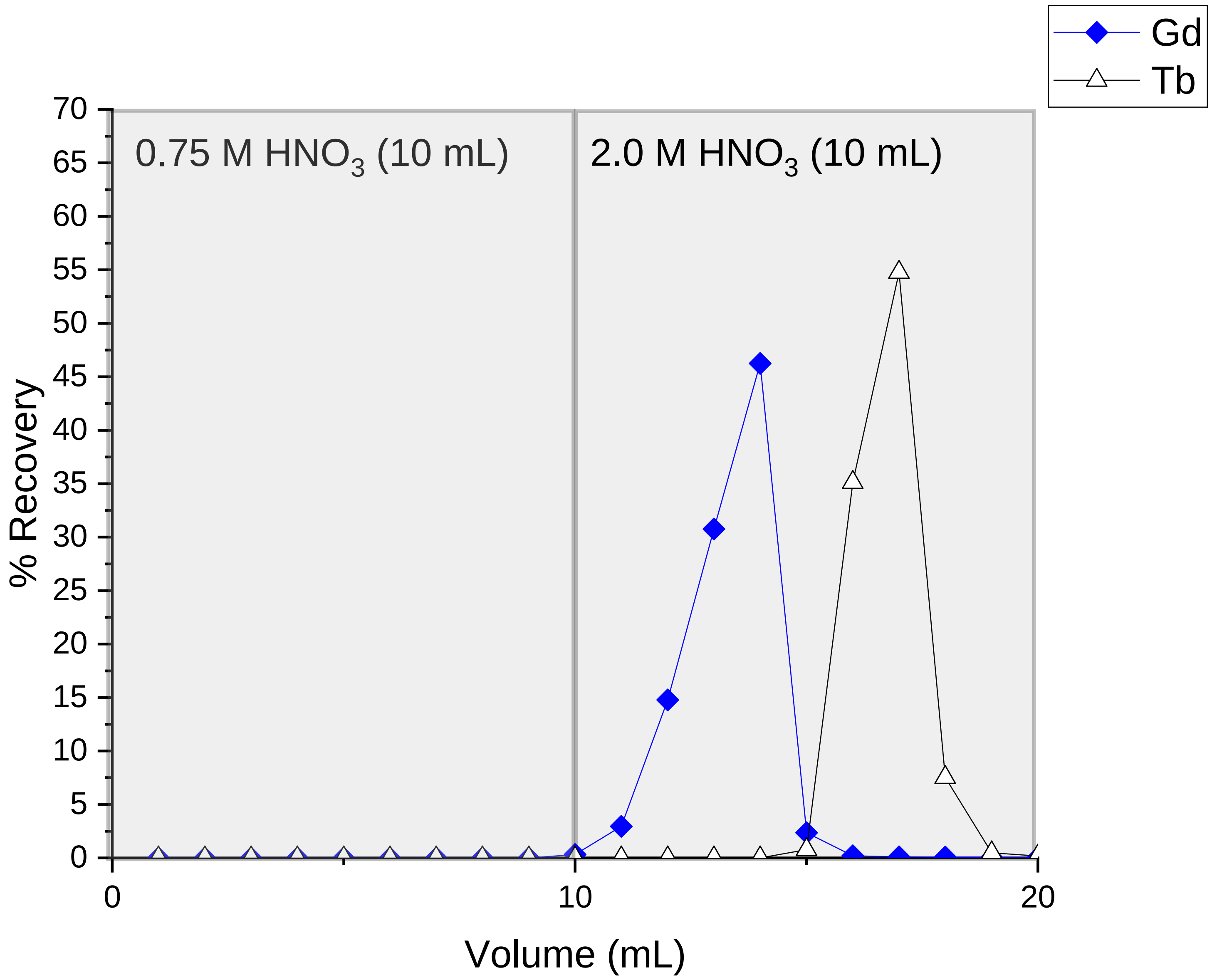
Column volume

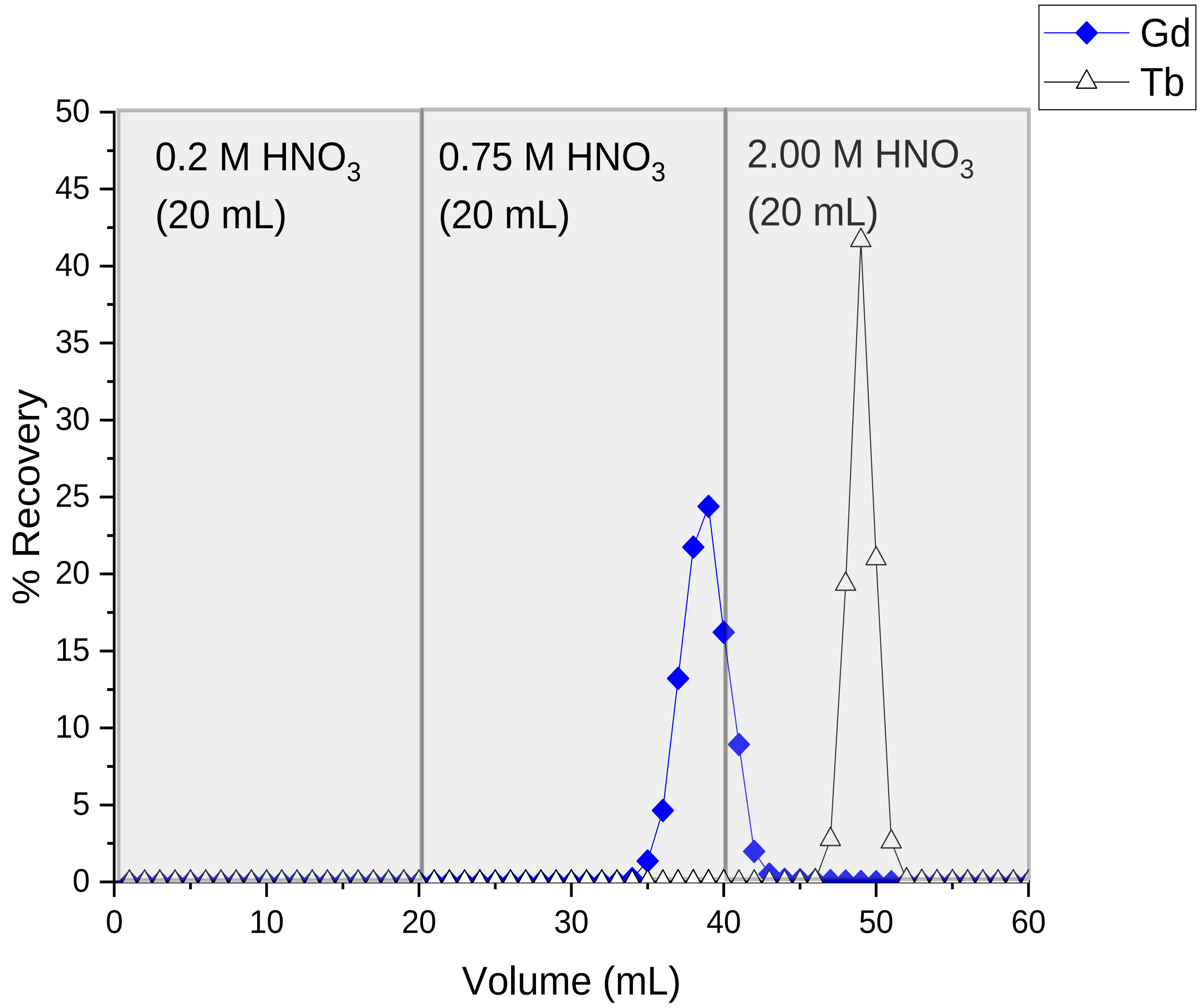
Flow rate

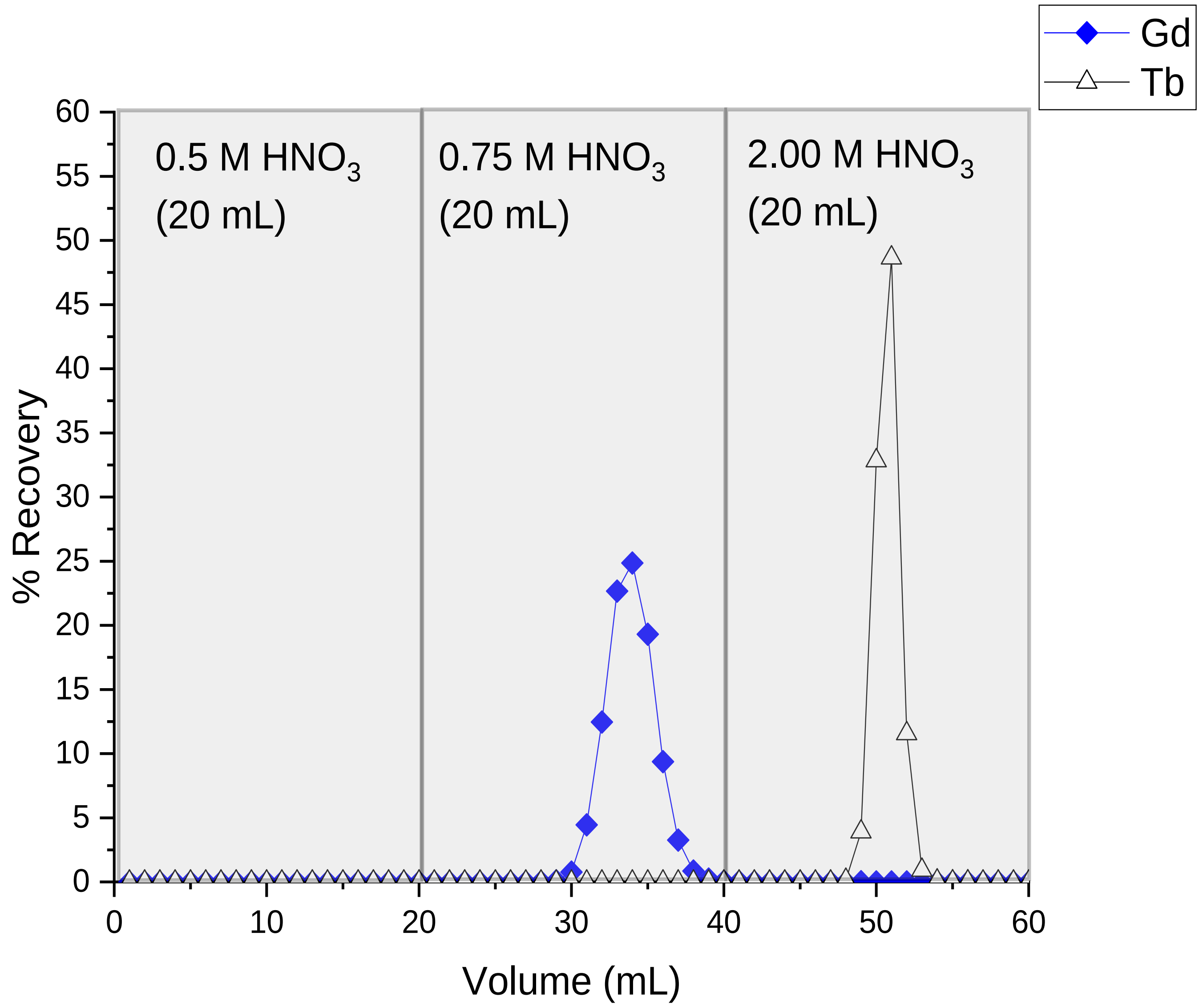
Resin particle size

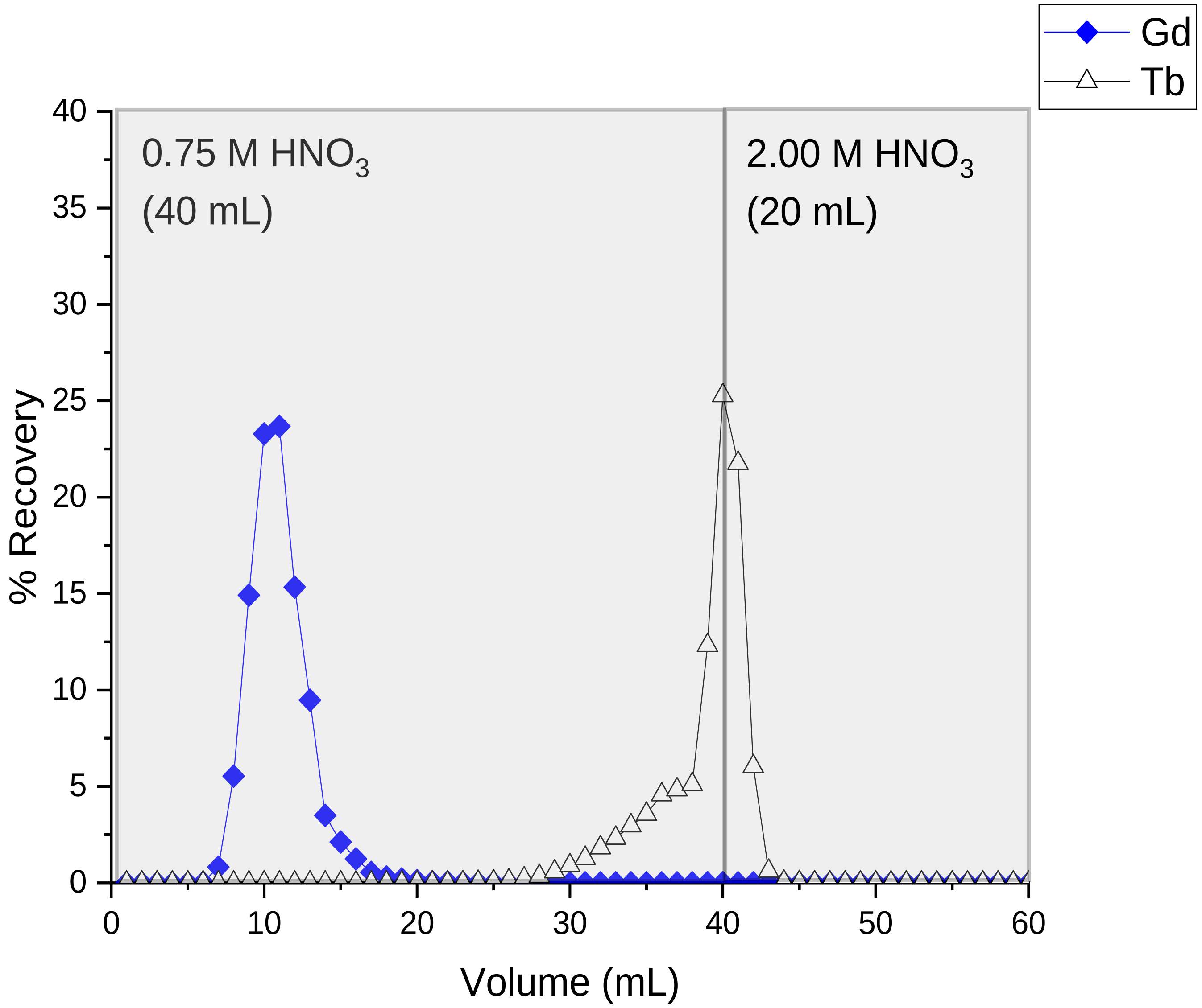
Mobile phase concentration and volume (and pH)

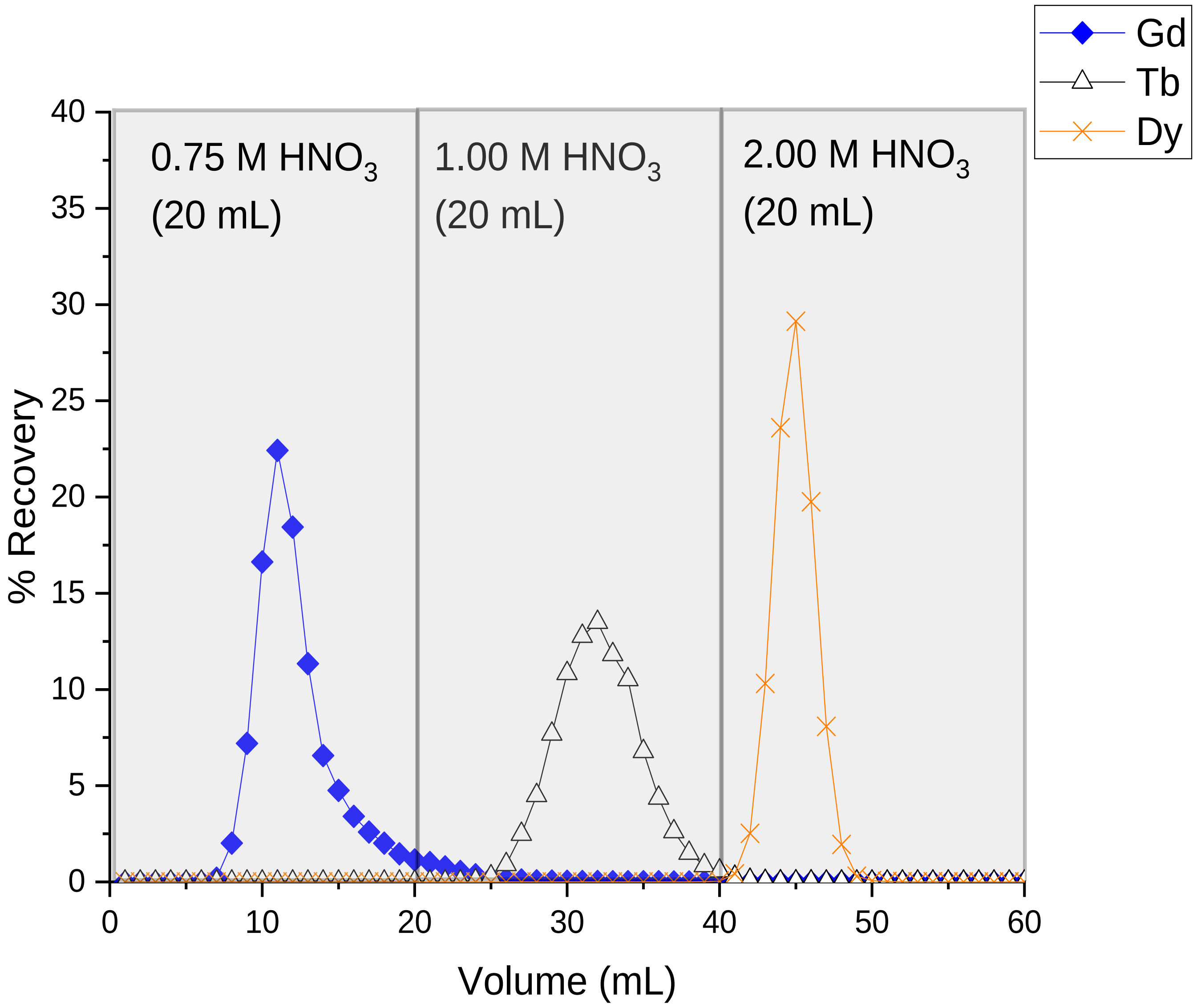
Temperature


Gd
Tb
0.75 M HNO_3 (10 mL)
2.0 M HNO_3 (10 mL)
% Recovery
Volume (mL)
0
10
20
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0

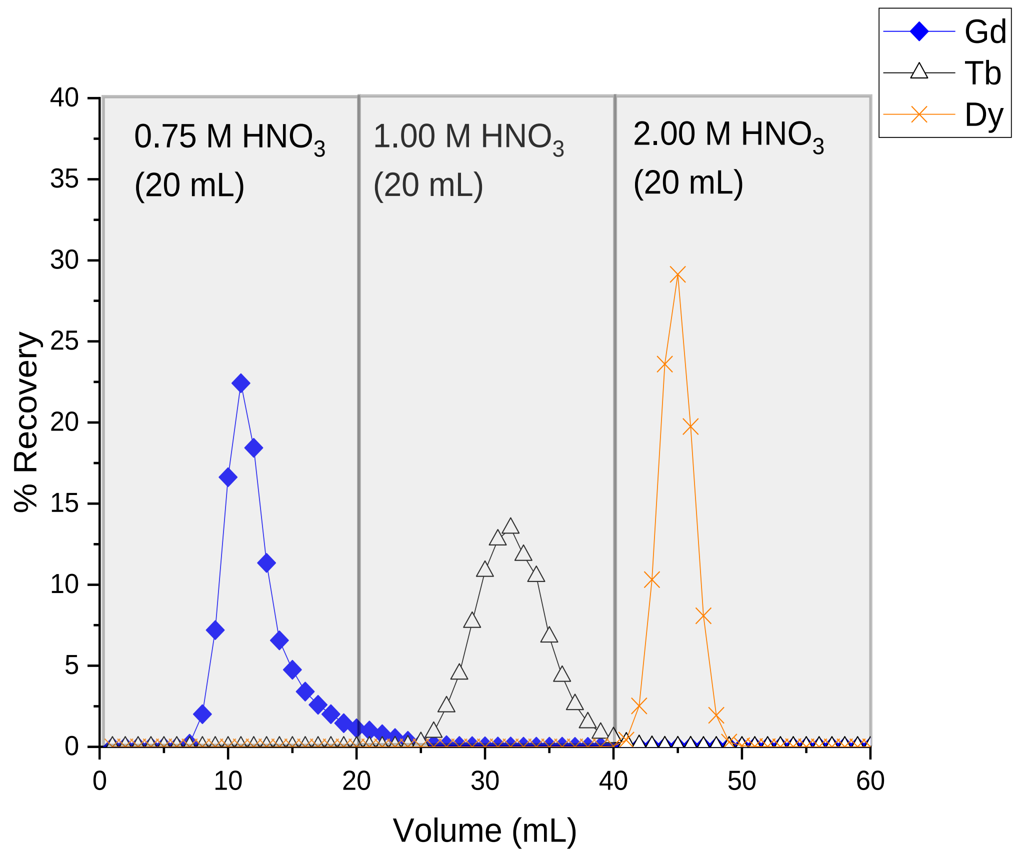

Gd
Tb
0.2 M HNO_3
(20 mL)
0.75 M HNO_3
(20 mL)
2.00 M HNO_3
(20 mL)
% Recovery
Volume (mL)
0
5
10
15
20
25
30
35
40
45
50
0
10
20
30
40
50
60


Gd
Tb
0.5 M HNO_3
(20 mL)
0.75 M HNO_3
(20 mL)
2.00 M HNO_3
(20 mL)
% Recovery
Volume (mL)
0
5
10
15
20
25
30
35
40
45
50
55
60
0
10
20
30
40
50
60

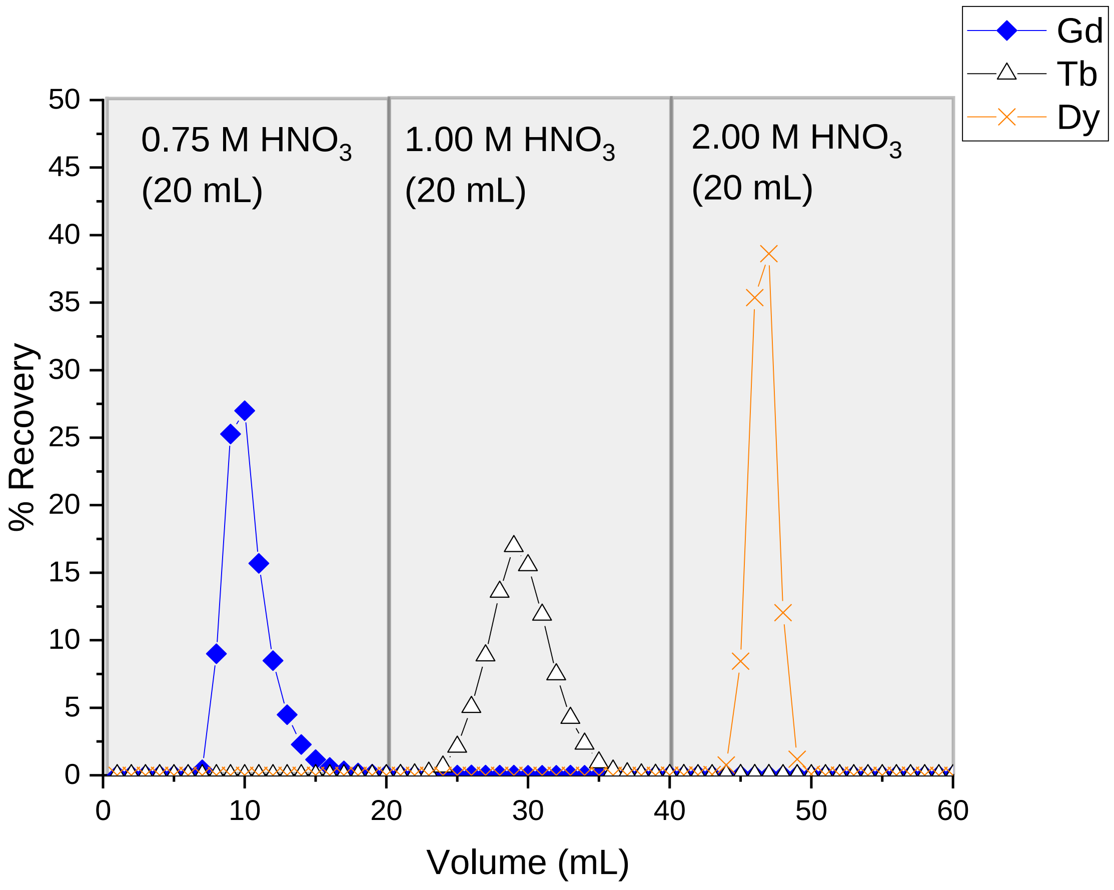

Gd
Tb
0.75 M HNO_3
(40 mL)
2.00 M HNO_3
(20 mL)
% Recovery
0
5
10
15
20
25
30
35
40
0
10
20
30
40
50
60
Volume (mL)



0.75 M HNO3
(20 mL)
1.00 M HNO3
(20 mL)
2.00 M HNO3
(20 mL)
Gd
Tb
Dy
% Recovery
Volume (mL)
0
5
10
15
20
25
30
35
40
0
10
20
30
40
50
60



1.0 mL/min



0.5 mL/min

Column separation variables

Column volume

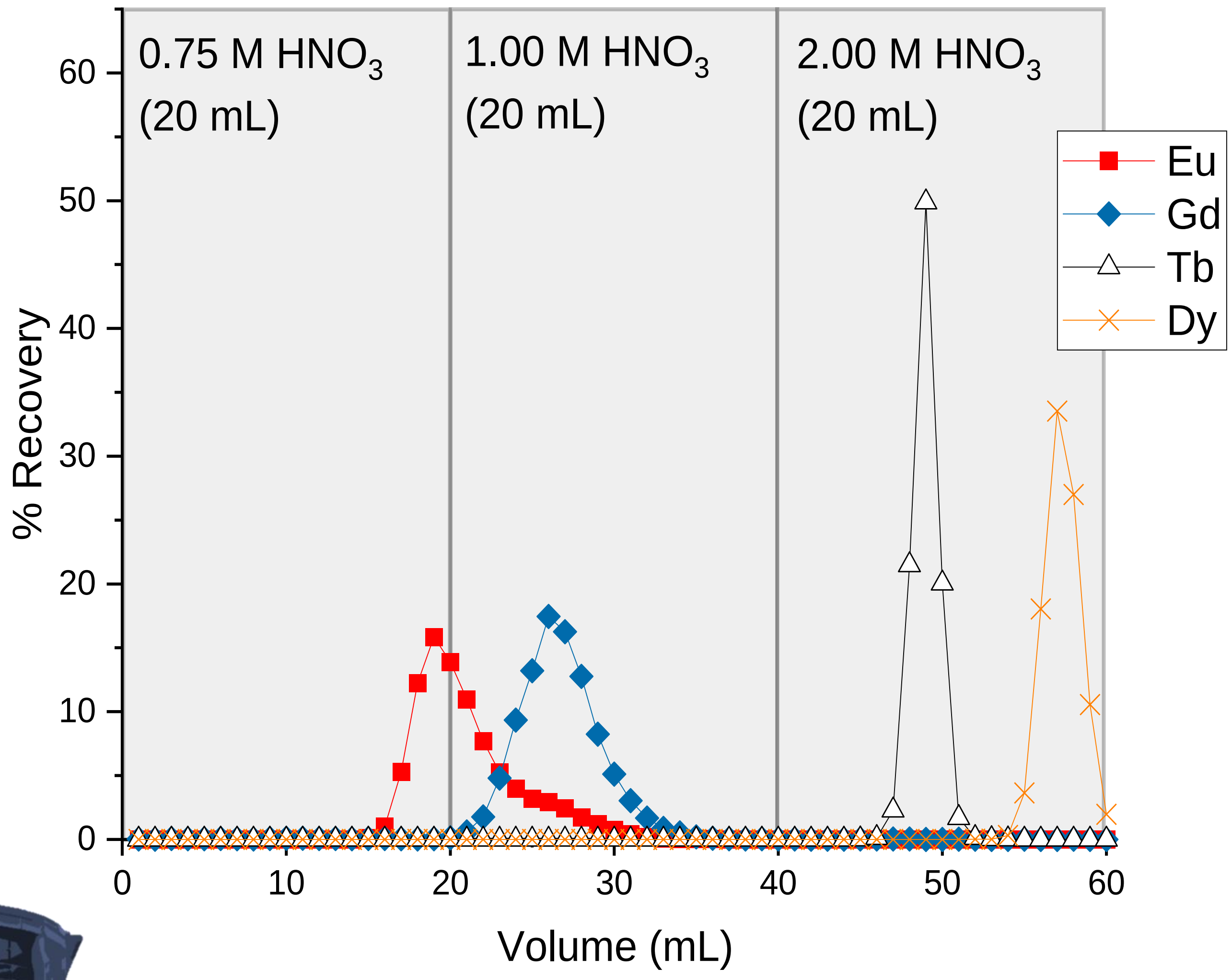
Flow rate

Resin particle size

Mobile phase concentration and volume (and pH)

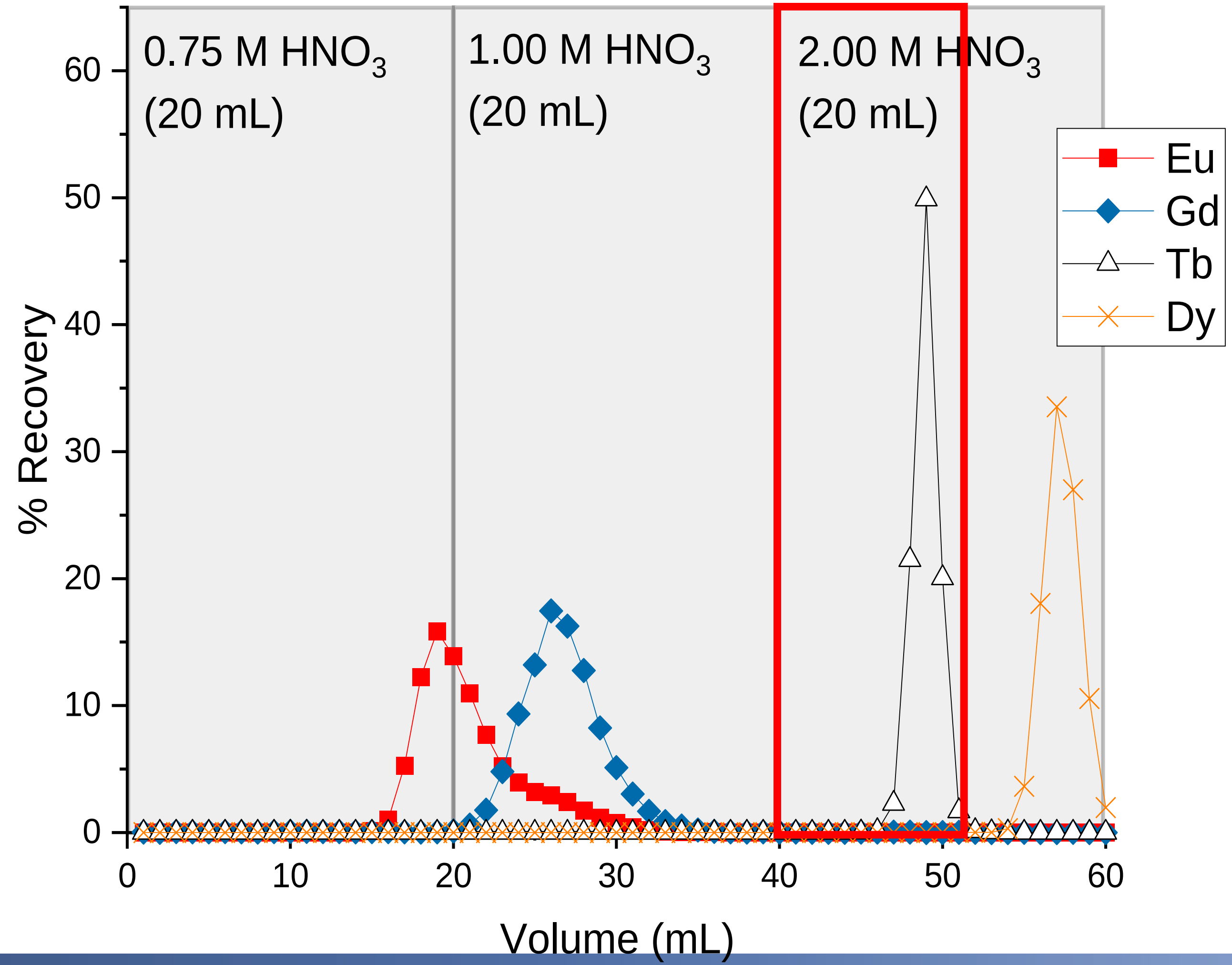
Temperature

...new batch of resin (?!?!)



Any suggestions to why we see this shift in elution?

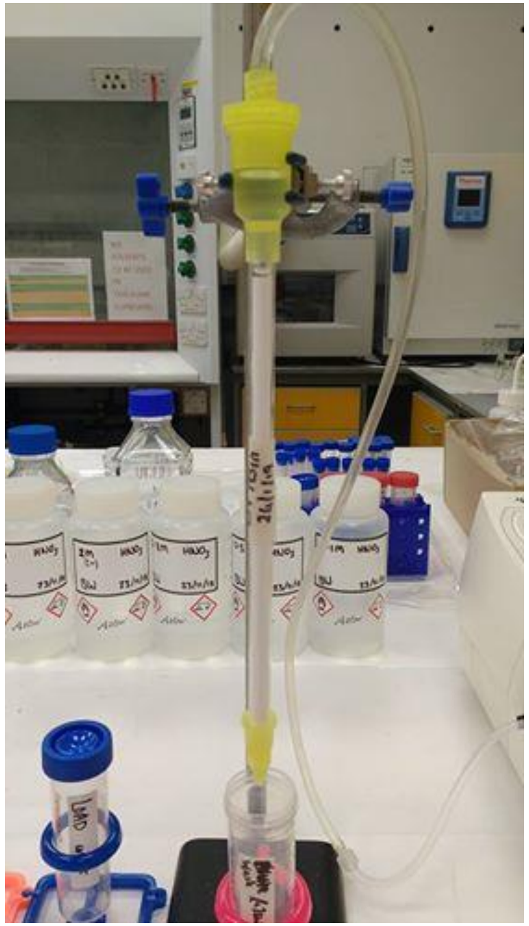
Fit-for-purpose... so we continue

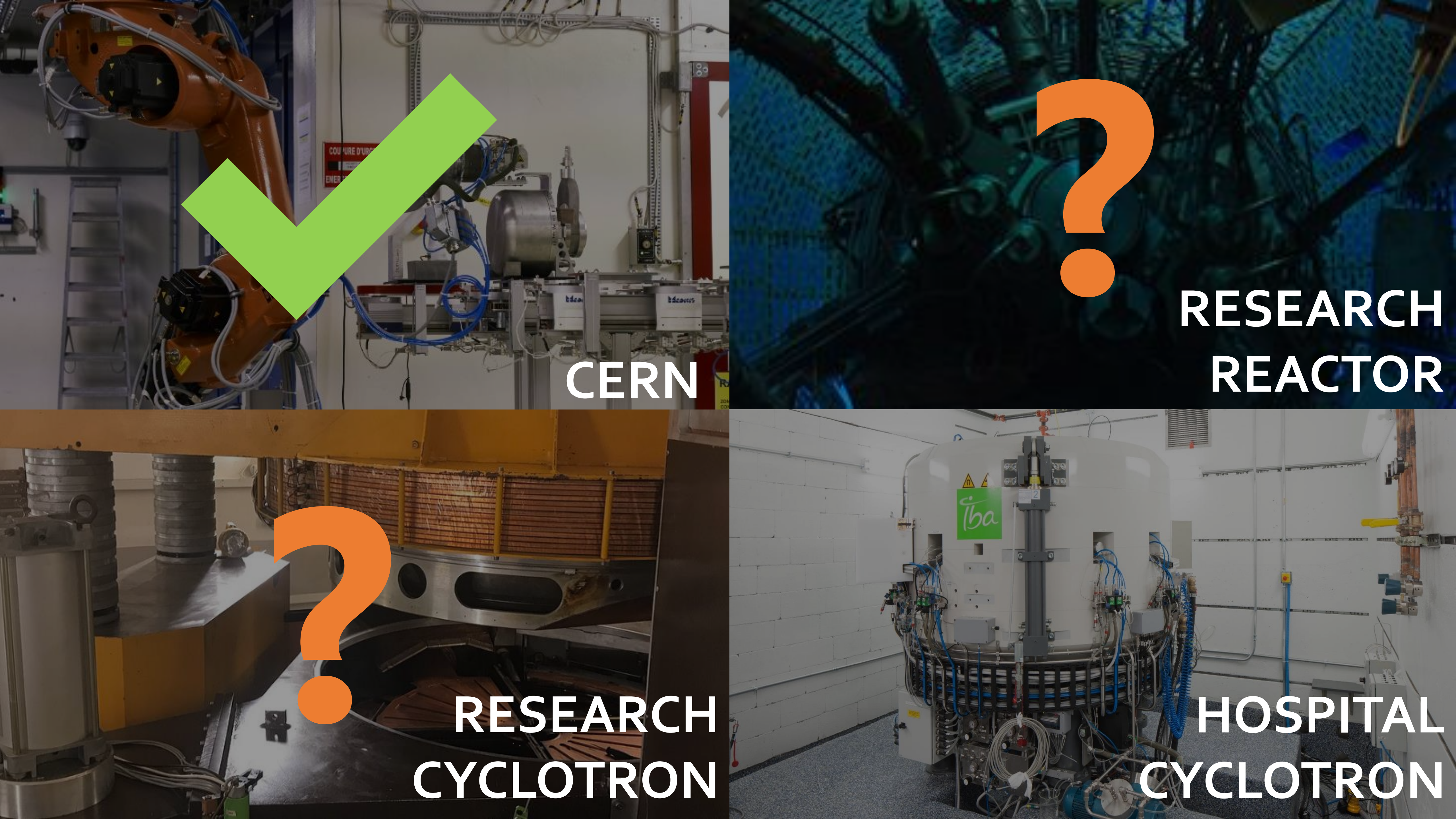


Developed method

- 3 step elution
  - Elute 1 – 0.75 M HNO_3, 20 mL
  - Elute 2 – 1.00 M HNO_3, 20 mL
  - Elute 3 – 2.00 M HNO_3, 20 mL
- Glass EconoColumn - 200×7 mm (~7.7 mL)
- LN resin (50-100 µm)
- 0.5 mL/min flow rate

<u>Able to isolate Tb from trace lanthanides</u>

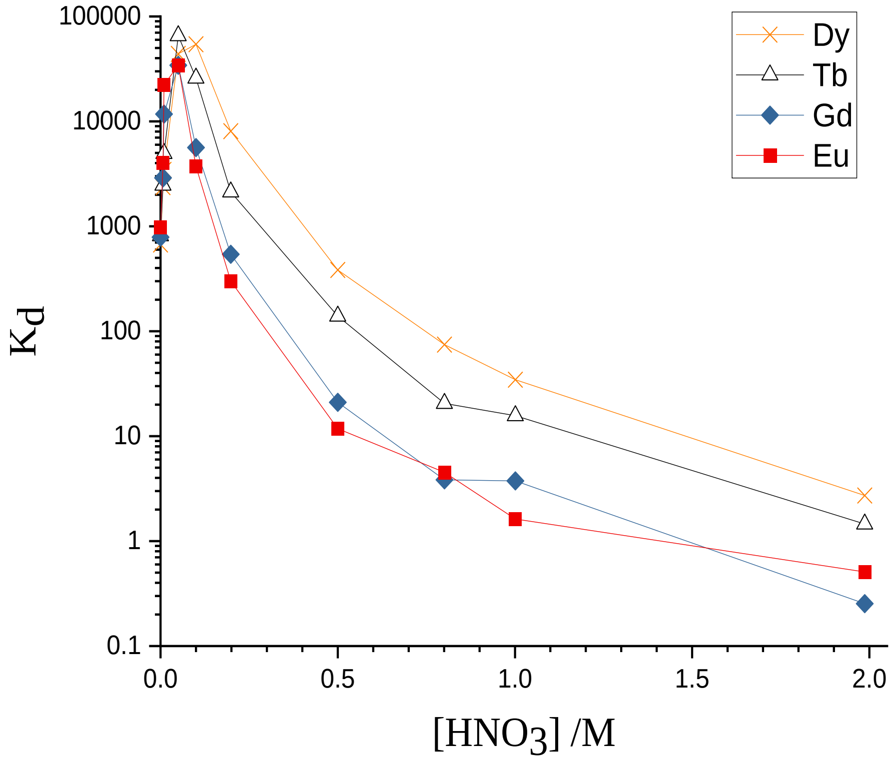



CERN
RESEARCH REACTOR
RESEARCH CYCLOTRON
HOSPITAL CYCLOTRON

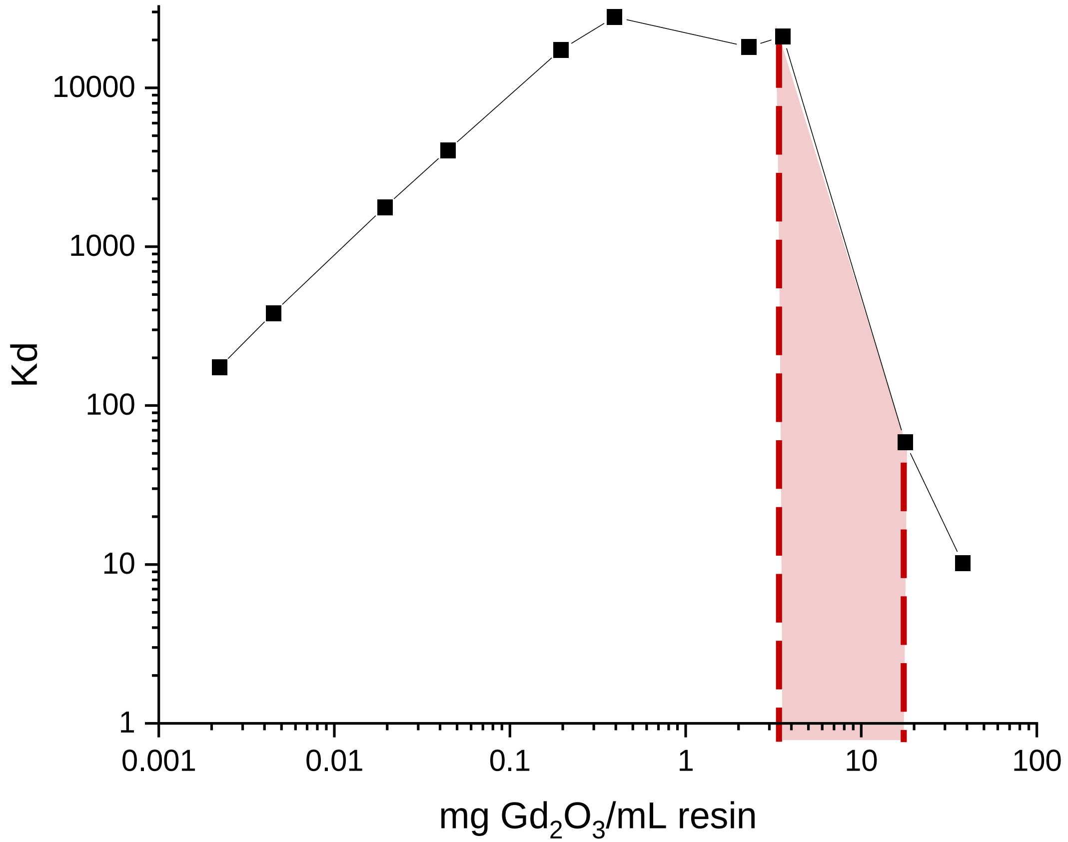
Bulk Gd, trace Tb separation

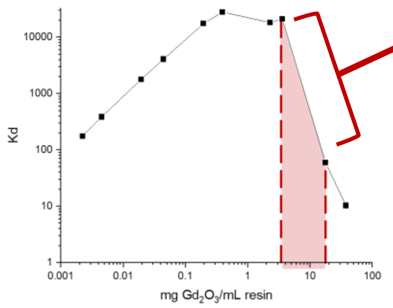
What is the capacity of the 200×7 mm LN resin column?

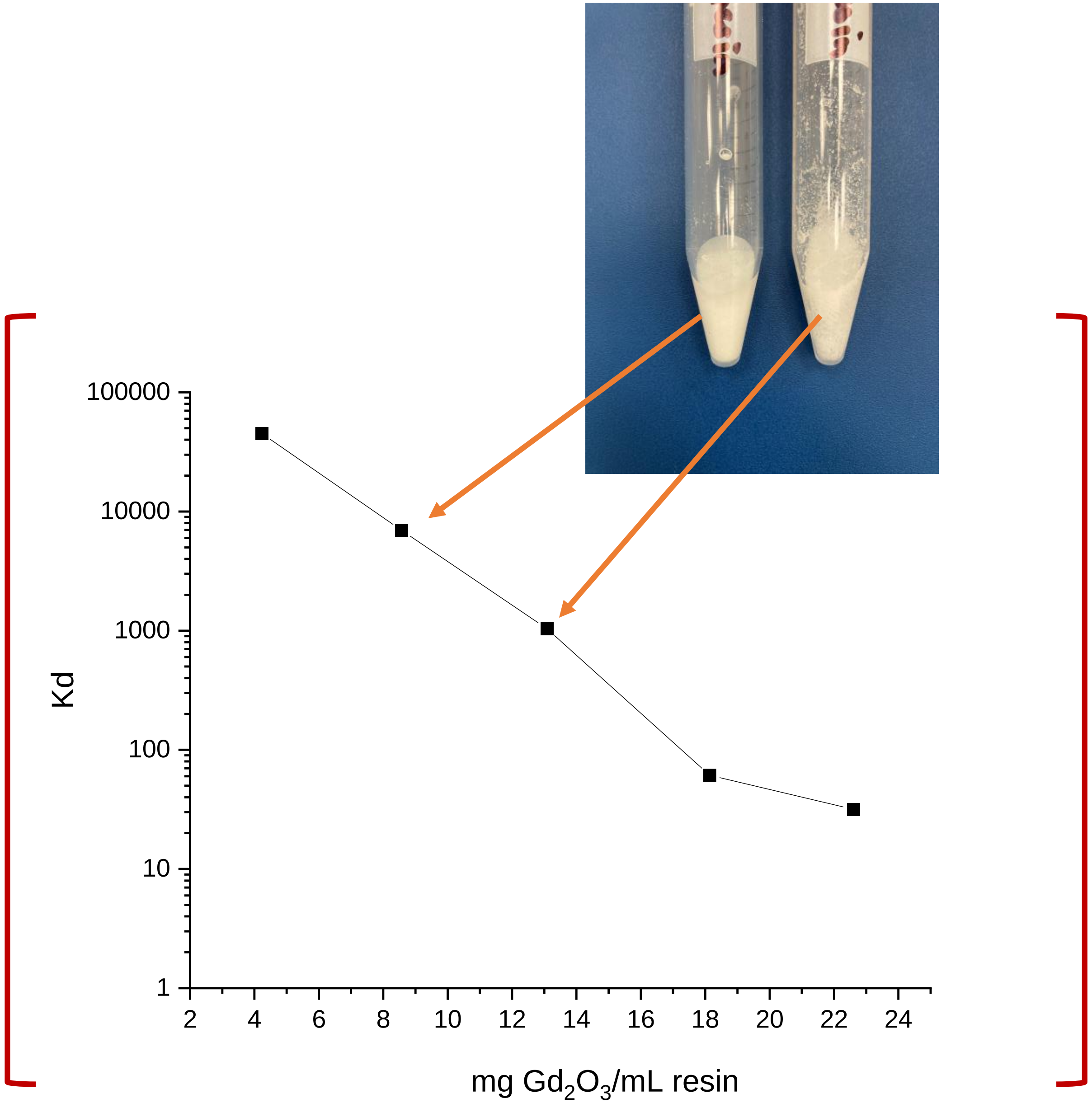
- Batch separation (K_d)
  - ~1 ug - ~50 mg Gd_2O_3/mL resin
  - from 0.1 M HNO_3



Column capacity




10000
1000
100
10
1
Kd
0.001
0.01
0.1
1
10
100
mg Gd_2O_3/mL resin

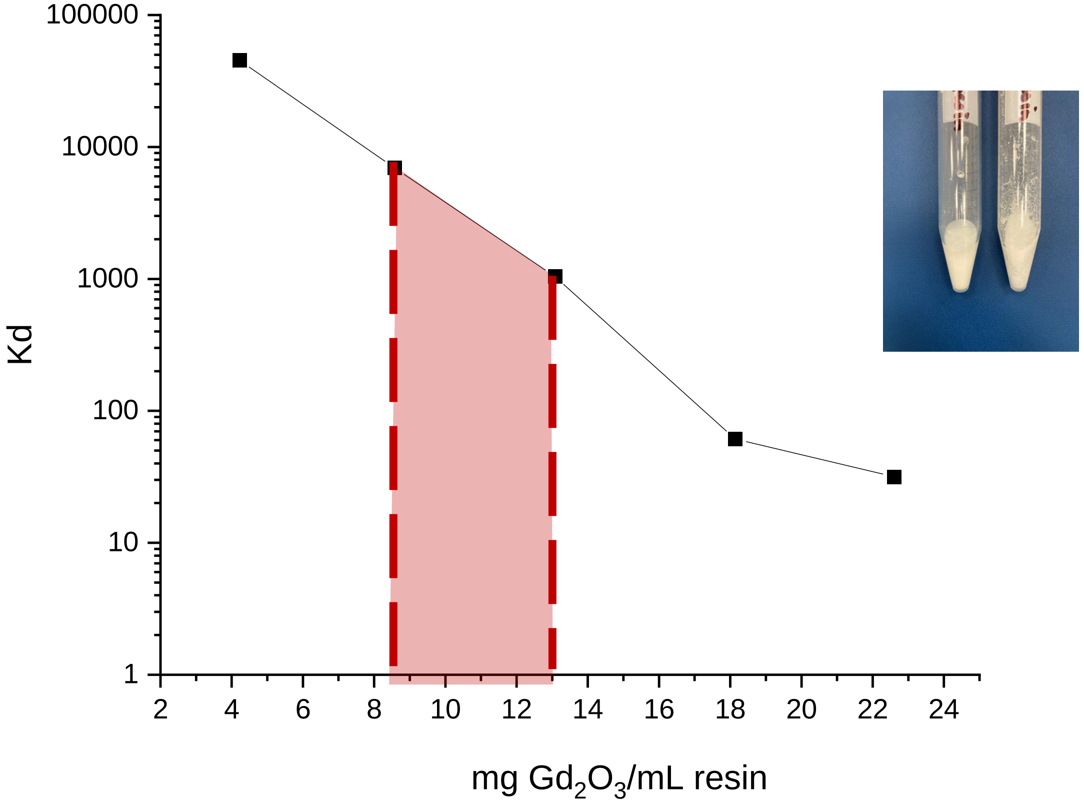

100000
10000
1000
100
10
1
Kd
2
4
6
8
10
12
14
16
18
20
22
24
mg Gd_2O_3/mL resin

Bulk Gd, trace Tb separation

Working capacity of the 200×7 mm column (~7.7 mL)

- 61.2 – 110.8 mg Gd_2O_3

Gd is still strongly held on the resin in this range



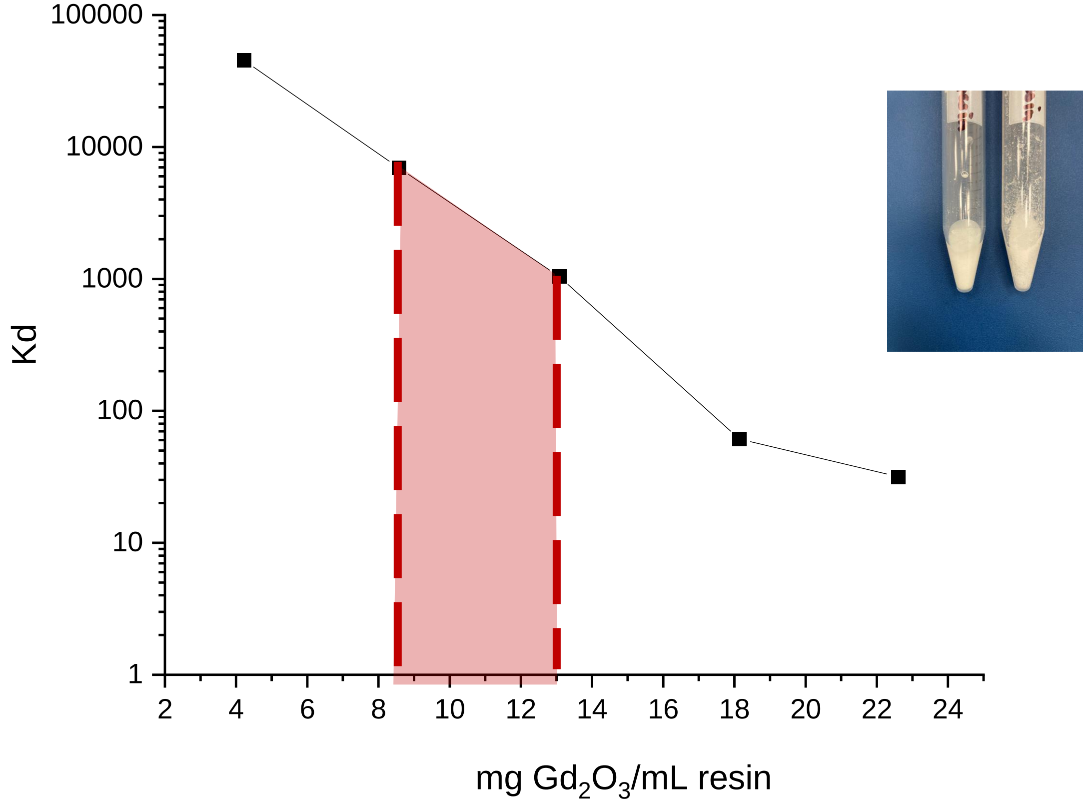
Bulk Gd, trace Tb separation

Working capacity of the 200×7 mm column (~7.7 mL)

- 61.2 – 110.8 mg Gd_2O_3

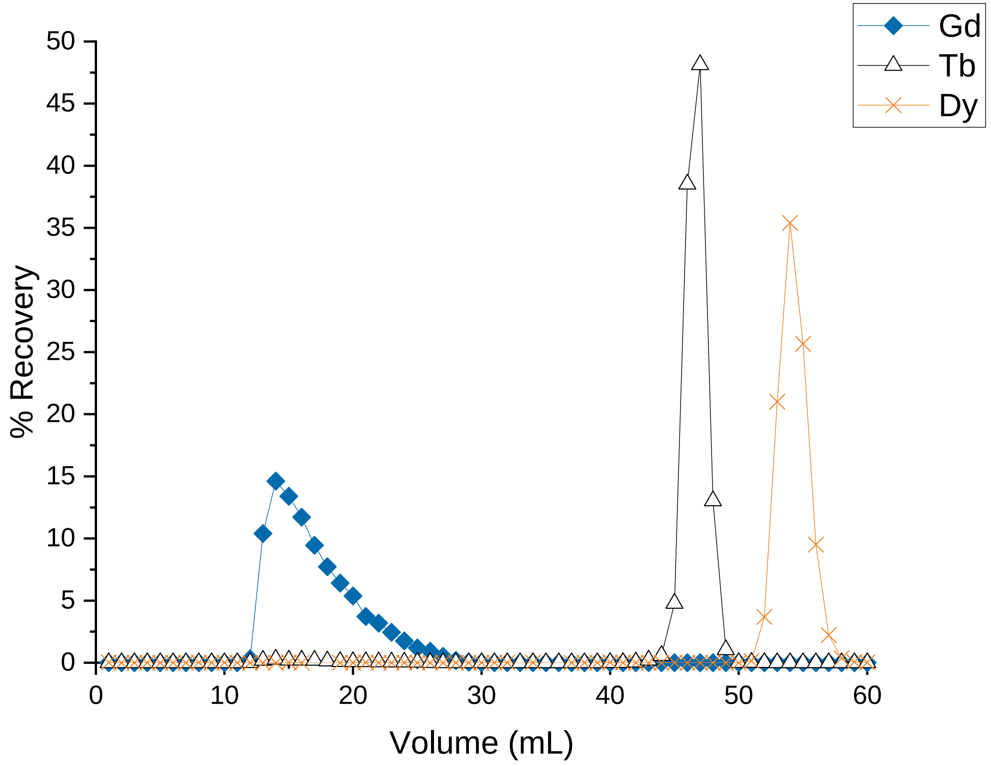
10 - 100 mg Gd_2O_3

targets for ^{155}Tb and ^{161}Tb production



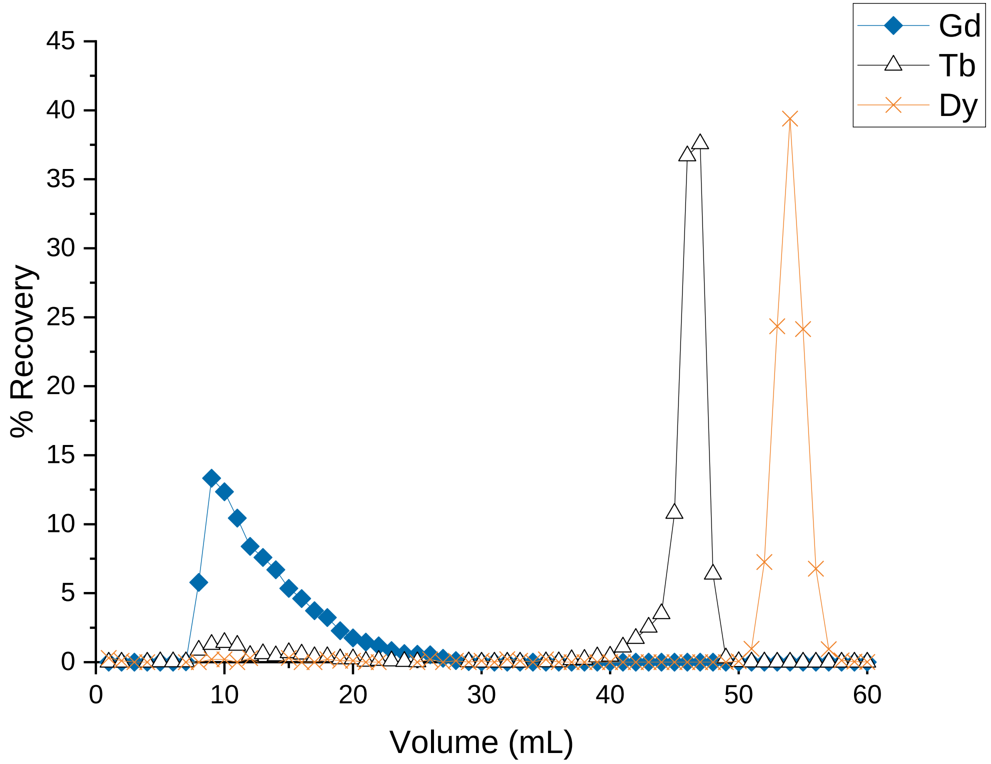
Bulk Gd, trace Tb separation

- 10 mg Gd_2O_3, 1 µg Tb, Dy – ~10,000x excess



Bulk Gd, trace Tb separation

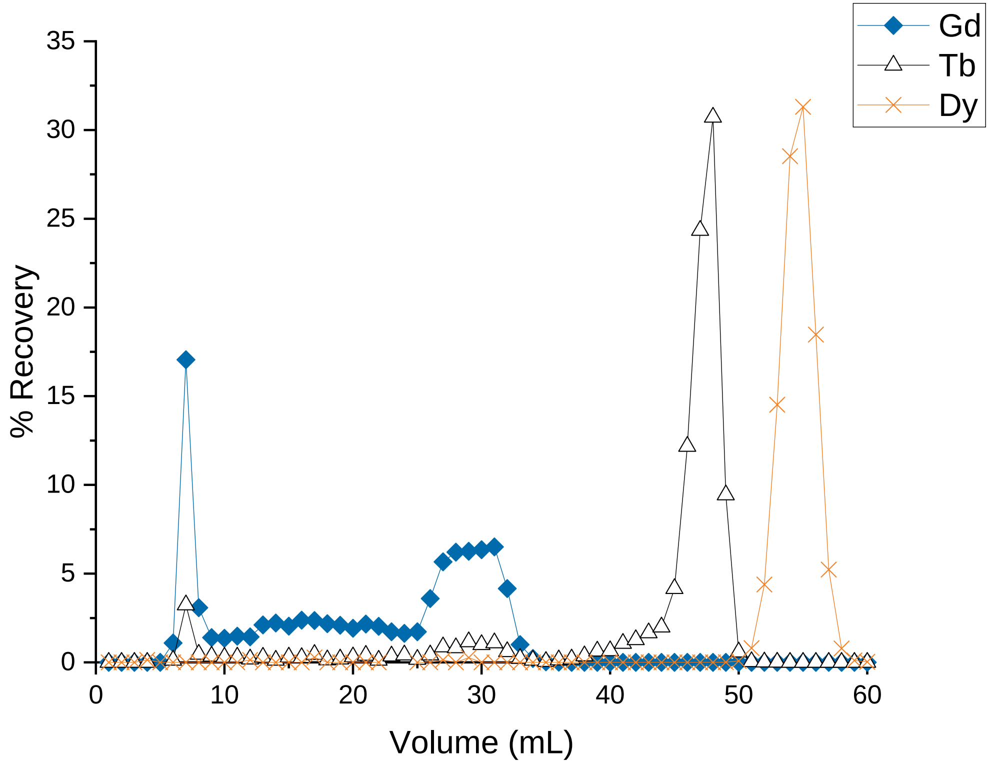
- 50 mg Gd_2O_3, 1 µg Tb, Dy – ~50,000x excess



Bulk Gd, trace Tb separation

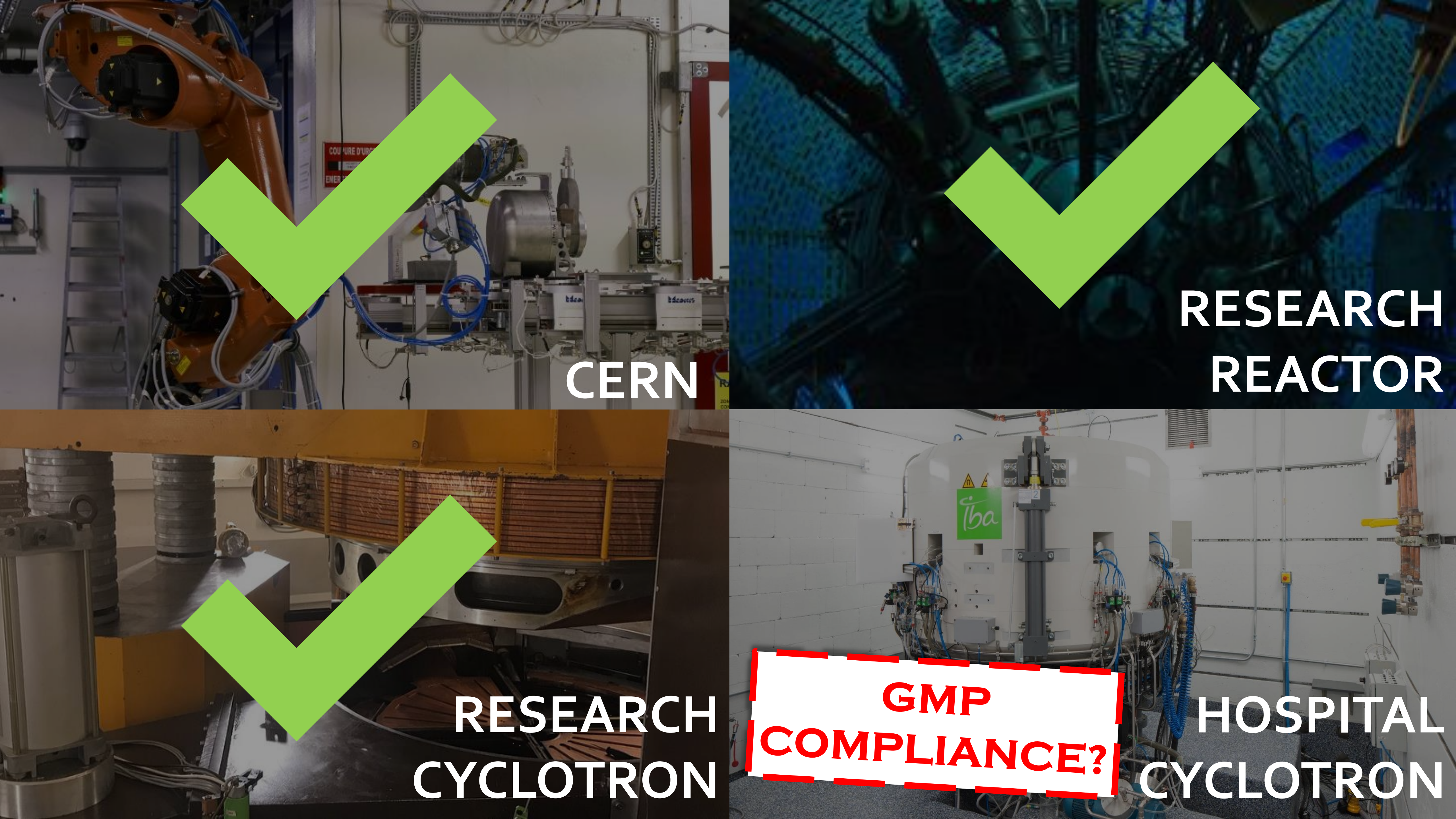
- 100 mg Gd_2O_3, 1 µg Tb, Dy - ~100,000x excess

We must be getting close to the working capacity of our column



* (n=3)

	10 mg Gd_2O_3* (10000x Gd excess)	50 mg Gd_2O_3 (50000x Gd excess)	100 mg Gd_2O_3 (100000x Gd excess)
Tb recovery	98.34 %	90.54 %	83.86 %
Gd removal	99.991 %	99.983 %	99.981%
Decontamination Factor	1.18×10^4	1.20×10^4	5.16×10^3
Tb purity	53.59 %	9.82 %	4.15 %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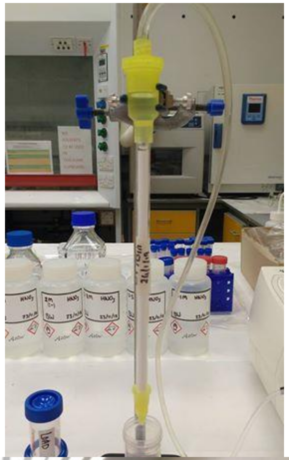
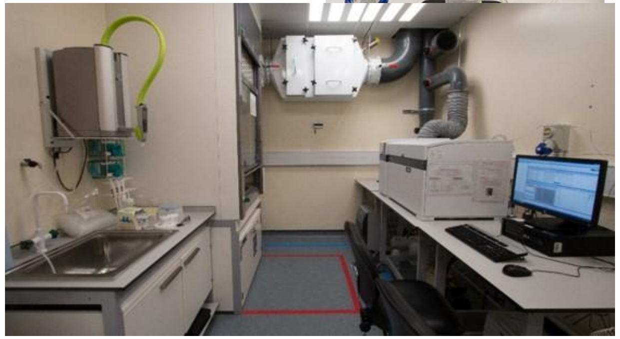
RESEARCH
CYCLOTRON
GMP
COMPLIANCE?
HOSPITAL
CYCLOTRON

Potential future work

- Test finer particle size LN resin (TK211C)
- Upscale the method to accommodate larger Gd targets
- Validate method on an irradiated target
- Fully automate the method (using a prep-HPLC method?)





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ANY QUESTIONS?

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