eichrom® TECHNOLOGIES
A GCI COMPANY

npo
eichrom

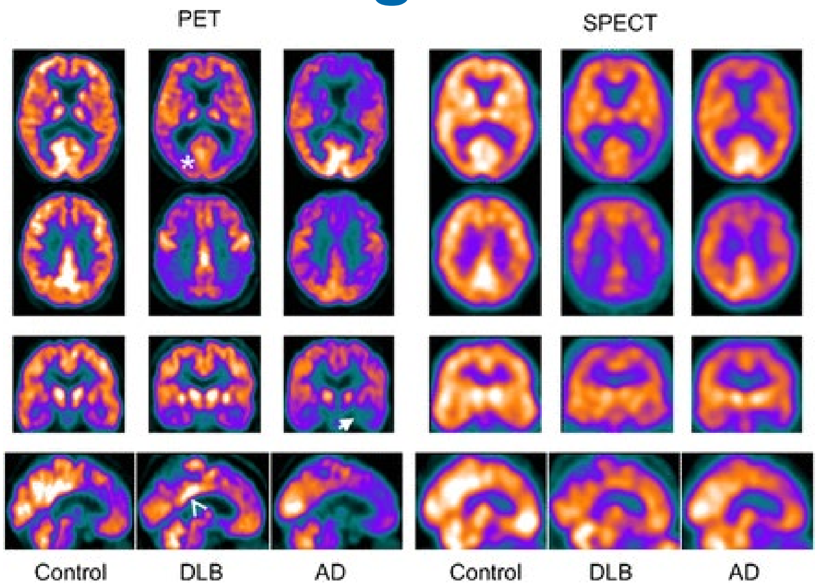
Recovery of nuclear medicine radionuclides in acetate buffer solution

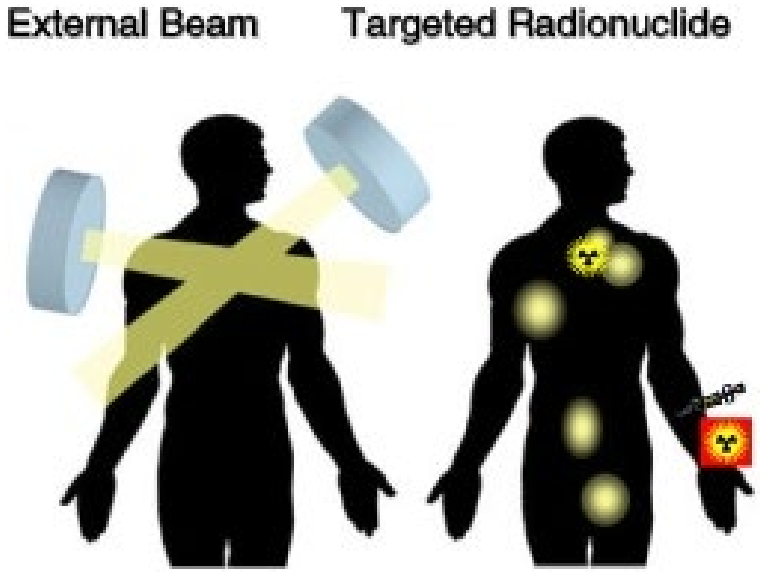
Madeleine Eddy
RRMC 2024
Purdue University
21 October 2024

Nuclear medicine

"The use of radioactive tracers to diagnose and treat disease"

- Diag*nostics* and Imaging
  - Single Photon Emission Computed Tomography (SPECT)
  - Positron Emission Tomography (PET)
- *Therapy*
  - External beam therapy
  - Targeted radionuclide therapy
- *Theranostics*
  - Matched pair isotopes to treat and image using the same targeting vectors

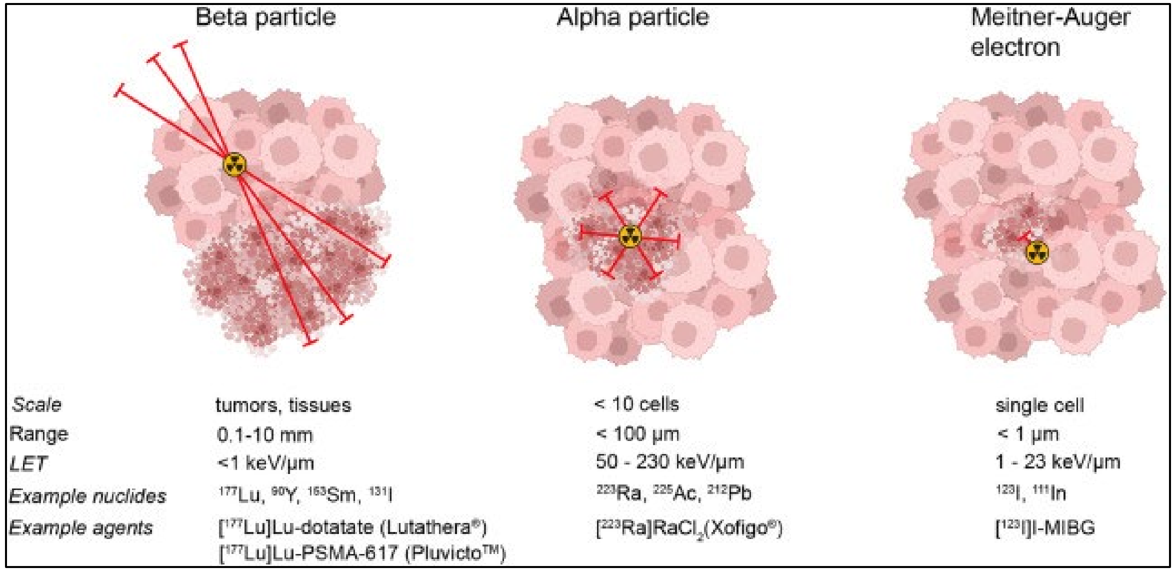


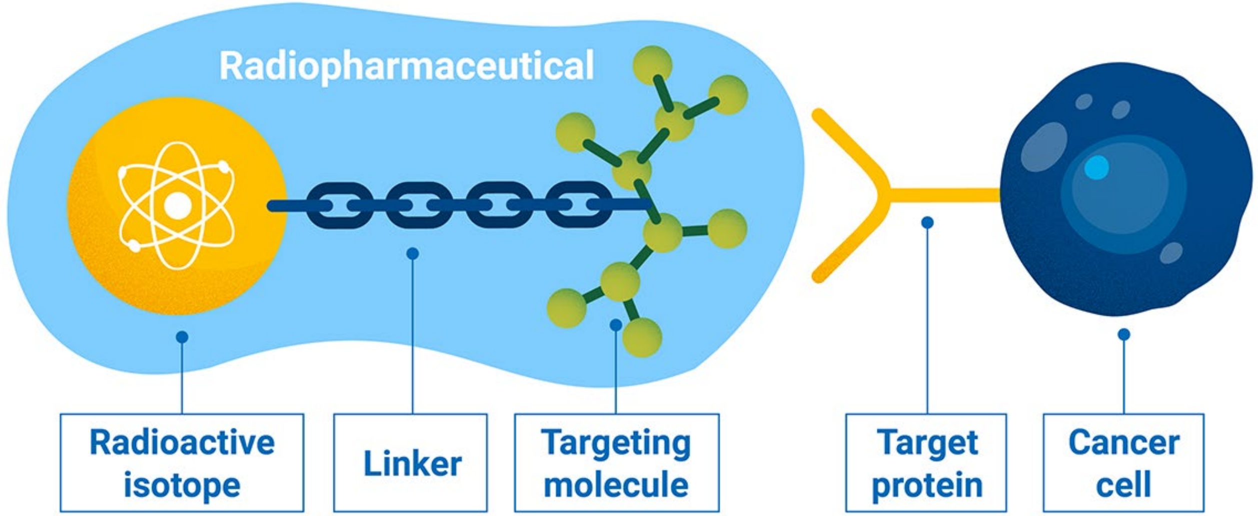


National Research Council (US) and Institute of Medicine (US) Committee on State of the Science of Nuclear Medicine. Advancing Nuclear Medicine Through Innovation. Washington (DC): National Academies Press (US); 2007. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11474/ DOI: 10.17226/11985
O'Brien, J.T. et al. J Muc Med 55(**12),** 1959-1965, (2014). DOI: 10.2967/jnumed.114.143347

Theranostics – the future

- A "best of both worlds" approach
  - Power of radiation therapy
  - Targeting of chemotherapy
- Requires multiple isotopes of the same or similar elements
  - Diagnostics via positron or gamma
  - Therapy via alpha, beta, or auger





Patient with extensive metastasis before and after therapy with ^{225}Ac-PSMA-617 showing complete imaging response.

Salerno, K.E. et al. *Int J Radiat Oncol Biol Phys* 15(**1**), 48-59, (2013).
https://medicalxpress.com/news/2016-12-alpha-therapy-results-metastatic-prostate.html
https://www.iaea.org/newscenter/news/what-are-radiopharmaceuticals

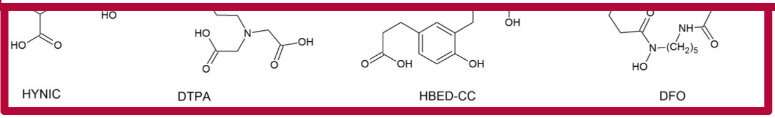
Theranostics – target to patient

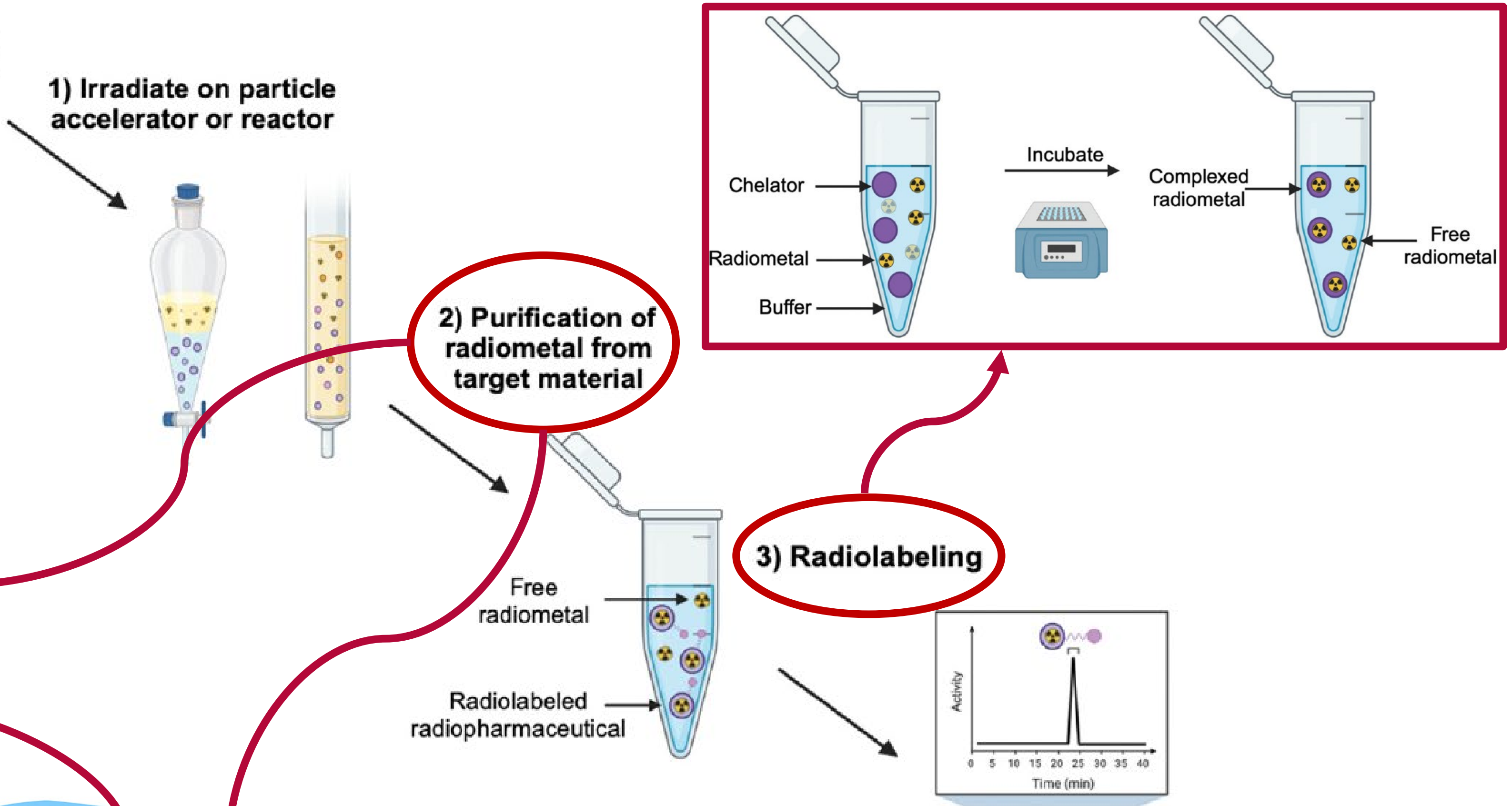
eichrom®

Radiolabeling Reactions:

- Binding of radioactive isotope

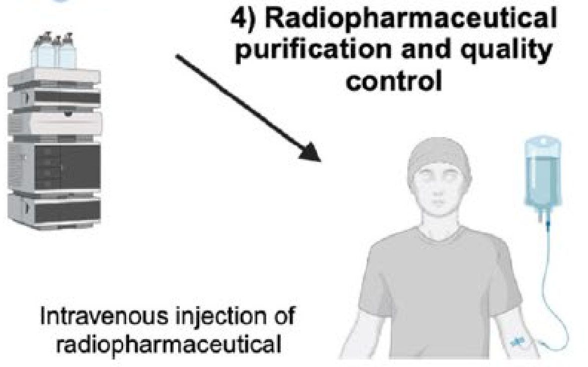
AN-1613	68Ga Generator	Download
AN-1614	Ac-225 Generator	Download
AN-1615	90Y Generator	Download
AN-1616a	210Po/210Bi Generator	Download
AN-1616b	210Po Generator	Download
AN-1617	227Th/223Ra Generator	Download
AN-1618	228Th/231Th Generator	Download
AN-1619	239Np Generator	Download
AN-1620	224Ra/212Pb Generator	Download
AN-1621	234Th Generator	Download
AN-1622	Separation of 89Zr from Y Target	Download
AN-1623	Separation of 86Y From Sr Target	Download





For more than 25 years, Eichrom scientists and partners have developed chromatographic separations for a wide range of nuclear medicine radionuclides. Click the links below for more information on key radionuclides.

- Actinium-225
- Bismuth-213
- Fluorine-18
- Gallium-68
- Germanium-68
- Indium-111
- Lead-203/212
- Lutetium-177
- Radium-223
- Scandium-44/47
- Strontium-82
- Terbium-161
- Thallium-201 (Lead-201)
- Thorium-227
- Yttrium-86
- Yttrium-90
- Zirconium-89



https://www.iaea.org/newscenter/news/what-are-radiopharmaceuticals

Current study – Background

eichrom®

- Existing separations are already done on Eichrom resins for many isotopes
  - SCX for Ga
  - DGA for Ac, REEs
- Recovery of nuclear medicine isotopes in buffer is ideal for labeling
  - Ammonium acetate commonly used
- High specific activity isotopes are more strongly impacted by acidic impurities or cation exchange sites.
  - Need to understand how tracers behave as it may differ from stable metal

Table 4. Selected $^{44/47}$Sc Radiopharmaceuticals with Targets and Relevant Labeling Parameters[a]

radioisotope	chelator (BFC)	standard labeling conditions	bioconjugate	target	molar/specific activity (% RCY)	reference
^{44}Sc	DOTA (DO3A)	0.25–0.5 M NH_4OAc pH 4, 95 °C, 10–30 min	BBN[2-14]NH_2	GRPR	4.8 GBq/μmol (>80)	149
			Tyr^3-octreotate (TATE)	SSTR	8 GBq/μmol (>95)	108
			PSMA-617	PSMA	6.7 ± 0.8 GBq/μmol (>98)	99
			Z-HER:2891	HER2	7.8 GBq/μmol (98 ± 2)	152
			NAP-amide	MC1-R	19 GBq/μmol (60–70)	150
	DOTA (*p*-SCN-Bn)	0.5 M NaOAc pH 4.5, 90 °C, 15 min	c(RGD)$_2$	integrin $\alpha_v\beta_3$	7.1 GBq/μmol (>90)	148
	AAZTA (CNAAZTA)	0.25 M NH_4OAc pH 4, RT, 5 min	c(RGDfK)	integrin $\alpha_v\beta_3$	0.36 GBq/μmol (99)	142
	CHX-A″-DTPA (*p*-SCN-Bn)	0.5 M NaOAc pH 4.5, RT, 30 min	Cetuximab Fab	EGFR	63 GBq/μmol (66 ± 5)	100
^{47}Sc	DOTA (DO3A)	0.25–0.5 M NH_4OAc pH 4, 95 °C, 10–25 min	folate (cm10)	FR	13 GBq/μmol (>96)	102
			Nal^3-octreotide (NOC)	SSTR	10 GBq/μmol (96.6–99)	101

Table 6. Selected $^{66/68}$Ga Radiopharmaceuticals with Targets and Relevant Labeling Parameters[a]

radioisotope	chelator (BFC)	standard labeling conditions	bioconjugate	target	molar/specific activity (% RCY)	reference
^{66}Ga	NOTA (*p*-SCN-Bn)	0.25 M NH_4OAc pH 7.2, 37 °C, 30 min	TRC-105	CD105	>74–222 GBq/μmol (>80)	691
	DFO	TRIS-buffered saline pH 7.4, 50 °C, 15 min	folate	FR		692
^{68}Ga	DOTA (DO3A)	0.1 M OAc pH 5.5, 100 °C, 10 min	Tyr^3-octreotate (TATE)	SSTR	185–260 GBq/7–45 mg (64)	693
	HBED (HBED-CC)	NaOAc, pH 4.5, 85 °C, 3 min	PSMA-11	PSMA	70 ± 20 GBq/μmol (86.5 ± 4.1)	244
	PCTA (*p*-SCN-Bn)	10 mM NaOAc pH 4.5, 30 min, RT	c(RGDyK)	integrin $\alpha_v\beta_3$	55 GBq/μmol (96.2 ± 0.5)	194
	THP (SCN)	0.6 M NH_4OAc, pH 6.5, RT, 2–5 min	c(RGDfK)	integrin $\alpha_v\beta_3$	60–80 GBq/μmol (>95)	250
	H_2dedpa (*p*-SCN-Bn)	10 mM NaOAc pH 4.5, RT, 10 min	c(RGDyK)	integrin $\alpha_v\beta_3$	34 GBq/μmol (97)	255
	TRAP	HEPES buffer pH 2, 95 °C, 5 min	(RGD)$_3$	integrin $\alpha_v\beta_3$	2009 ± 61 GBq/μmol (90.0 ± 2.7)	215

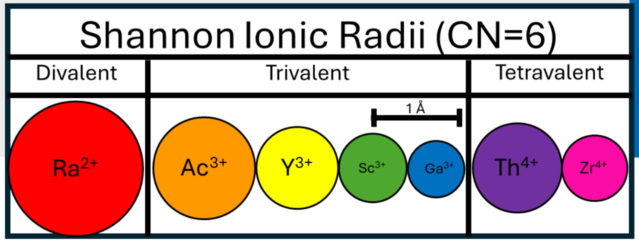
[a]FR (folate receptor); SSTR (somatostatin receptor); and PSMA (prostate-specific membrane antigen).

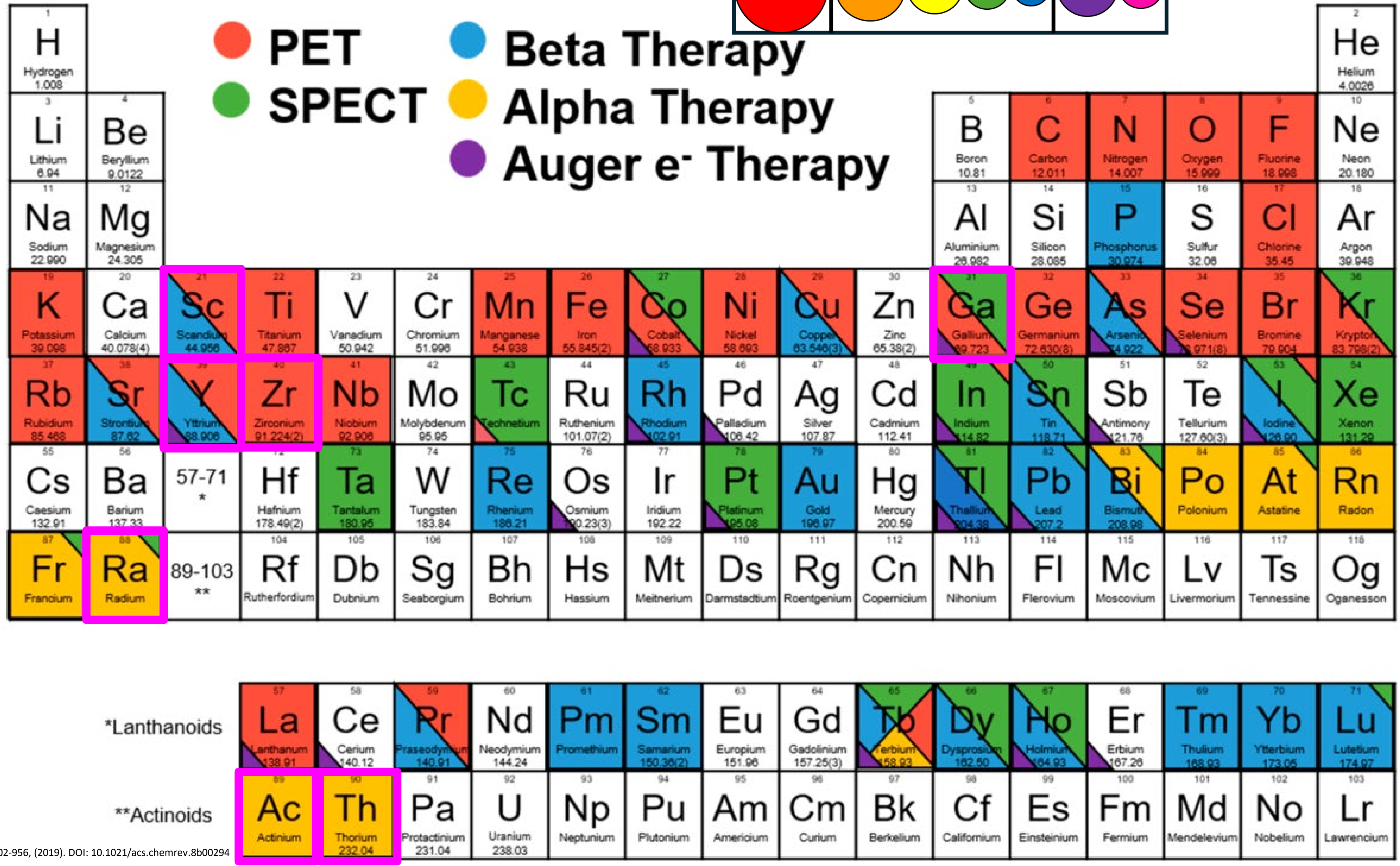
Table 8. Selected $^{86/90}$Y Radiopharmaceuticals with Targets and Relevant Labeling Parameters[a]

radioisotope	chelator (BFC)	standard labeling conditions	bioconjugate	target	molar/specific activity (% RCY)	reference
^{86}Y	DOTA (DO3A)	0.15 M NH_4OAc pH 4.5, 100 °C, 15 min	Phe^1-Tyr^3-octreotide (TOC)	SSTR	28 GBq/μmol (>98.5)	372, 374
	DOTA (*p*-SCN-Bn)	0.2 M NH_4OAc pH 5.5–6, 95 °C, 20 min	PSMA peptide "6"	PSMA	>83.9 GBq/μmol (90–95)	376
	CHX-A″-DTPA (*p*-SCN-Bn)	0.1 M NH_4OAc pH 5–6, RT, 30–60 min	Antimindin/RG-1	Mindin/RG-1	29.6–39.6 MBq/mg (82–96)	378

Kostelnik, T., Orvig, C.; *Chem Rev*, 119**(2)**, 902-956, (2019).

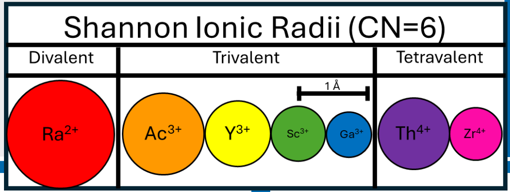
Isotopes of interest





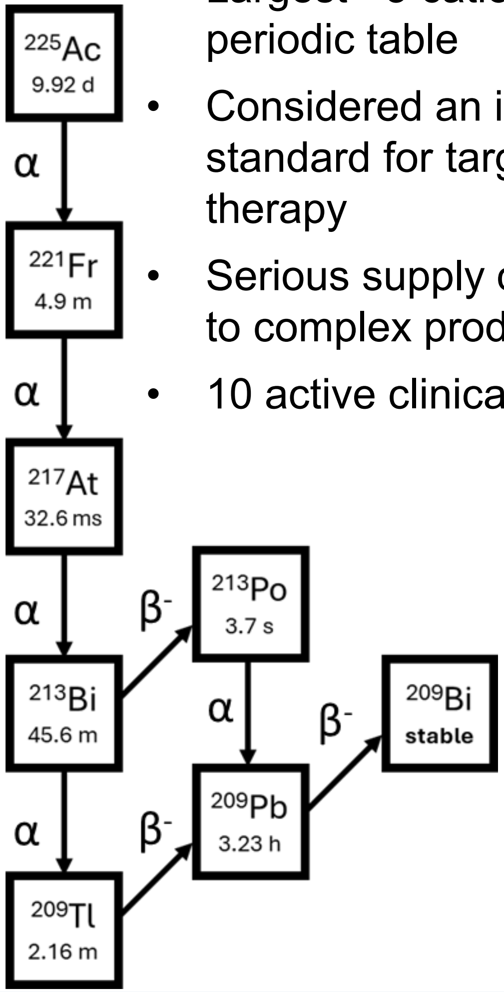
Kostelnik, T. I.; et al. *Chem Rev* **119,** 902-956, (2019). DOI: 10.1021/acs.chemrev.8b00294

Alpha Emitting Therapeutics



Actinium (^{225}Ac)

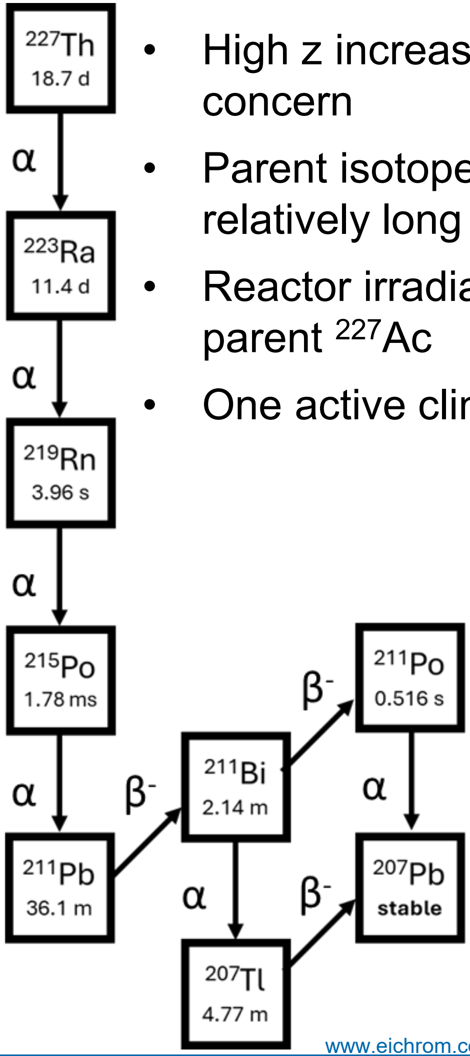
Ox: +3 **IR: 1.12 Å** **z/r: 2.68**



- Largest +3 cation on the periodic table
- Considered an industry standard for targeted alpha therapy
- Serious supply chain issues due to complex production routes
- 10 active clinical trials

Thorium (^{227}Th)

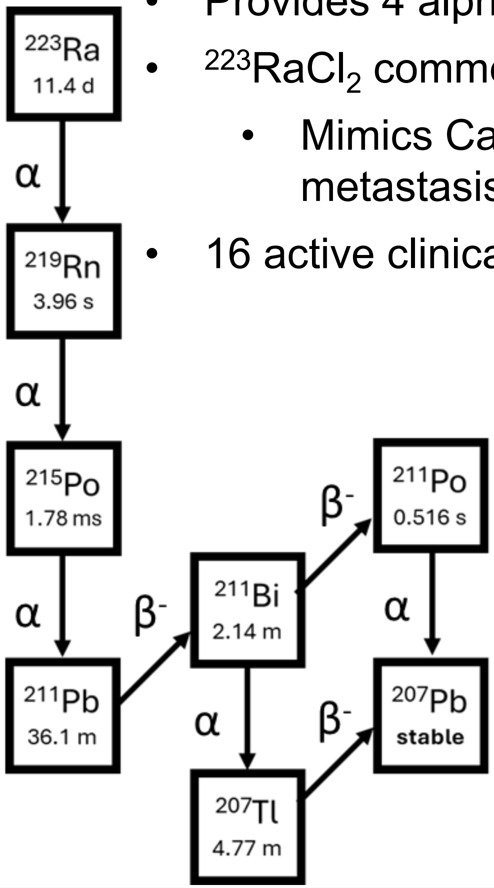
Ox: +4 **IR: 0.94 Å** **z/r: 4.25**



- High z increases hydrolysis concern
- Parent isotope to ^{223}Ra, but relatively long half-life
- Reactor irradiation to produce parent ^{227}Ac
- One active clinical trial

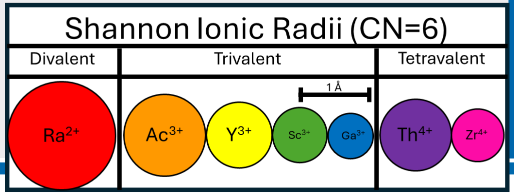
Radium (^{223}Ra)

Ox: +2 **IR: 1.48 Å** **z/r: 1.35**



- Largest +2 cation on the periodic table.
- Provides 4 alpha emissions
- $^{223}RaCl_2$ commercially Xofigo®
  - Mimics Ca to target bone metastasis
- 16 active clinical trials

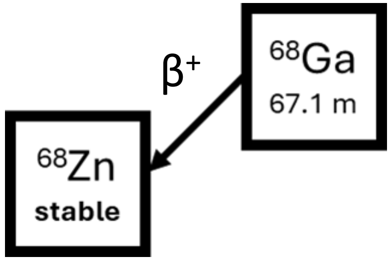
Positron Emitting Diagnostics



Gallium (^{68}Ga)

Ox: +3 **IR: 0.62 Å** **z/r: 4.83**

- One of the smallest +3 cations
- Readily susceptible to hydrolysis
- ^{68}Ga was one of the first PET emitters used in imaging
- Readily available via $^{68}Ge/^{68}Ga$ generators.
- 81 active clinical trials



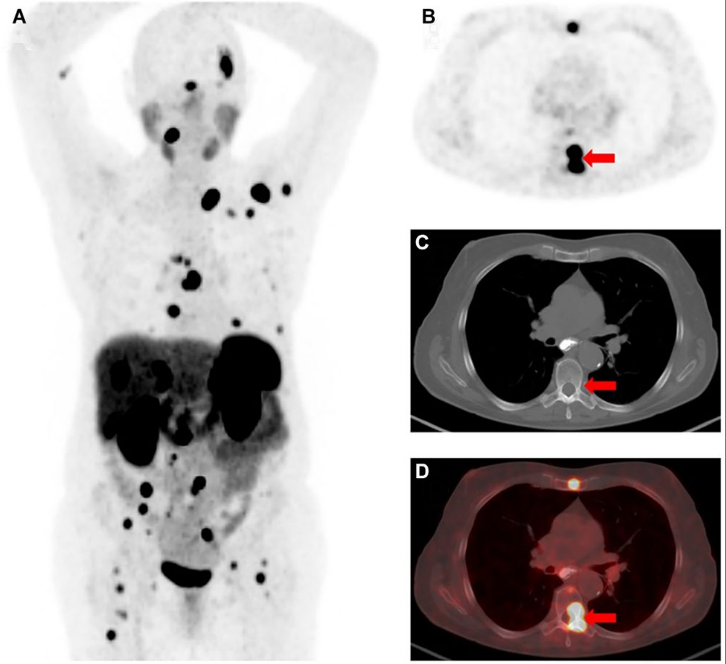


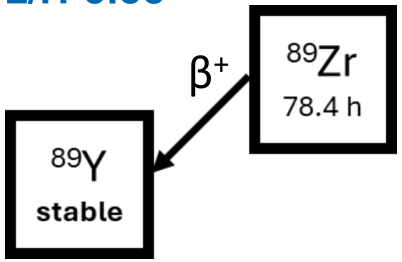
FIGURE 5. A 74-Year-Old Woman With Metastatic Small Bowel Neuroendocrine Tumor. (A) This maximum intensity projection, gallium-68 (^{68}Ga)-DOTATATE, positron emission tomography (PET) image shows numerous sites of abnormal uptake in lymph nodes and bones. Axial (B) ^{68}Ga-DOTATATE PET, (C) computed tomography (CT), and (D) fused ^{68}Ga-DOTATATE PET/CT images demonstrate that many of the bone lesions are easily visible on the PET image but are occult on the corresponding CT anatomic images (red arrows). This case demonstrates the high sensitivity that is achievable with optimized PET radiotracers and that normal-appearing anatomic structures can harbor disease that is well visualized with molecular imaging.

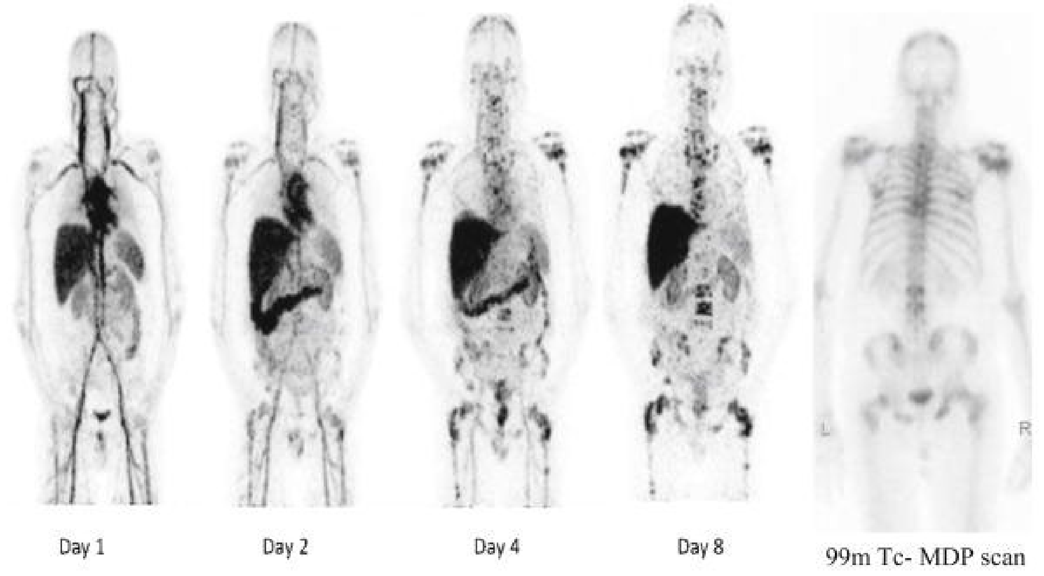
Rowe, S.P.; et al. *CA Cancer J Clin* 72(**4**), 333-352, (2021). DOI: 10.3322/caac.21713
Pandit-Taskar, N.; et al. *Eur J Nucl Med Mol Imaging,* **41,** 2094-2105 (2014). DOI:10.1007/s00259-014-2830-7

Zirconium (^{89}Zr)

Ox: +4 **IR: 0.72 Å** **z/r: 5.55**

- Extremely prone to hydrolysis
- Typically requires a complexing agent
- PET emitter with a long half-life
- Cyclotron production by irradiation of monoisotopic ^{89}Y
- 12 active clinical trials

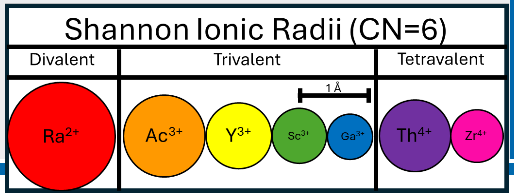




Serial whole-body ^{89}Zr-huJ591 scans (MIP images). Images show physiological distribution in cardiac and vascular blood pool, decreasing with time, in liver, spleen, kidneys, and GI tract. Images show increased accumulation in multiple bone lesions, best seen in day 8 image. Many of these lesions are not clearly visualized on ^{99m}Tc-MDP scan (*right*) lesions otherwise not detected by CT or FDG scan; in one patient ^{89}Zr-huJ591 imaged disease was seen on MRI.

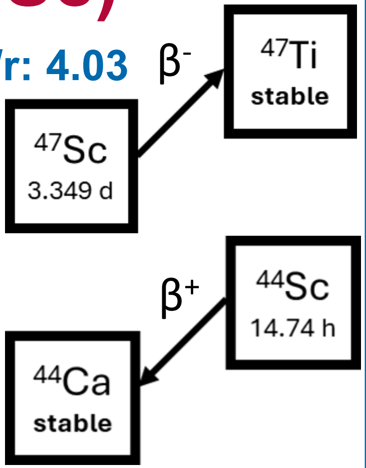
rom.com

Match Pair Theranostics

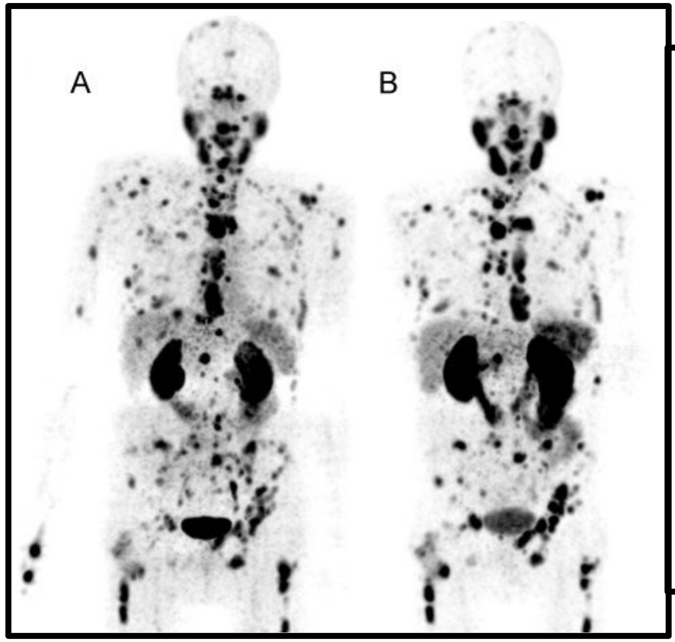


Scandium (^{44}Sc / ^{47}Sc)

Ox: +3 **IR: 0.75 Å** **z/r: 4.03**



- Smallest of the +3 Rare Earth Elements
- Susceptible to hydrolysis
- ^{44}Sc is a short-lived PET emitter readily available via ^{44}Ti/^{44}Sc generators.
- ^{47}Sc provides low-energy beta treatment

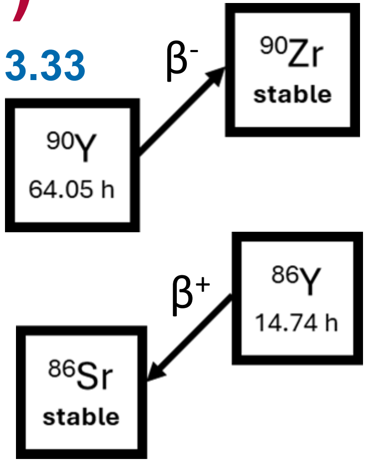


Maximal intensity projection of PET/CT examination of a 77-year-old patient suffering of mCRPC with high tumor load using:
(A) [^{44}Sc]Sc-PSMA-617 (50 MBq, 60 min p.i.)
(B) (B) [^{68}Ga]Ga-PSMA-11 (120 MBq, 60 min p.i.).

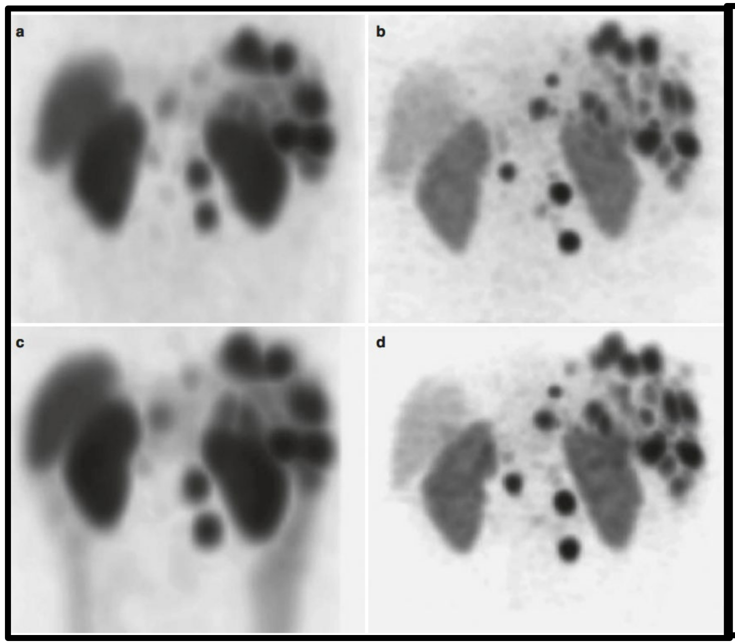
Eppard, E.; et al. *Theranostics,* 7**(18)**, 4359-4369, (2017). DOI: 10.7150/thno.20586

Yttrium (^{86}Y / ^{90}Y)

Ox: +3 **IR: 0.9 Å** **z/r: 3.33**



- Rare Earth element with low z/r
- Regenerative ^{90}Sr/^{90}Y generators
- Accelerator production of ^{86}Y
- 79 active clinical trials



The same patient imaged via SPECT with [111In]In-DTPA-octreotide (A = 4 h, C = 24 h) and via PET with [86Y]Y-DOTATOC (B = 4 h, D = 24 h) showing hepatic and para-aortic metastases of a carcinoid tumor.

Khozeimeh Sarbisheh, E., Price, E.W. (2019). The Radiopharmaceutical Chemistry of the Radioisotopes of Lutetium and Yttrium. In: Lewis, J., et al. Radiopharmaceutical Chemistry. Springer, Cham. DOI: 10.1007/978-3-319-98947-1_20

Current study – Experimental Design

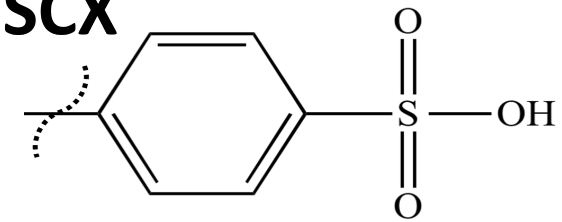
eichrom®

Determine minimum volume required for 95% recovery

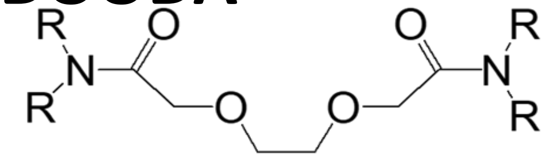
- QML Column
- 10 mL HCl load
  - 0.05 M HCl for SCX
  - 6 + M HCl for DOODA, DGA, and DGA+DAAP
- 5 mL 1 M NH_4OAc pH = 6 strip
  - Forward direction
- Gravimetric fraction collection
- High specific activity tracers for each isotope
  - Analysis by HPGe or NaI

Elements of Interest			
	Ox State	IR (Å)	z/r
^{225}Ac	+3	1.12	2.68
^{223}Ra	+2	1.48	1.35
^{227}Th	+4	0.92	4.25
^{68}Ga	+3	0.62	4.83
$^{86/90}Y$	+3	0.9	3.33
^{89}Zr	+4	0.72	5.55
$^{44/47}Sc$	+3	0.75	4.03

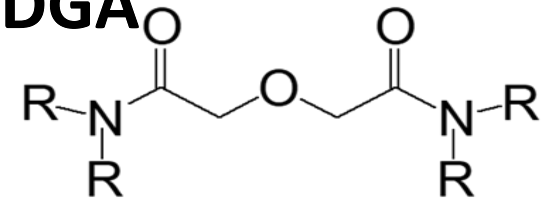
SCX



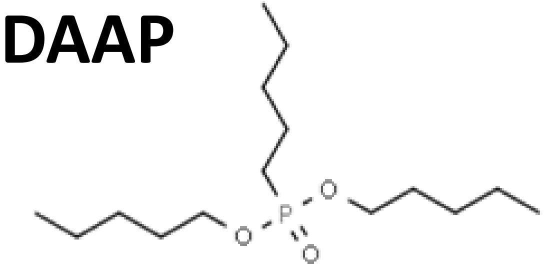
DOODA



DGA

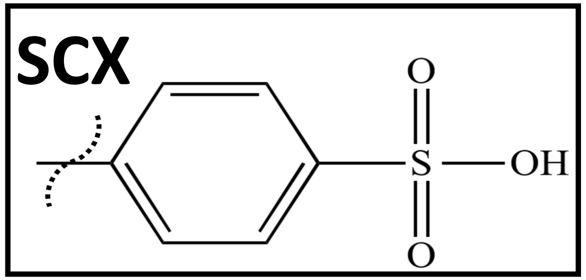


DAAP

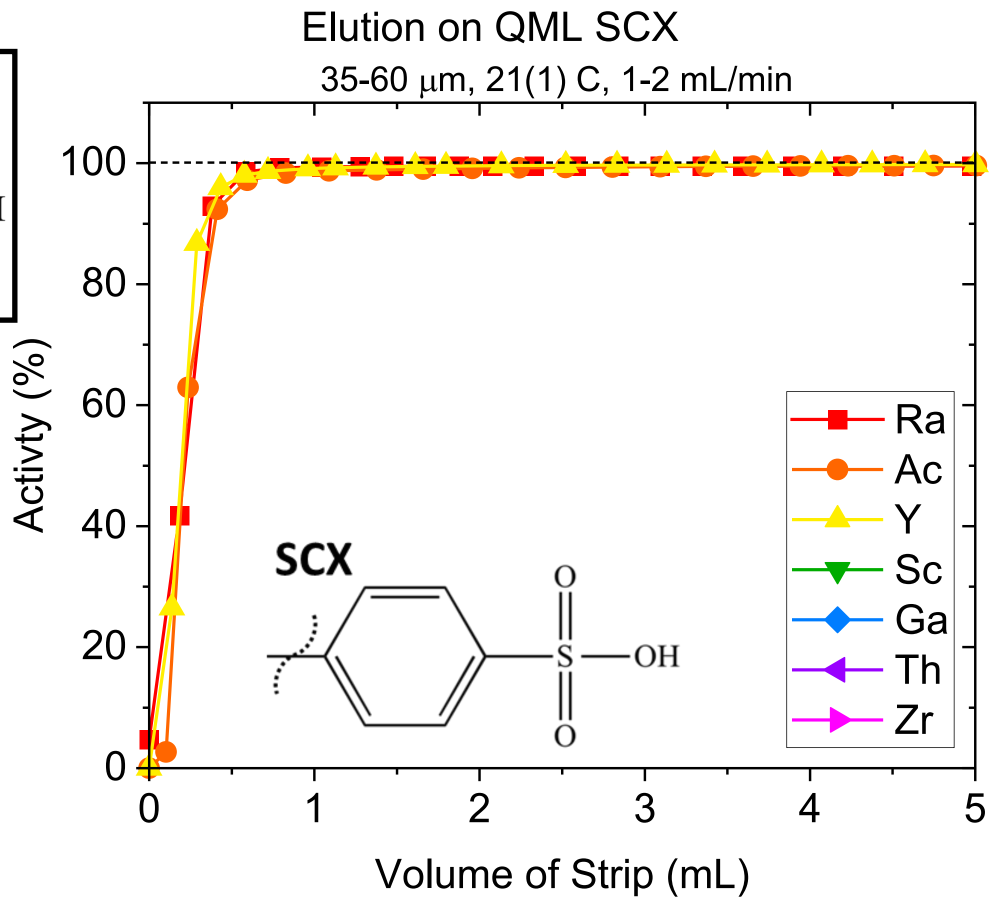


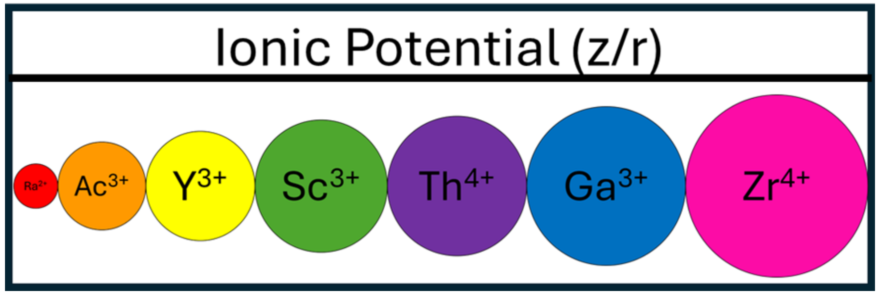
SCX

- Strong cation exchange resin
- Currently used in Ga generators
- Affinity for metal ions increases with:
  - Charge
  - Charge density (z/r)
- Only resin that extracted Ra
- No recovery of Th, Ga, Zr, or Sc
- Tried increasing acetate solution ionic strength



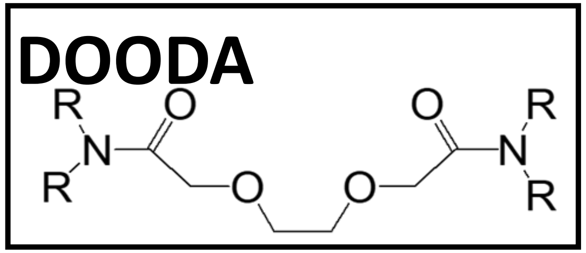
95% recovery (mL)	
^{225}Ac	0.59
^{223}Ra	0.79
^{227}Th	
^{68}Ga	
$^{86/90}$Y	0.43
^{89}Zr	
$^{44/47}$Sc	





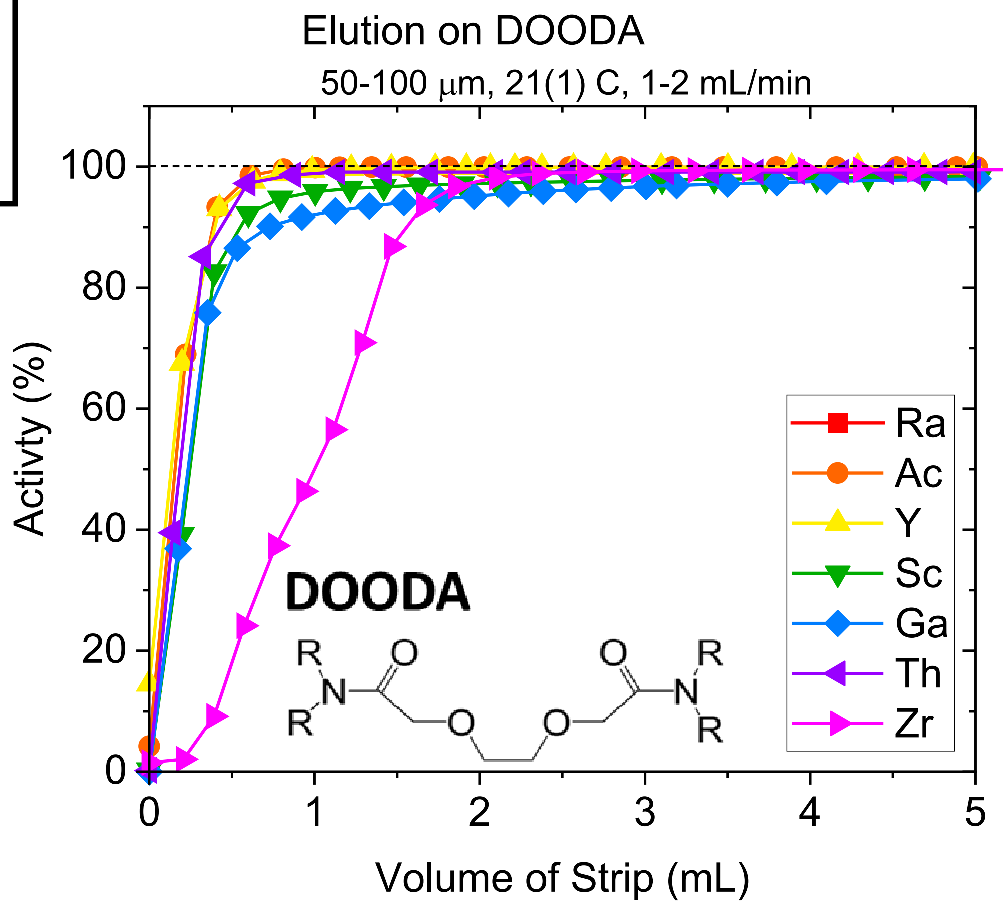
DOODA

- *N,N,N',N'*-tetraoctyl-3,6-dioxaoctane diamide
- Large, flexible neutral extractant
- Complete loading of all isotopes except Ra and Y*
  - *Y was loaded on 2ML cartridge
- All isotopes were successfully recovered in acetate
- Limited loading conditions for some low (z/r) isotopes



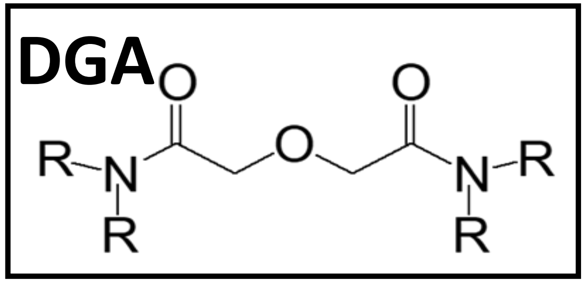
95% recovery (mL)	
^{225}Ac	0.81
^{223}Ra	
^{227}Th	0.59
^{68}Ga	1.97
$^{86/90}$Y	2.00*
^{89}Zr	1.86
$^{44/47}$Sc	1.00

* 2ML cartridge instead of QML to reduce breakthrough on load

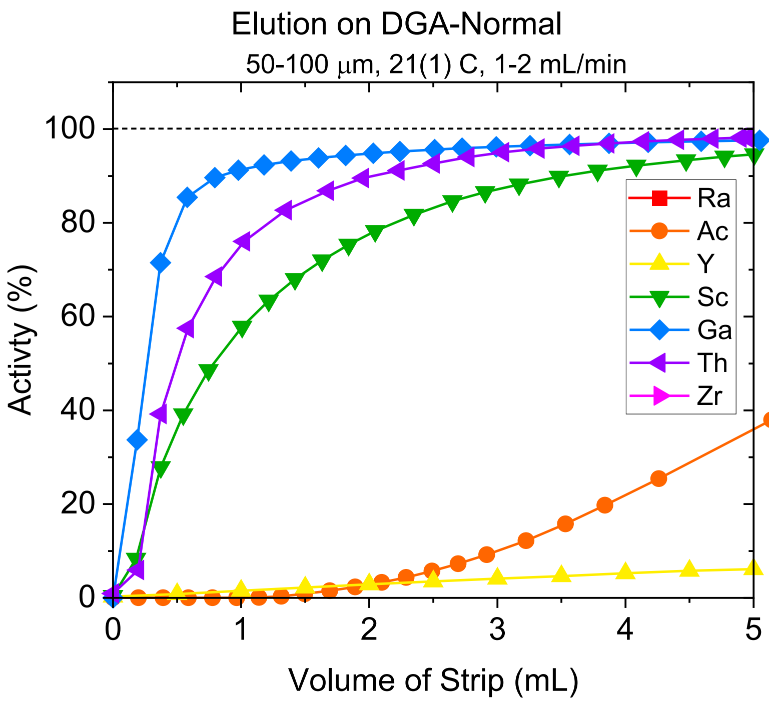


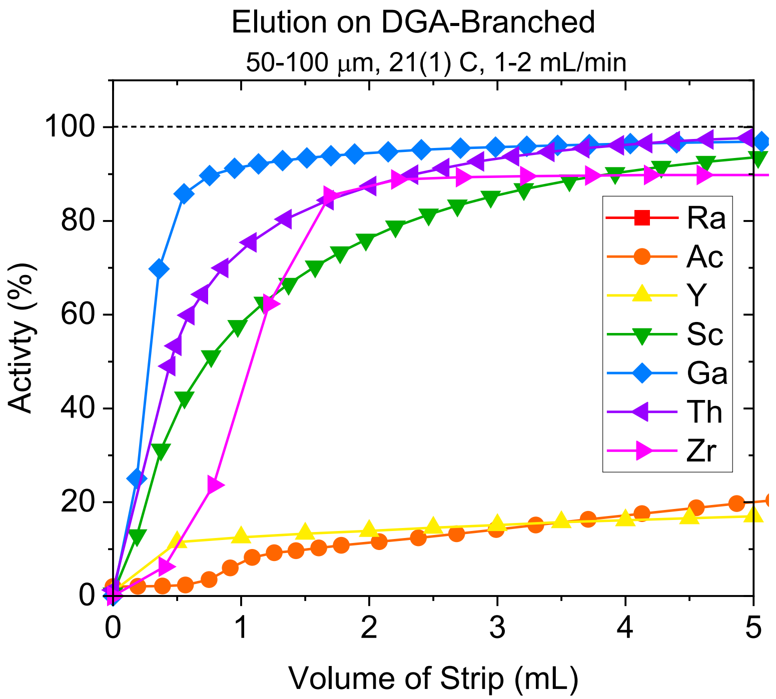
DGA

- *N,N,N’,N’*-tetra(R)-diglycolamide
  - R = octyl (DGA-N)
  - R = 2-ethyl-1-hexyl (DGA-B)
- Recovery of Th and Ga in relatively large volume
- Stable Y recovered but not tracer
- Sc maxes out at 94%
- Ac breakthrough on QML, incomplete strip on 2ML
- Breakthrough of Ra
- Extractant may contain ion-exchange impurities



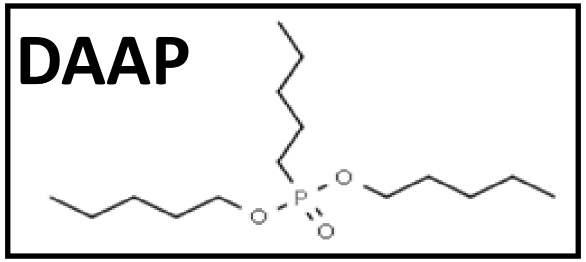
95% recovery (mL)		
	DGA-N	DGA-B
^{225}Ac	[redacted]	[redacted]
^{223}Ra	[redacted]	[redacted]
^{227}Th	3.32	3.94
^{68}Ga	2.24	2.41
$^{86/90}Y$	[redacted]	[redacted]
^{89}Zr	[redacted]	[redacted]
$^{44/47}Sc$	[redacted]	[redacted]



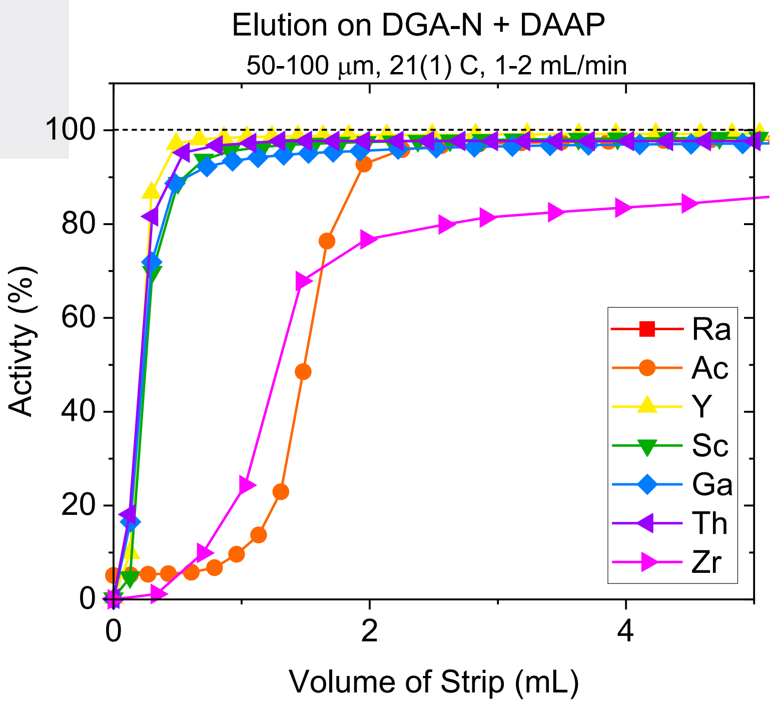


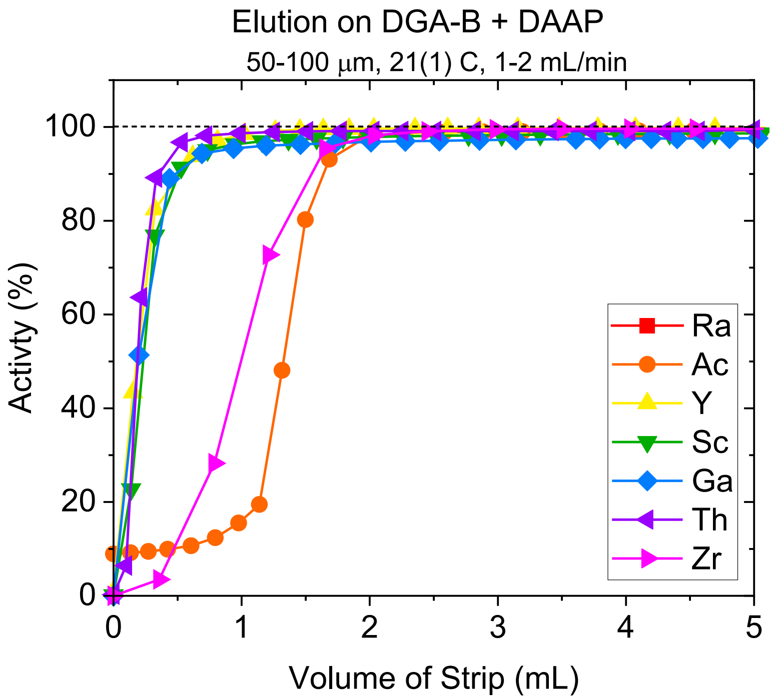
DGA + DAAP

- Diamyl-amylphosphonate
- DAAP acts as a masking agent to complex cation exchange sites
- Improves isotope recovery
  - Reduces volume of Th and Ga recovery
  - Successfully recovers Y, Zr, and Sc unlike DGA alone
- Reduction of DGA content by 50%
  - Improves recovery volume
  - Increase Ac breakthrough during loading on 2ML



95% recovery (mL)		
	DGA-N + DAAP	DGA-B + DAAP
^{225}Ac		
^{223}Ra		
^{227}Th	0.55	0.53
^{68}Ga	1.52	0.94
$^{86/90}$Y	0.49	0.81
^{89}Zr		1.65
$^{44/47}$Sc	0.91	0.73





Conclusions

- **SCX** elution controlled by ionic potential, ionic strength, and hydrolysis reactions
- **DGA** elution dictated by DGA-complex strength and cation-exchange impurities
- Adding **DAAP** to **DGA** will mask ion exchange sites allowing for the elution of smaller metal ions
- **DOODA** is a large, relatively weak extractant allowing for easy stripping of metal ions

95% isotope recovery in 1 M NH_4OAc pH=6 (mL)

	SCX	DOODA	DGA (N/B)	DGA + DAAP (N/B)
^{225}Ac	0.59	0.81		
^{223}Ra	0.79			
^{227}Th		0.59	3.32 / 3.94	0.55 / 0.53
^{68}Ga		1.97	2.24 / 2.41	1.52 / 0.94
$^{86/90}$Y	0.43	2.00*		0.49 / 0.81
^{89}Zr		1.86		5.00+ / 1.65
$^{44/47}$Sc		1.00		0.91 / 0.73

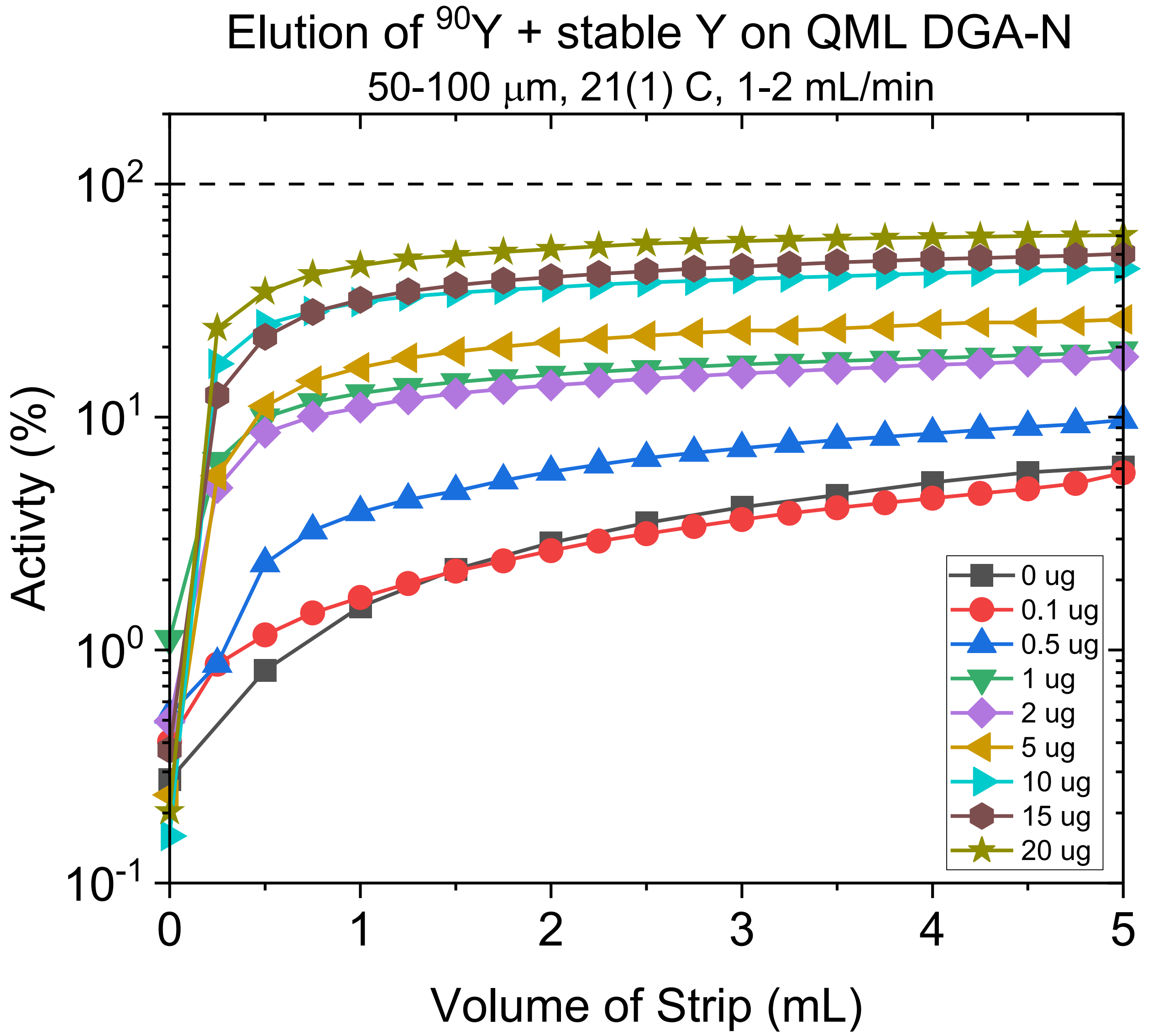
* 2ML cartridge instead of QML to reduce breakthrough on load

Future work

- More isotopes
- More resins
- More buffers
- Write papers

Future work (for real)

- Research and probe acetate complexation and speciation with metals of interest
- Improve our understanding of how hydrolysis impacts recovery
  - Especially for Zr
- Investigate the strength and nature of Y-DGA complexes
- Probe the role of DAAP in improving recovery on DGA resins
- BONUS: understand how rare-earth microprecipitation performs in acetate solutions
  - Could this be the low-acid alternative we have been looking for to improve alpha spec resolution all along???



Questions?