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ALABAMA AT BIRMINGHAM.

Targeted Alpha-Particle Therapies

Jonathan D. Burns

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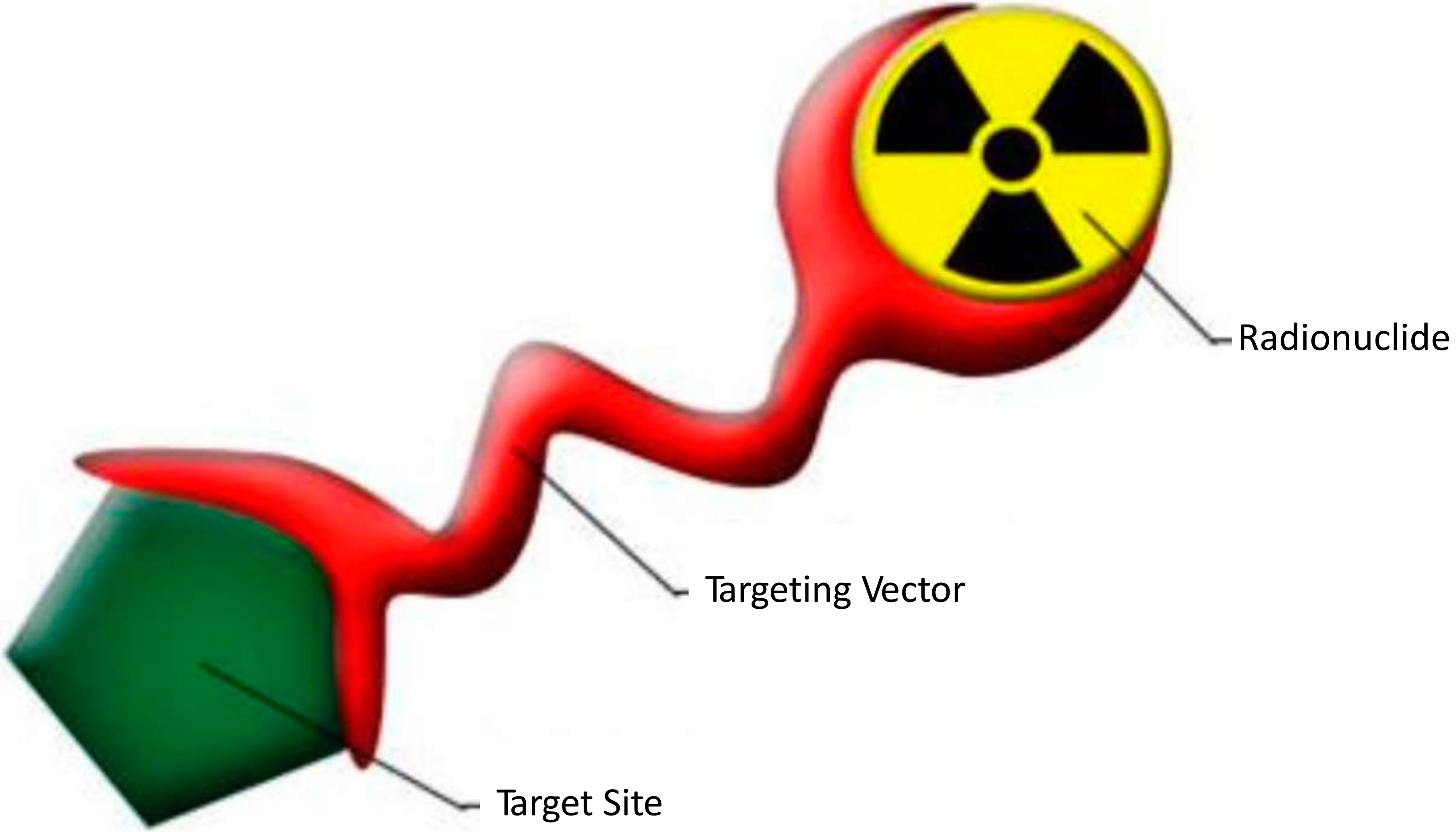
Nuclear Science Symposium
International Union of Pure and Applied Physics (IUPAP),
June 15, 2022, Washington, DC

Outline

- Background on TAT
- ^{225}Ac
  - Background
  - Uses
  - Sources Material and Production
  - Separation and Purification
- ^{211}At
  - Background
  - Production
  - Separation and Purification
  - Uses
- Summary
- Acknowledgement

https://cen.acs.org/magazine/100/10013.html (accessed 4/25/22)

Basic Concept of Targeted Radionuclide Therapy



- Diagnostics
  - SPECT
  - PET
- Therapy
  - beta
  - alpha
  - auger electron
- Theranostics

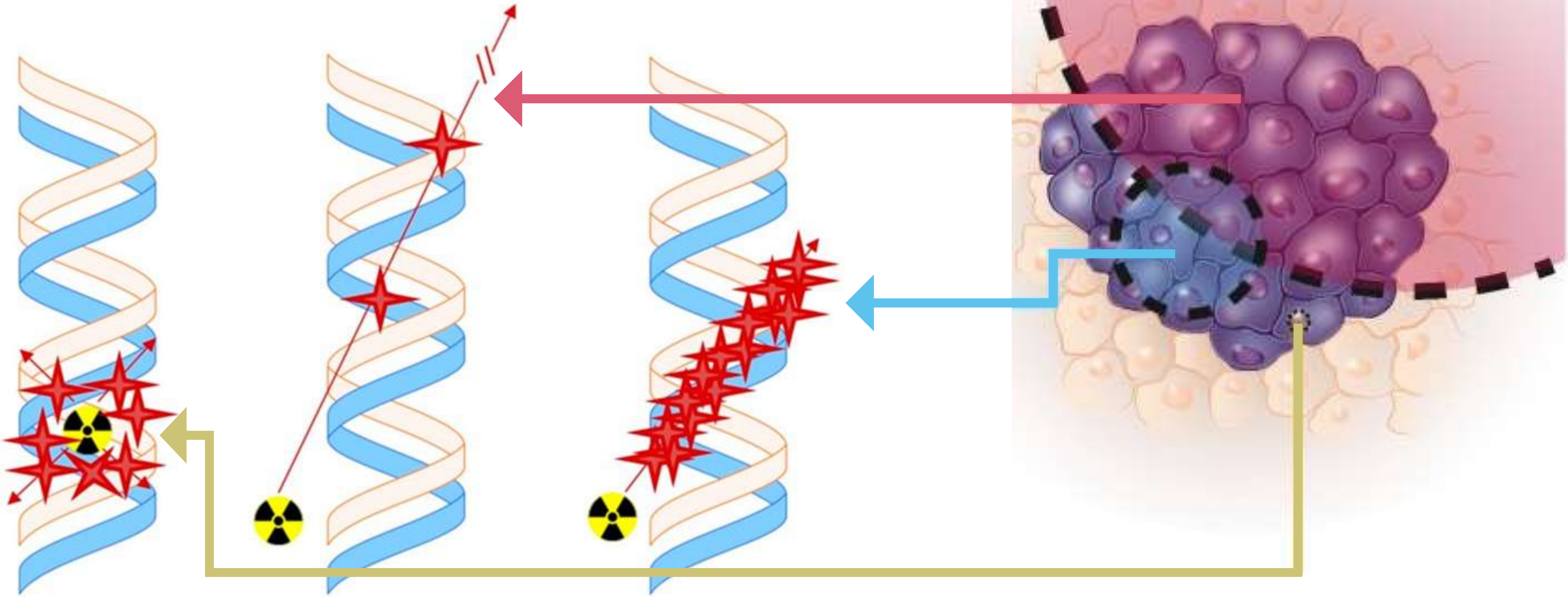
Adapted from De Kruijff, R.M.; *et al., Pharmaceuticals* 2015, 8, 321-336.

Types of Targeted Radionuclide Therapy

Auger (e^-):
Range 2-500 nm
LET: 4–26 Kev/µm

Beta (β^-):
Range 0.050–12 mm
LET: 0.2 Kev/µm

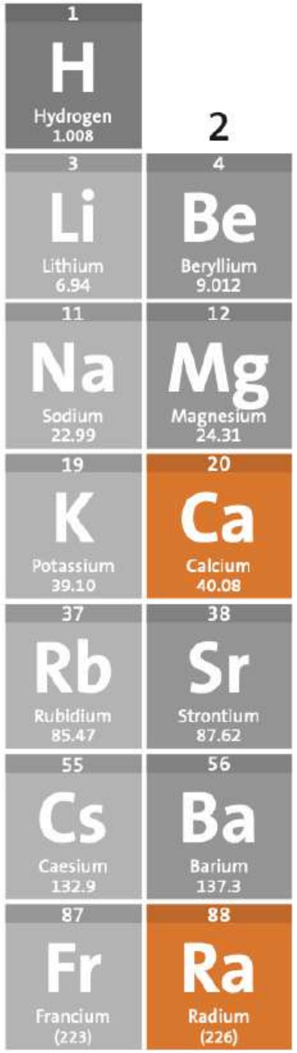
Alpha (α):
Range 40–100 µm
LET: 50–230 Kev/µm



Adapted from de Jong, M.; et al. *Pharmaceutics* **2019**, *11*, 560.

Adapted from Poty S.; *et al. J Nucl Med*. 2018;59(6):878-884.

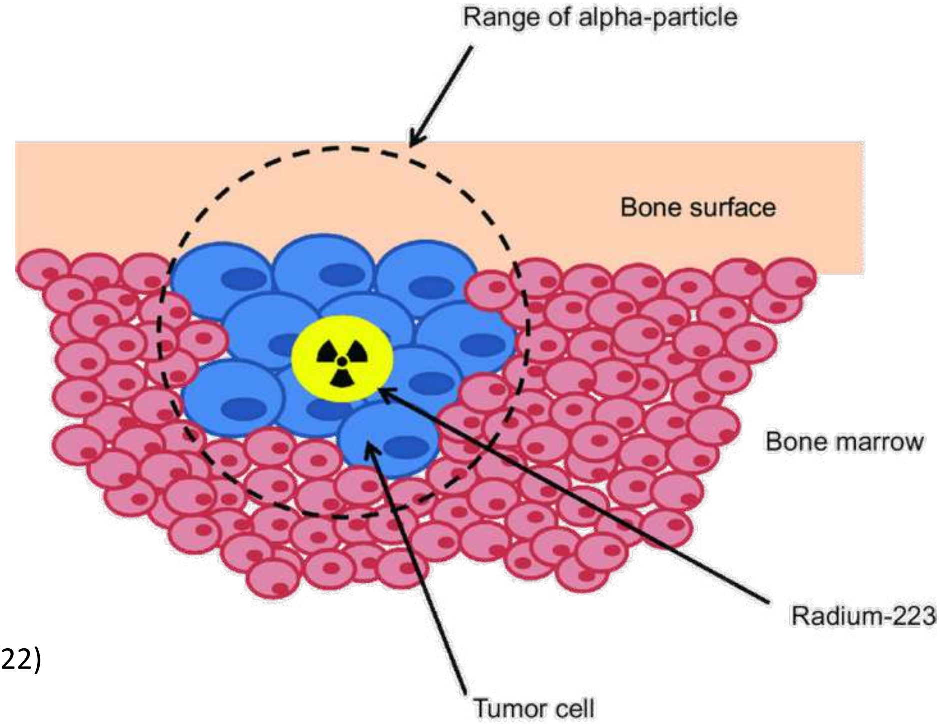
Xofigo® (^{223}Ra dichloride)



1	2
1 **H** Hydrogen 1.008	
3 **Li** Lithium 6.94	4 **Be** Beryllium 9.012
11 **Na** Sodium 22.99	12 **Mg** Magnesium 24.31
19 **K** Potassium 39.10	20 **Ca** Calcium 40.08
37 **Rb** Rubidium 85.47	38 **Sr** Strontium 87.62
55 **Cs** Caesium 132.9	56 **Ba** Barium 137.3
87 **Fr** Francium (223)	88 **Ra** Radium (226)

https://www.xofigo-us.com/patient/how-xofigo-works (accessed 4/19/22)

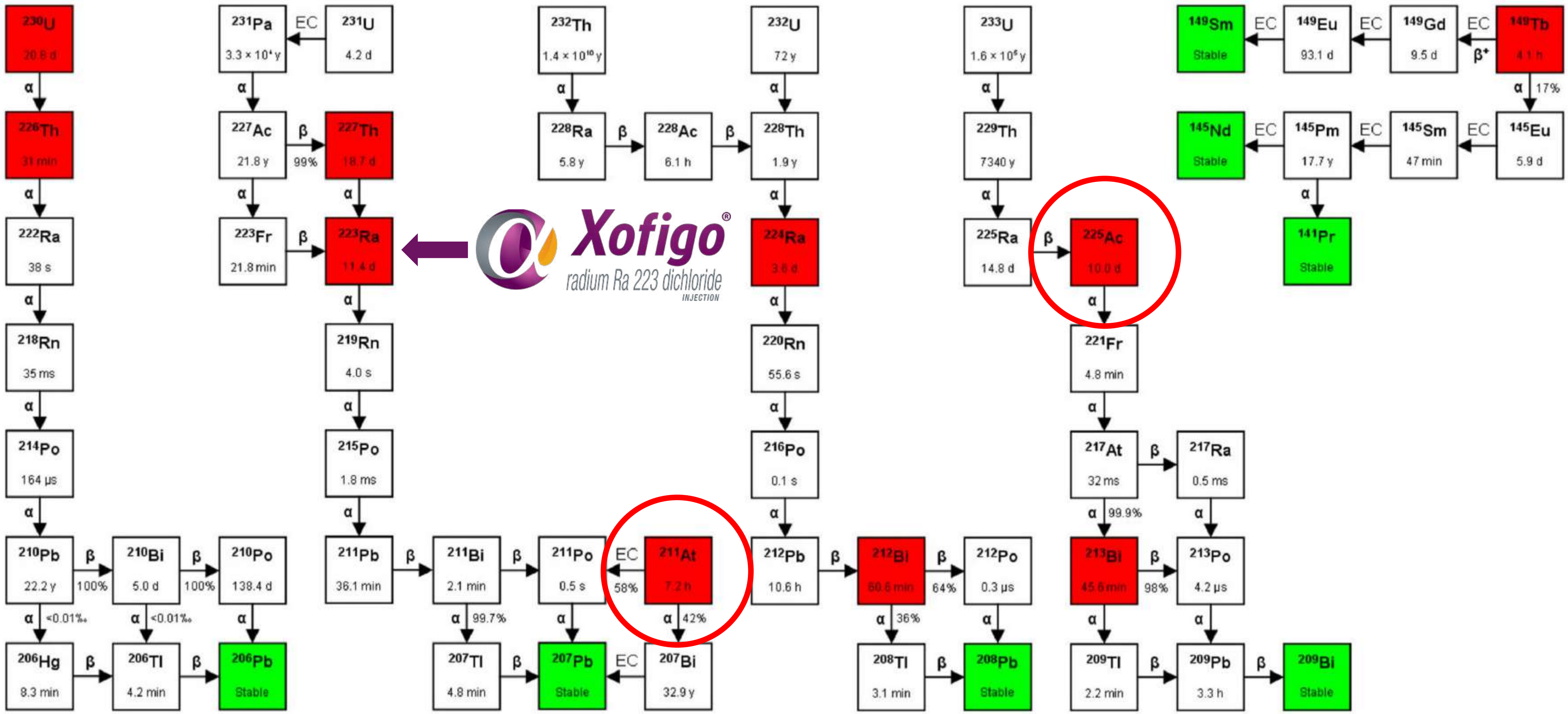
Xofigo®
radium Ra 223 dichloride
INJECTION



https://www.acs.org/content/acs/en/education/whatischemistry/periodictable.html (accessed 4/19/22)

Mukherji D.; *et al*. *Ther. Clin. Risk Manag*. **2014**;10:373-380

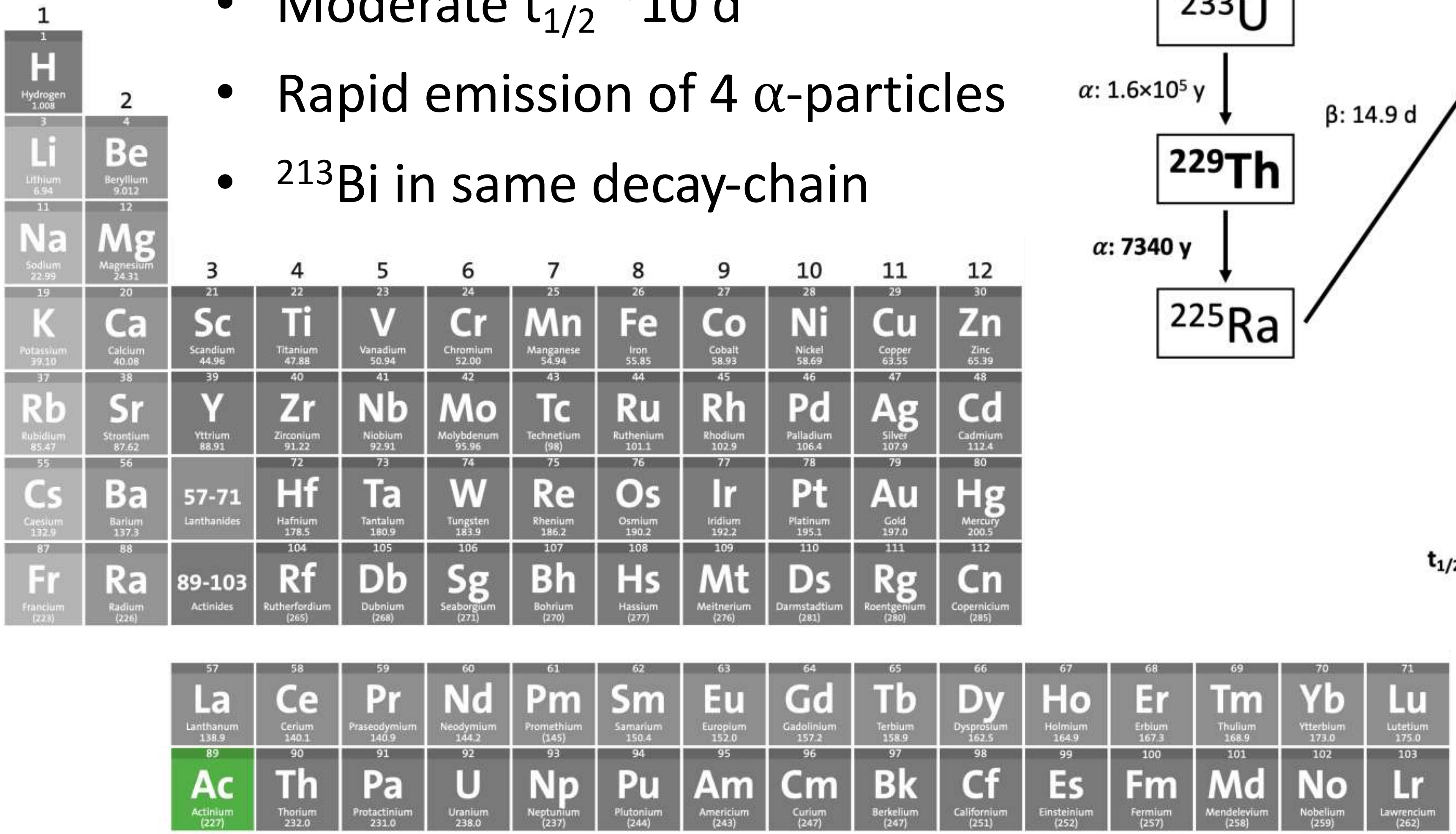
Promising TAT Radionuclides



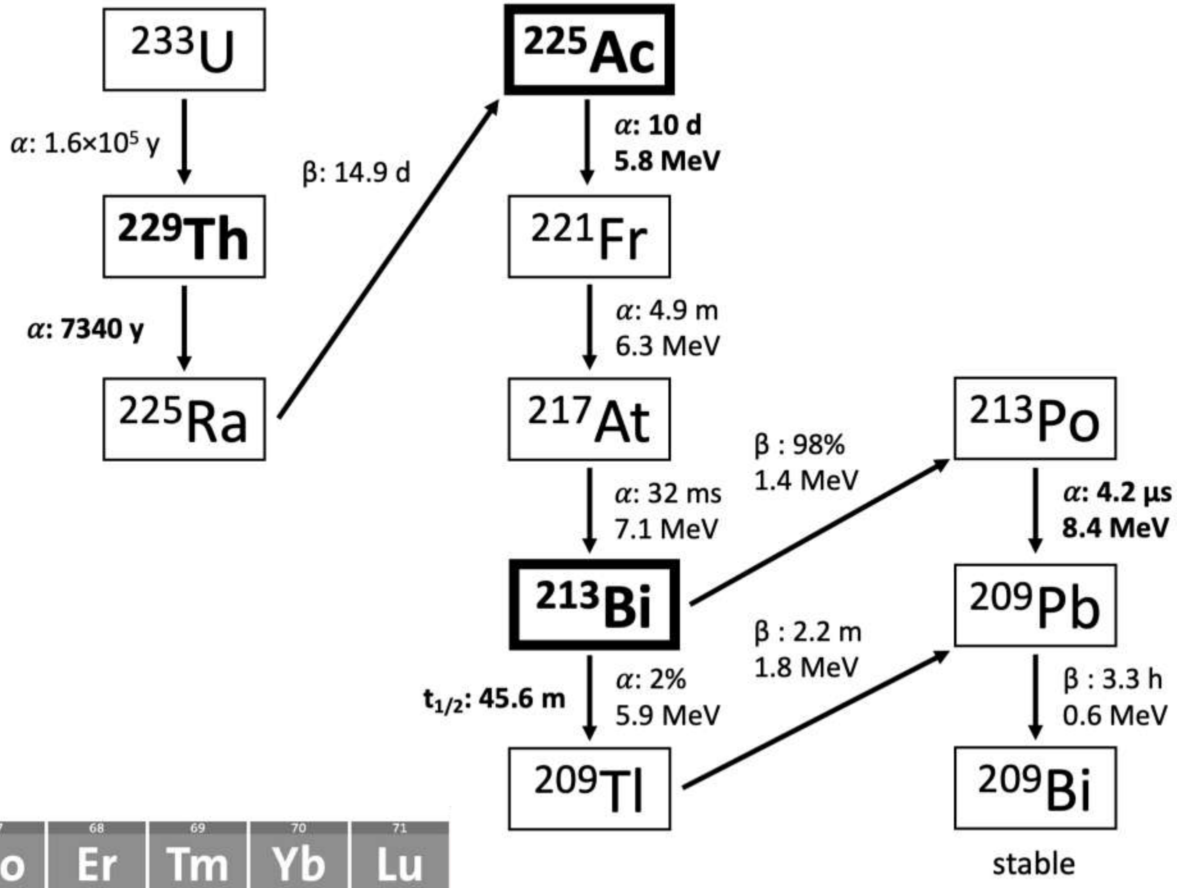
Adapted from Elgqvist, J.; et al. *Front. Oncol.* **2014**, *3*, 324.

^{225}Ac Background

- Moderate $t_{1/2}$ ~10 d
- Rapid emission of 4 α-particles
- ^{213}Bi in same decay-chain



https://www.acs.org/content/acs/en/education/whatischemistry/periodictable.html (accessed 4/19/22)



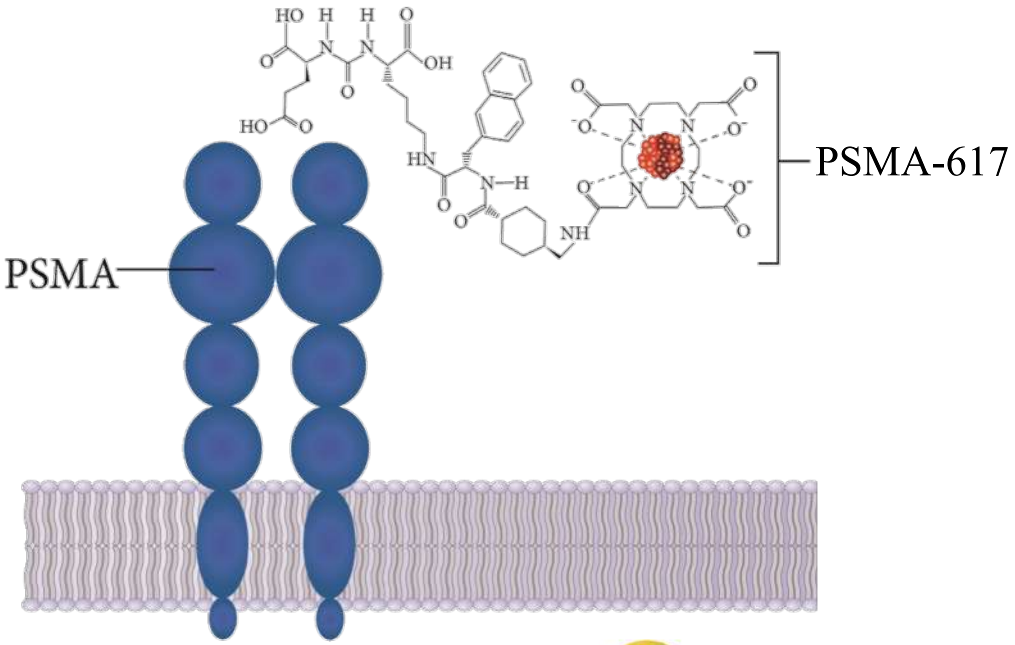
Adapted from Pozzi, O. R. et al. IAEA-TM-44815
https://inis.iaea.org/search/search.aspx?orig_q=RN:45091405

Clinical Use of ^{225}Ac or ^{213}Bi Daughter

Cancer Type	Radioconjugate	Patients
Leukemia	^{213}Bi-anti-CD33-mAb	49
	^{225}Ac-anti-CD33-mAb	76
Lymphoma	^{213}Bi-anti-CD20-mAb	12
Melanoma	^{213}Bi-anti-MCSP-mAb	54
Bladder cancer	^{213}Bi-anti-EGFR-mAb	12
Glioma	^{213}Bi-Substance P	68
	^{225}Ac-Substance P	20
Neuroendocrine tumors	^{213}Bi-DOTATOC	25
	^{225}Ac-DOTATOC	39
Prostate cancer	^{225}Ac-PSMA617	>400

Morgenstern, A.; *et al*. *Semin. Nucl. Med.* **2020,** *50* (2), 119-123.

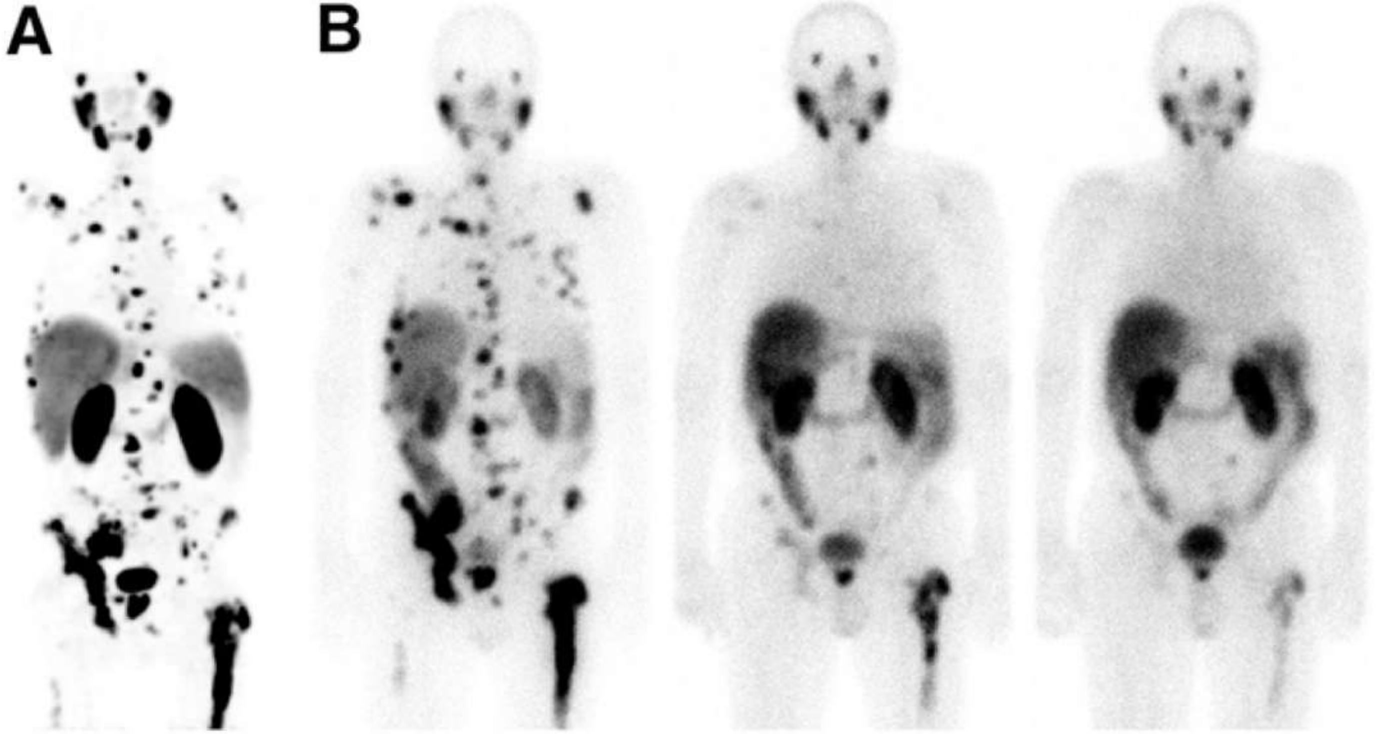
Recent FDA Approval for PSMA Radiopharmaceuticals



PSMA-11 ^{68}Ga → LOCAMETZ®

PSMA-617 ^{177}Lu→ PLUVICTO™

Approved by FDA on 3/23/2022

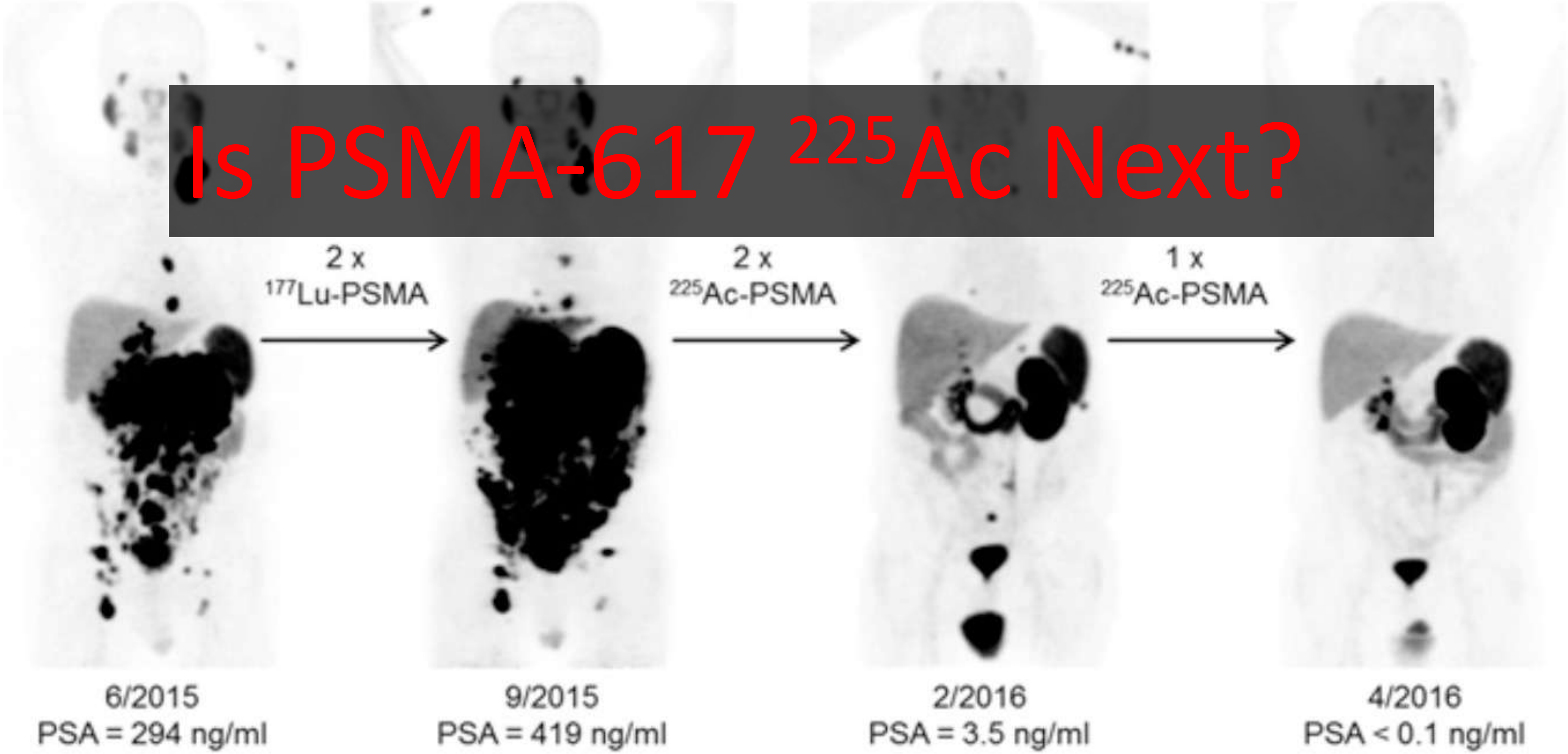


A	B		
12/2014 PSA 387.06 ng/mL	12/2014 PSA 387.06 ng/mL	02/2015 PSA 9.21 ng/mL	04/2015 PSA 1.98 ng/mL
150 MBq ^{68}Ga-PSMA11 PET/CT (MIP) 1 h p.i.	6 GBq ^{177}Lu-PSMA617 Planar scan (GM) 20 h p.i.	6 GBq ^{177}Lu-PSMA617 Planar scan (GM) 20 h p.i.	6 GBq ^{177}Lu-PSMA617 Planar scan (GM) 20 h p.i.

De Vincentis, G, *et al*. *Ann. Oncol*. **2019**;30(11) 1728-1739

Kratochwil, C.; *et al J Nucl Med* **2016,** *57* (8), 1170-6

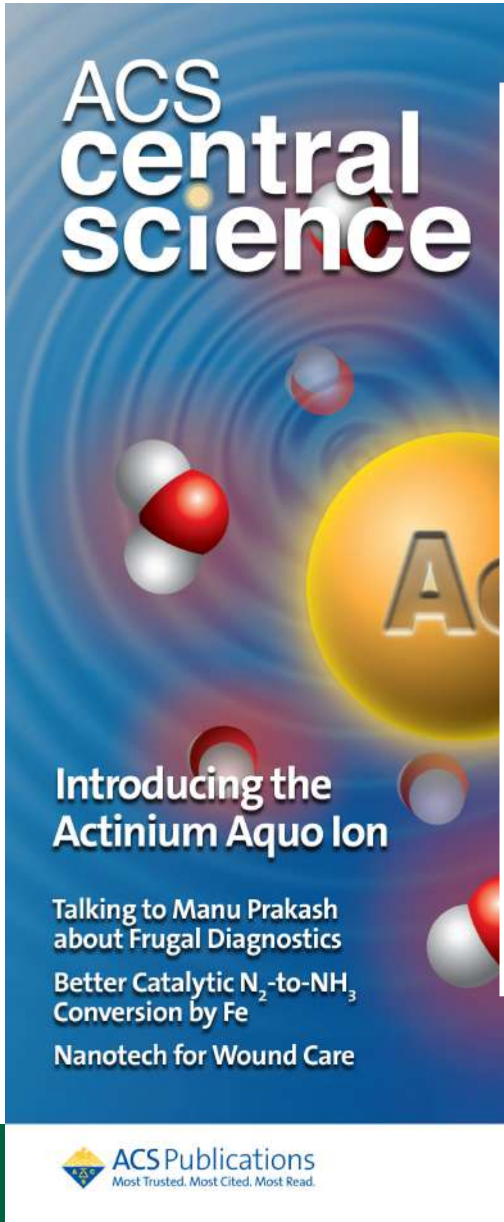
PSMA-617 ^{177}Lu or ^{225}Ac

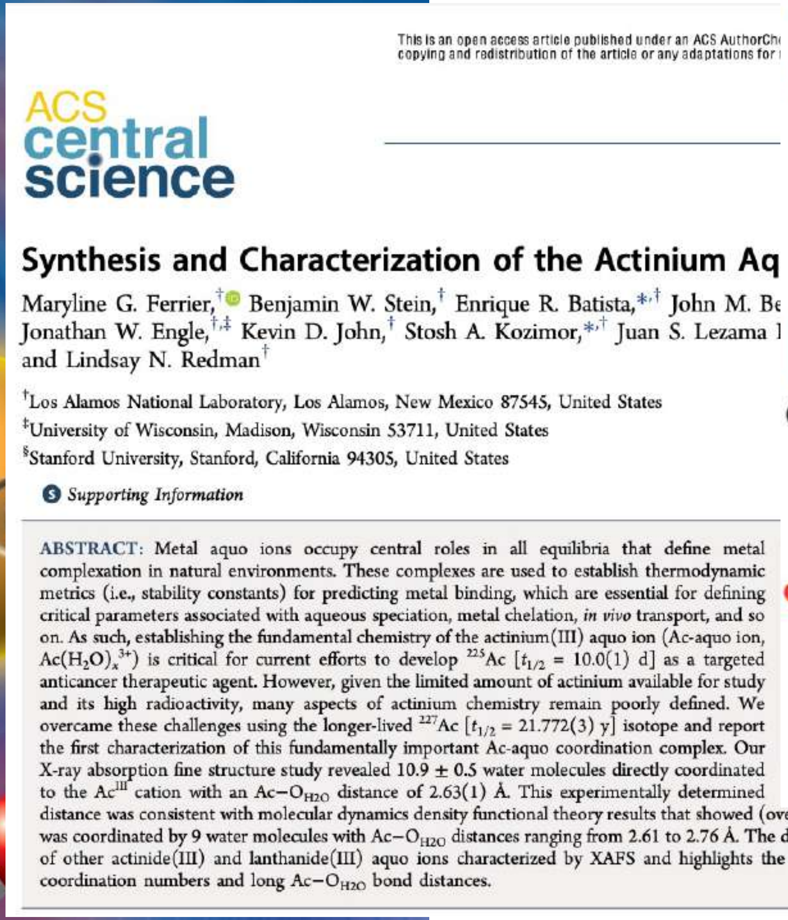


Is PSMA-617 ^{225}Ac Next?

Kratochwil, C.; *et al*. *J. Nucl. Med*. **2016**;57(12) 1941-1944

Gap in Knowledge of Ac Basic Properties





ACS central science

Synthesis and Characterization of the Actinium Aq

Maryline G. Ferrier,† Benjamin W. Stein,† Enrique R. Batista,*,† John M. Be
Jonathan W. Engle,†,‡ Kevin D. John,† Stosh A. Kozimor,*,† Juan S. Lezama
and Lindsay N. Redman†

†Los Alamos National Laboratory, Los Alamos, New Mexico 87545, United States
‡University of Wisconsin, Madison, Wisconsin 53711, United States
§Stanford University, Stanford, California 94305, United States

Supporting Information

ABSTRACT: Metal aquo ions occupy central roles in all equilibria that define metal complexation in natural environments. These complexes are used to establish thermodynamic metrics (i.e., stability constants) for predicting metal binding, which are essential for defining critical parameters associated with aqueous speciation, metal chelation, *in vivo* transport, and so on. As such, establishing the fundamental chemistry of the actinium(III) aquo ion (Ac-aquo ion, $Ac(H_2O)_x^{3+}$) is critical for current efforts to develop ^{225}Ac [$t_{1/2}$ = 10.0(1) d] as a targeted anticancer therapeutic agent. However, given the limited amount of actinium available for study and its high radioactivity, many aspects of actinium chemistry remain poorly defined. We overcome these challenges using the longer-lived ^{227}Ac [$t_{1/2}$ = 21.772(3) y] isotope and report the first characterization of this fundamentally important Ac-aquo coordination complex. Our X-ray absorption fine structure study revealed 10.9 ± 0.5 water molecules directly coordinated to the Ac^{III} cation with an $Ac-O_{H2O}$ distance of 2.63(1) Å. This experimentally determined distance was consistent with molecular dynamics density functional theory results that showed (over the course of 8 ps) that Ac^{III} was coordinated by 9 water molecules with $Ac-O_{H2O}$ distances ranging from 2.61 to 2.76 Å. The data is presented in the context of other actinide(III) and lanthanide(III) aquo ions characterized by XAFS and highlights the uniqueness of the large Ac^{III} coordination numbers and long $Ac-O_{H2O}$ bond distances.

Inorganic Chemistry

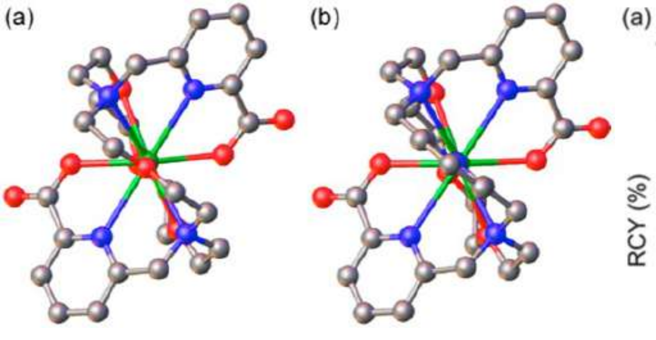
pubs.acs.org/IC Communication

Chelating the Alpha Therapy Radionuclides $^{225}Ac^{3+}$ and $^{213}Bi^{3+}$ with 18-Membered Macrocyclic Ligands Macrodipa and Py-Macrodipa

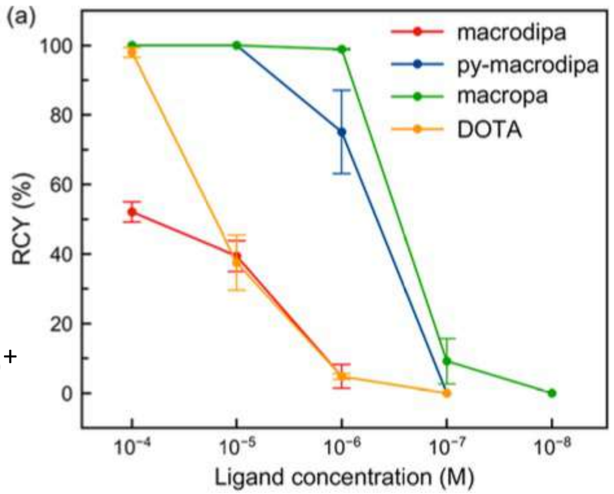
Aohan Hu, Victoria Brown, Samantha N. MacMillan, Valery Radchenko, Hua Yang, Luke Wharton, Caterina F. Ramogida, and Justin J. Wilson*

Cite This: *Inorg. Chem.* 2022, 61, 801−806

Read Online



$Ac(marodipa)^+$ $Ac(py-marodipa)^+$

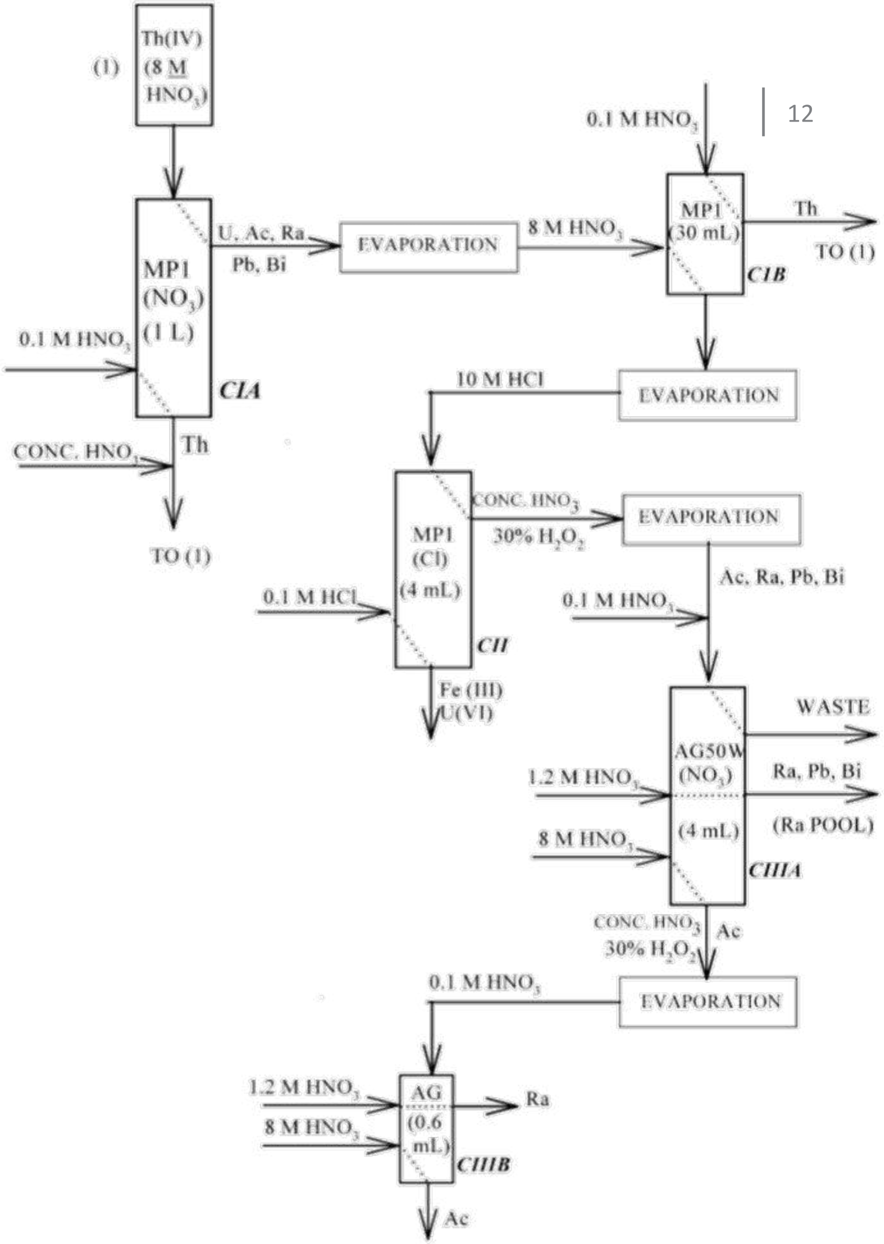


^{225}Ac at Oak Ridge National Laboratory

- ~130 mCi of ^{229}Th recovered from legacy ^{233}U material at ORNL
- ~1 Ci of ^{225}Ac can be produced every year
- Estimated ~8 Ci unrecovered ^{229}Th form ^{233}U stockpile at ORNL
    - 2019 - Isotek Systems and TerraPower took over management of unrecovered ^{229}Th stock via a public-private partnership agreement with the US DOE

$$\boxed{^{233}\mathrm{U}} \xrightarrow[1.6\times10^{5}\ \mathrm{y}]{\alpha} \boxed{^{229}\mathrm{Th}} \xrightarrow[7340\ \mathrm{y}]{\alpha} \boxed{^{225}\mathrm{Ra}} \xrightarrow[14.9\ \mathrm{d}]{\beta^{-}} \boxed{^{225}\mathrm{Ac}} \xrightarrow[9.92\ \mathrm{d}]{\alpha}$$

https://www.isotopes.gov/information/actinium-225 (accessed 4/19/22)
https://www.world-nuclear-news.org/Articles/Partnership-to-produce-medical-isotope-from-legacy (accessed 4/25/22)



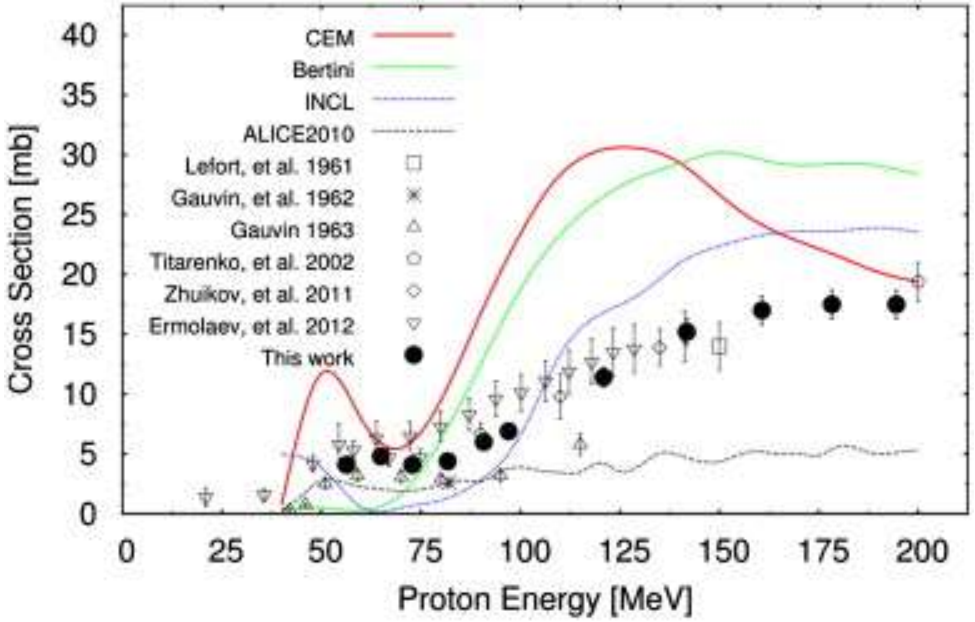
Boll, R. A. et al. *Appl. Radiat. Isot.* **2005,** *62* (5), 667-679.

Tri-Lab Effort for ^{225}Ac Production

https://www.isotopes.gov/accelerator-facilities, (accessed 4/20/22)
https://www.ornl.gov/section/radioisotope-production (accessed on 4/20/22)

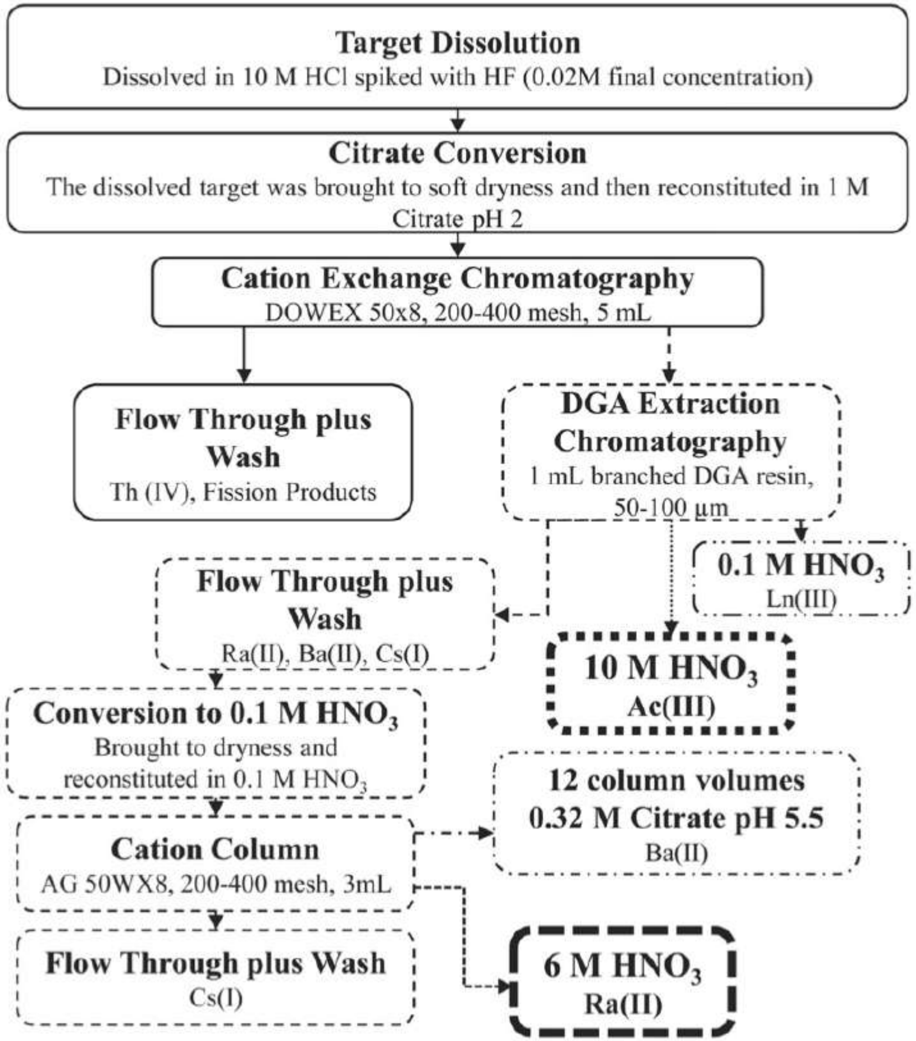
Accelerator Production of ^{225}Ac at LANL and BNL

^{232}Th(p,x)^{225}Ac



Facility	Projected Single Target ^{225}Ac Yields (10-day irradiation)
LANL-IPF(100 MeV, 250-450 µA)	1.3-2.3 Ci
BNL-BLIP (200 MeV, 165 µA)	2.2 Ci

Weidner, J. W.; et al. *Appl. Radiat. Isot.* **2012,** *70* (11), 2602.
https://www.isotopes.gov/information/actinium-225 (accessed on 4/25/22



Target Dissolution
Dissolved in 10 M HCl spiked with HF (0.02M final concentration)

Citrate Conversion
The dissolved target was brought to soft dryness and then reconstituted in 1 M Citrate pH 2

Cation Exchange Chromatography
DOWEX 50x8, 200-400 mesh, 5 mL

Flow Through plus Wash
Th (IV), Fission Products

DGA Extraction Chromatography
1 mL branched DGA resin, 50-100 µm

0.1 M HNO_3
Ln(III)

Flow Through plus Wash
Ra(II), Ba(II), Cs(I)

10 M HNO_3
Ac(III)

Conversion to 0.1 M HNO_3
Brought to dryness and reconstituted in 0.1 M HNO_3

12 column volumes 0.32 M Citrate pH 5.5
Ba(II)

Cation Column
AG 50WX8, 200-400 mesh, 3mL

Flow Through plus Wash
Cs(I)

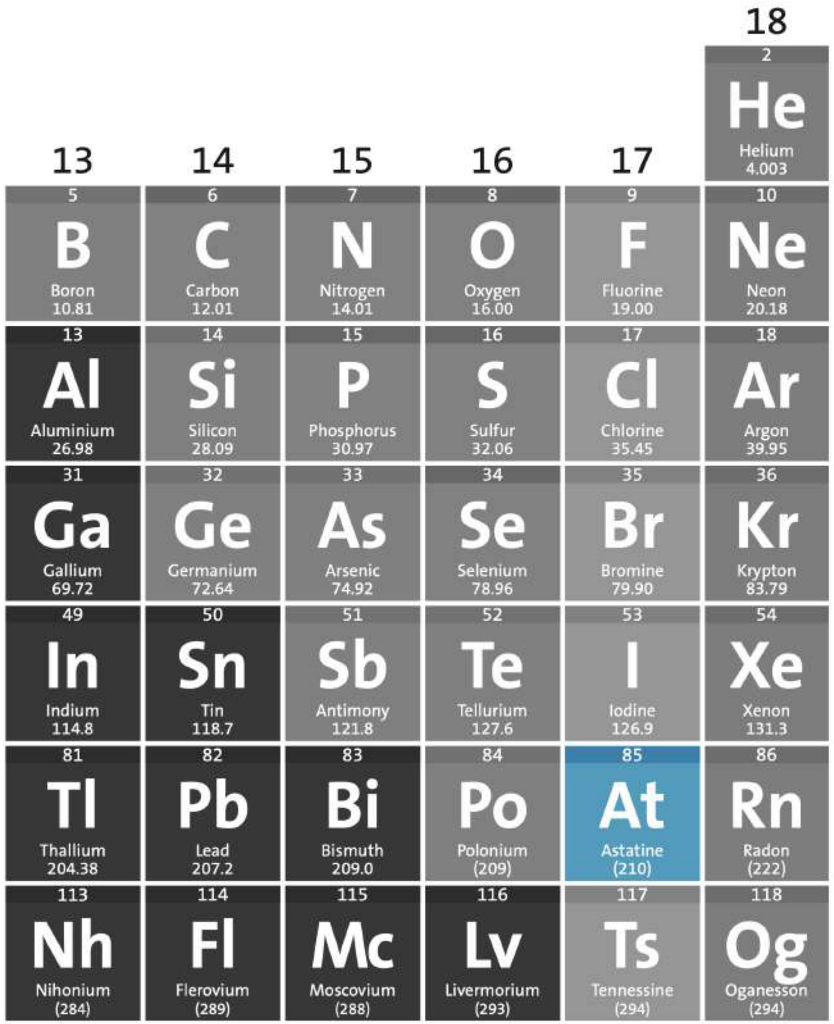
6 M HNO_3
Ra(II)

Mastren, T.; et al. *Sci. Rep.* **2017,** *7* (1), 8216.

^{225}Ac Summary

- The recent success of the PSMA class of radiopharmaceuticals, including the FDA approval of the ^{68}Ga and ^{177}Lu in March of 2022, has led to a rapidly growing interest in ^{225}Ac.
- Barriers towards progress of ^{225}Ac TAT radiopharmaceuticals include
  - Limited supply
  - Lack in understanding of the fundamental properties of ^{225}Ac
- To help address these needs, the DOE IP has initiated the Tri-Lab Effort for accelerator-based ^{225}Ac production.

^{211}At Background



13	14	15	16	17	18
					2 He Helium 4.003
5 B Boron 10.81	6 C Carbon 12.01	7 N Nitrogen 14.01	8 O Oxygen 16.00	9 F Fluorine 19.00	10 Ne Neon 20.18
13 Al Aluminium 26.98	14 Si Silicon 28.09	15 P Phosphorus 30.97	16 S Sulfur 32.06	17 Cl Chlorine 35.45	18 Ar Argon 39.95
31 Ga Gallium 69.72	32 Ge Germanium 72.64	33 As Arsenic 74.92	34 Se Selenium 78.96	35 Br Bromine 79.90	36 Kr Krypton 83.79
49 In Indium 114.8	50 Sn Tin 118.7	51 Sb Antimony 121.8	52 Te Tellurium 127.6	53 I Iodine 126.9	54 Xe Xenon 131.3
81 Tl Thallium 204.38	82 Pb Lead 207.2	83 Bi Bismuth 209.0	84 Po Polonium (209)	85 At Astatine (210)	86 Rn Radon (222)
113 Nh Nihonium (284)	114 Fl Flerovium (289)	115 Mc Moscovium (288)	116 Lv Livermorium (293)	117 Ts Tennessine (294)	118 Og Oganesson (294)

https://www.acs.org/content/acs/en/education/whatischemistry/periodictable.html (accessed 4/19/22)

^{211}At α-particles

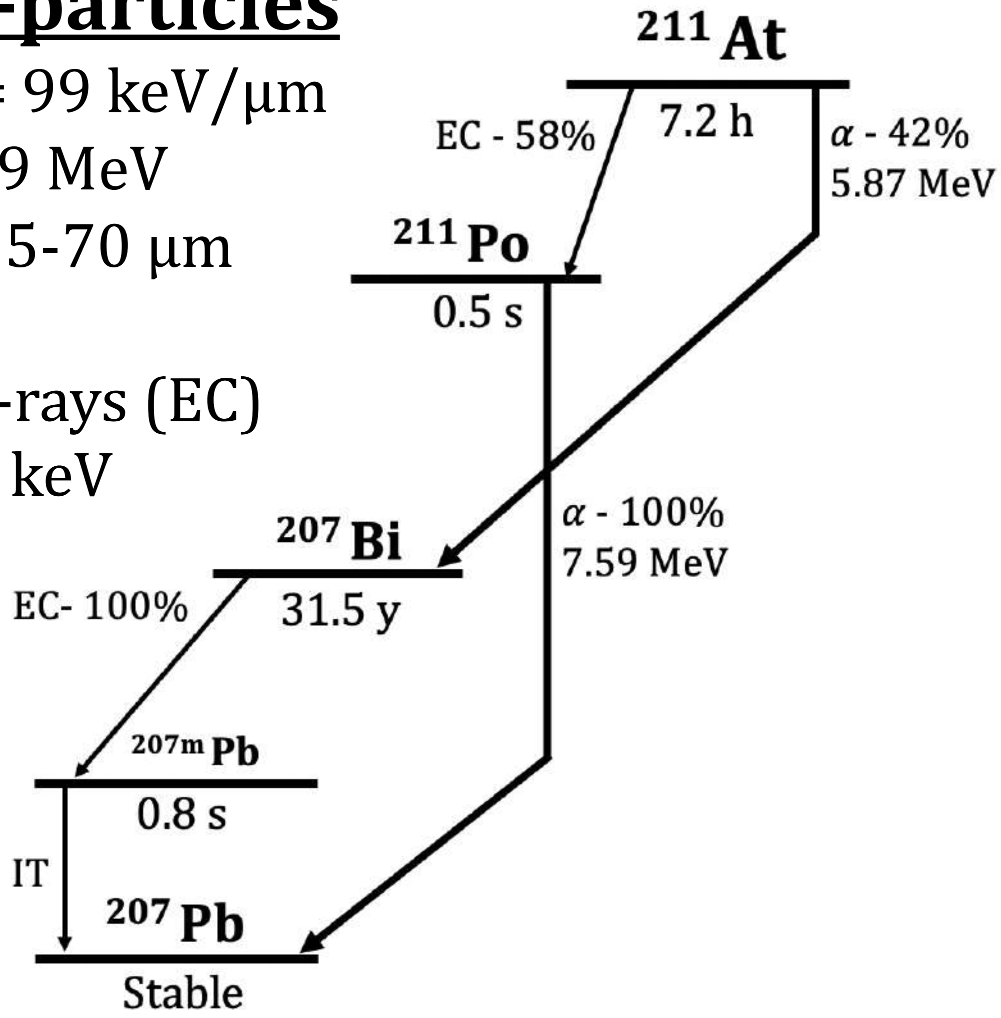
$\mathrm{LET}_{\mathrm{mean}}$ = 99 keV/μm

E_{avg} = 6.79 MeV

range = 55-70 μm

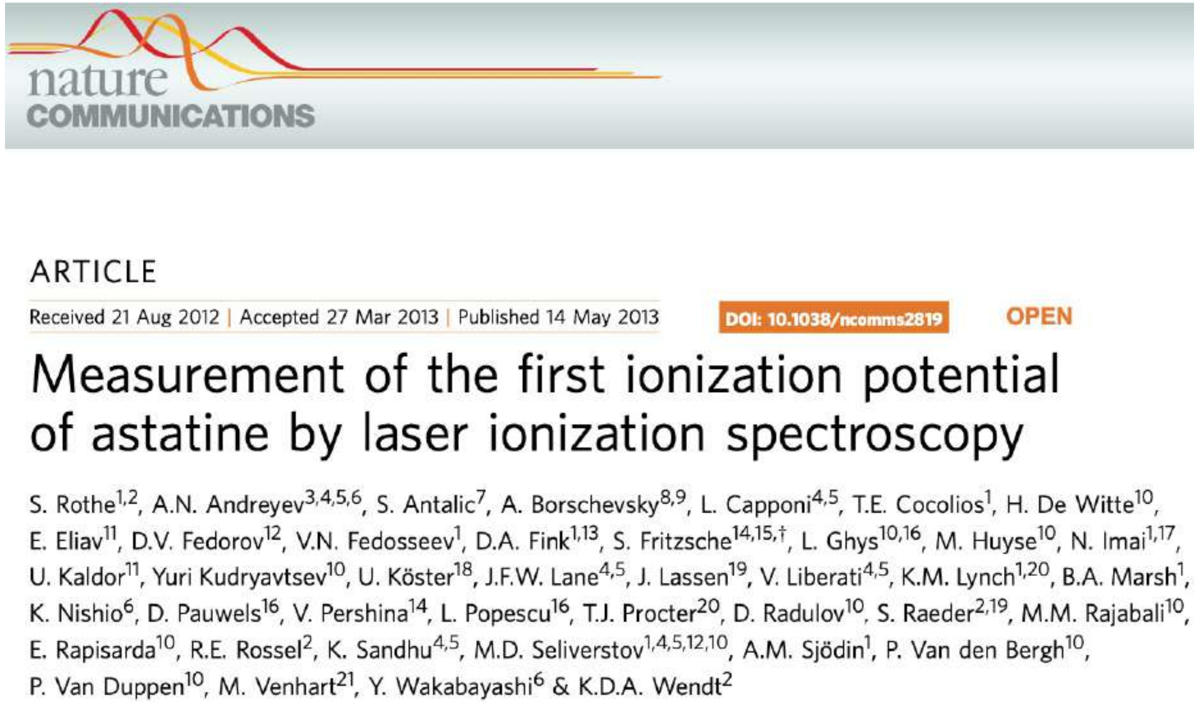
Imaging:

^{211}Po K X-rays (EC)
77–92 keV



Adapted from Zalutsky, M. and Pruszynski M. *Curr. Radiopharm.* **2008**, *1*, 177−196.

Gap in Knowledge of At Basic Properties



nature COMMUNICATIONS

ARTICLE

Received 21 Aug 2012 | Accepted 27 Mar 2013 | Published 14 May 2013 DOI: 10.1038/ncomms2819 OPEN

Measurement of the first ionization potential of astatine by laser ionization spectroscopy

S. Rothe[1,2], A.N. Andreyev[3,4,5,6], S. Antalic[7], A. Borschevsky[8,9], L. Capponi[4,5], T.E. Cocolios[1], H. De Witte[10], E. Eliav[11], D.V. Fedorov[12], V.N. Fedosseev[1], D.A. Fink[1,13], S. Fritzsche[14,15,†], L. Ghys[10,16], M. Huyse[10], N. Imai[1,17], U. Kaldor[11], Yuri Kudryavtsev[10], U. Köster[18], J.F.W. Lane[4,5], J. Lassen[19], V. Liberati[4,5], K.M. Lynch[1,20], B.A. Marsh[1], K. Nishio[6], D. Pauwels[16], V. Pershina[14], L. Popescu[16], T.J. Procter[20], D. Radulov[10], S. Raeder[2,19], M.M. Rajabali[10], E. Rapisarda[10], R.E. Rossel[2], K. Sandhu[4,5], M.D. Seliverstov[1,4,5,12,10], A.M. Sjödin[1], P. Van den Bergh[10], P. Van Duppen[10], M. Venhart[21], Y. Wakabayashi[6] & K.D.A. Wendt[2]

nature COMMUNICATIONS

ARTICLE

Check for updates

https://doi.org/10.1038/s41467-020-17599-2 OPEN

The electron affinity of astatine

David Leimbach[1,2,3✉], Julia Karls[2], Yangyang Guo[4], Rizwan Ahmed[5], Jochen Ballof[1,6], Lars Bengtsson[2], Ferran Boix Pamies[1], Anastasia Borschevsky[4], Katerina Chrysalidis[1,3], Ephraim Eliav[7], Dmitry Fedorov[8], Valentin Fedosseev[1], Oliver Forstner[9,10], Nicolas Galland[11], Ronald Fernando Garcia Ruiz[1,12], Camilo Granados[1], Reinhard Heinke[3], Karl Johnston[1], Agota Koszorus[13], Ulli Köster[14], Moa K. Kristiansson[15], Yuan Liu[16], Bruce Marsh[1], Pavel Molkanov[8], Lukáš F. Pašteka[17], João Pedro Ramos[20], Eric Renault[11], Mikael Reponen[18], Annie Ringvall-Moberg[1,2], Ralf Erik Rossel[1], Dominik Studer[3], Adam Vernon[19], Jessica Warbinek[2,3], Jakob Welander[2], Klaus Wendt[3], Shane Wilkins[1], Dag Hanstorp[2] & Sebastian Rothe[1]

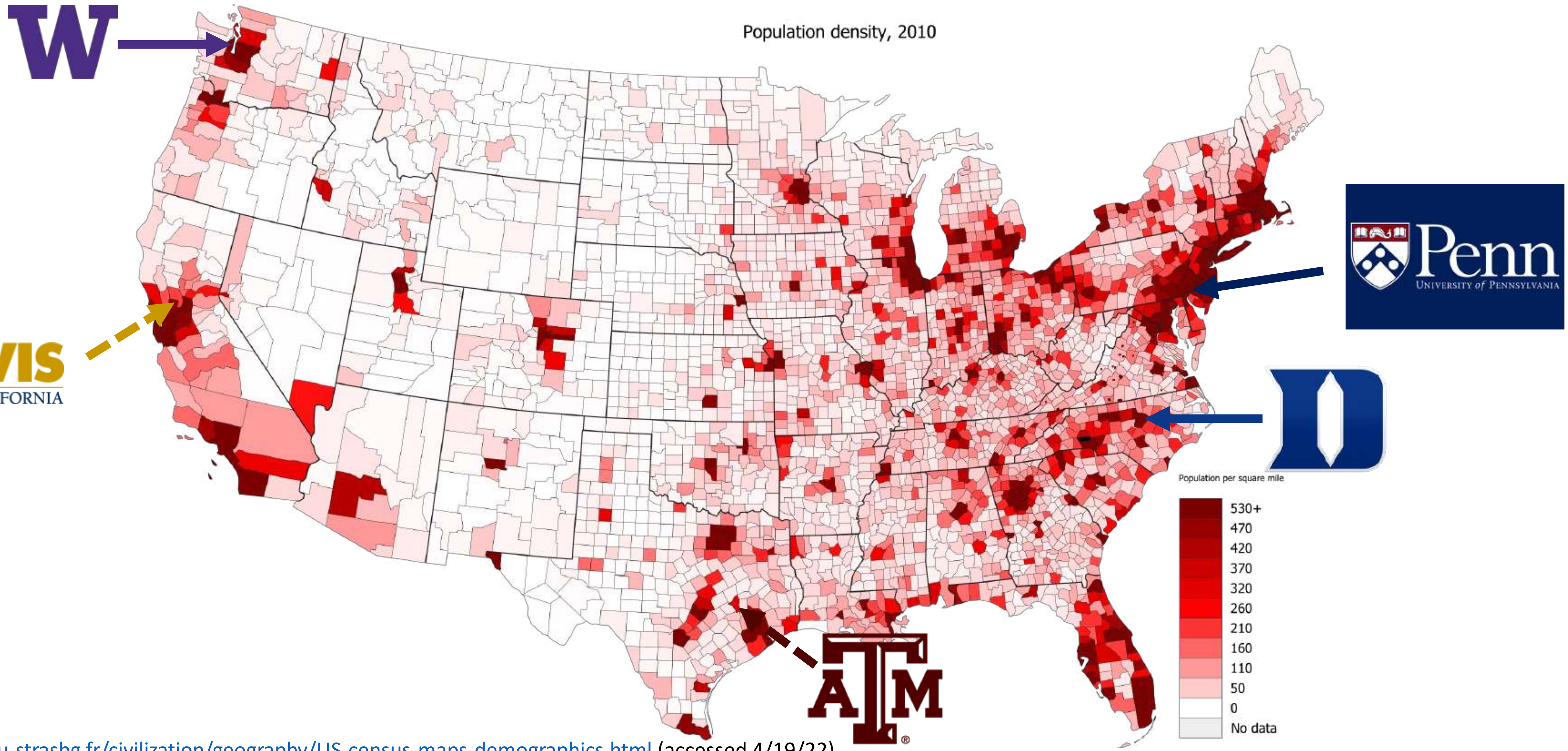
$$\mathrm{At}_{(g)} \rightarrow \mathrm{At}^{+}_{(g)} + e^{-} \quad 9.31751(8)\ \mathrm{eV}$$

$$\mathrm{At}_{(g)} + e^{-} \rightarrow \mathrm{At}^{-}_{(g)} \quad 2.41578(7)\ \mathrm{eV}$$

Published on May 14, 2013!

Published on July 30, 2020!

^{211}At Production Sites in US

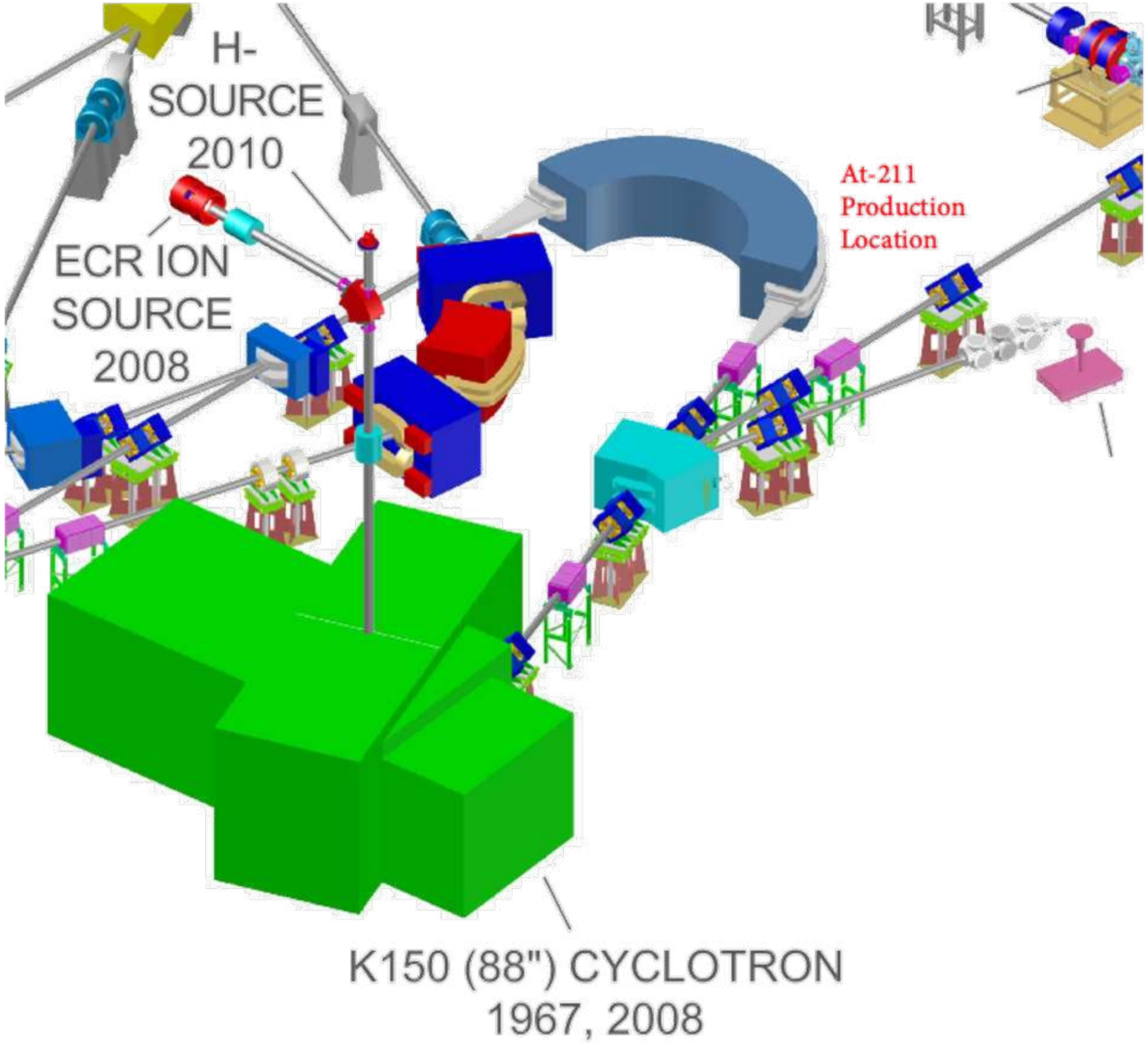


http://ecpmlangues.u-strasbg.fr/civilization/geography/US-census-maps-demographics.html (accessed 4/19/22)

^{211}At Production at Texas A&M

$^{209}Bi + \alpha \rightarrow\ ^{211}At + 2n$

- K150 Cyclotron
- Energy: 28.8 MeV
- $I\alpha_{Avg}$: 2–12.5 pμA
- Length: 8–18 h
- Yield: 8–100 mCi



^{211}At Chemistry at Texas A&M

Production

$^{209}Bi(\alpha,2n)^{211}At$

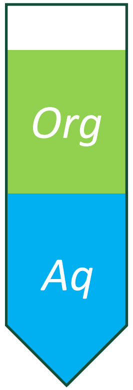
Dissolution of Target

8–12 M HNO_3

Experimental Chemistry

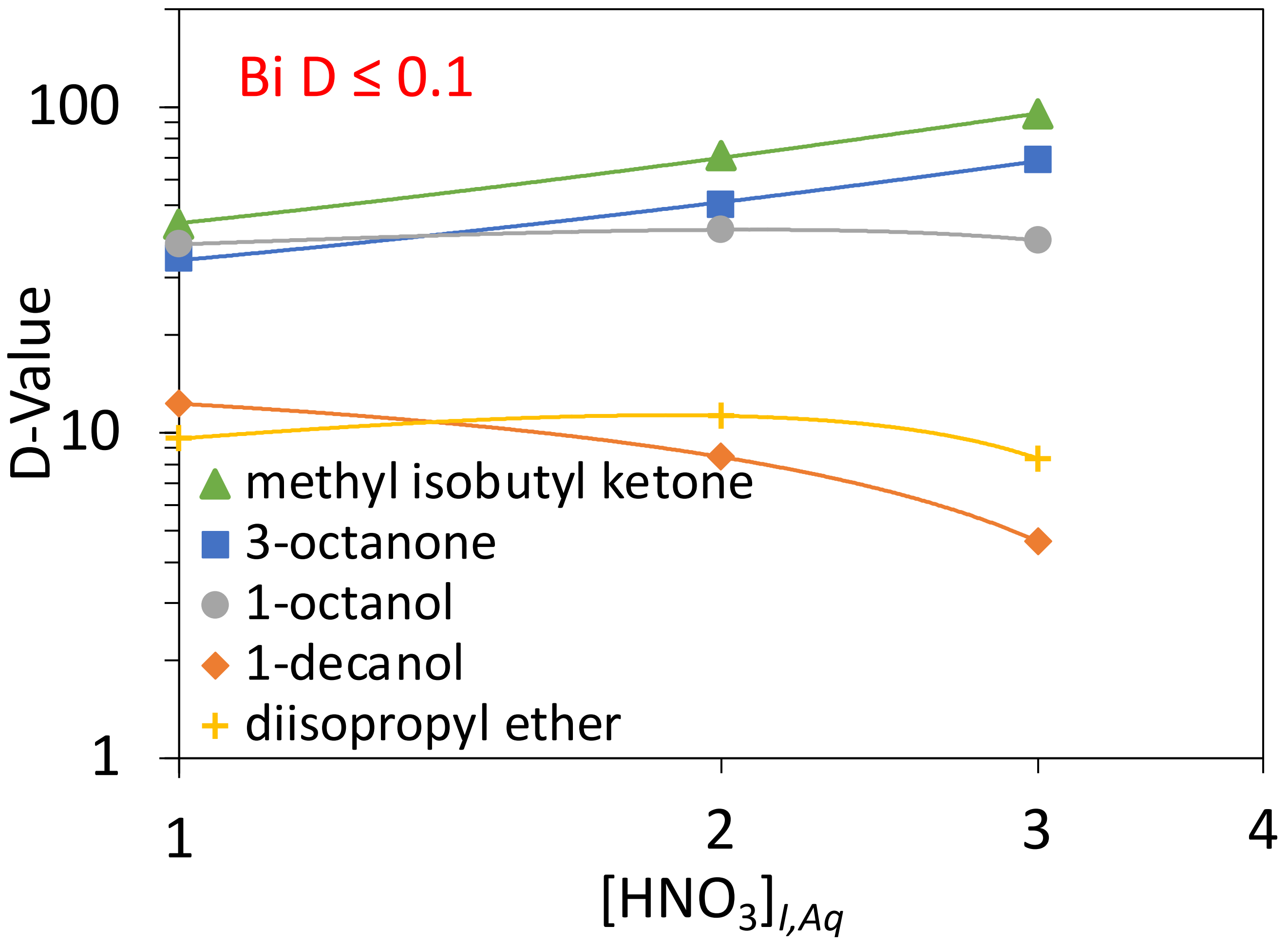
Separations and Fundamental

^{211}At Separations: Solvent Extraction



$$D = \frac{C_{Org}}{C_{Aq}}$$

Solvent	Dielectric Constant
methyl isobutyl ketone	13.11
3-octanone	10.5
1-octanol	10.3
1-decanol	7.93
diisopropyl ether	3.81

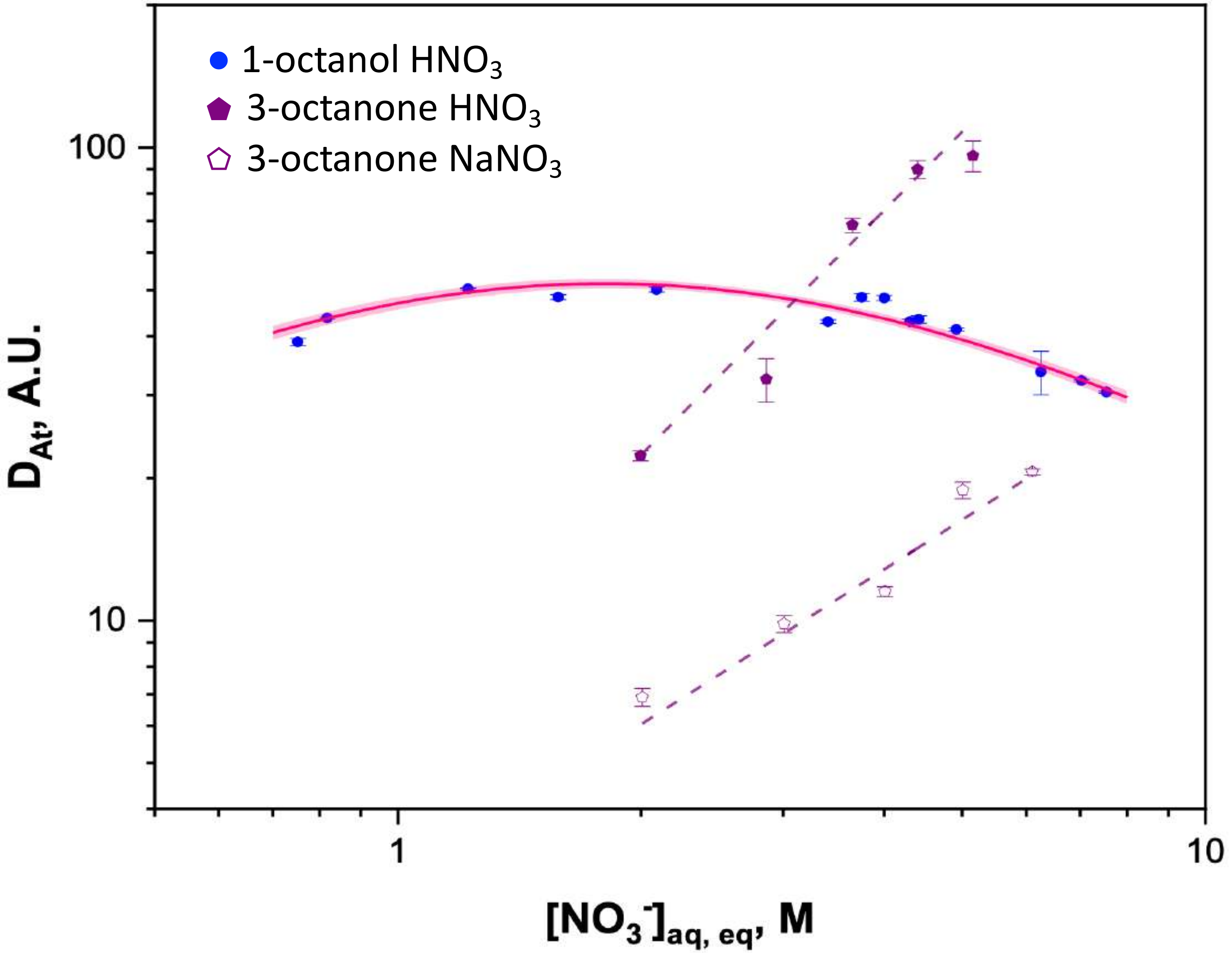


Bi D ≤ 0.1

Burns, J. D. et al. *Chem. Commun.* **2020**, *56* (63), 9004.
Burns, J. D. et al. 2021 Rapid At-211 Purification Method, US Patent Application PCT/US21/25156, filled March 2021. Patent Pending.

Extraction of ^{211}At: ketone vs alcohol

- 1-octanol extraction
  - Peaks 2–3 M HNO_3
- 3-octanone extraction
  - Dependance on $[NO_3^-]$
  - Stoichiometry $At:NO_3^- \rightarrow 1:1$



Burns, J. D. et al. *Inorg. Chem.* ***in revision***

^{211}At Chemistry in HNO_3

Inorganica Chimica Acta 362 (2009) 2654–2661

Contents lists available at ScienceDirect

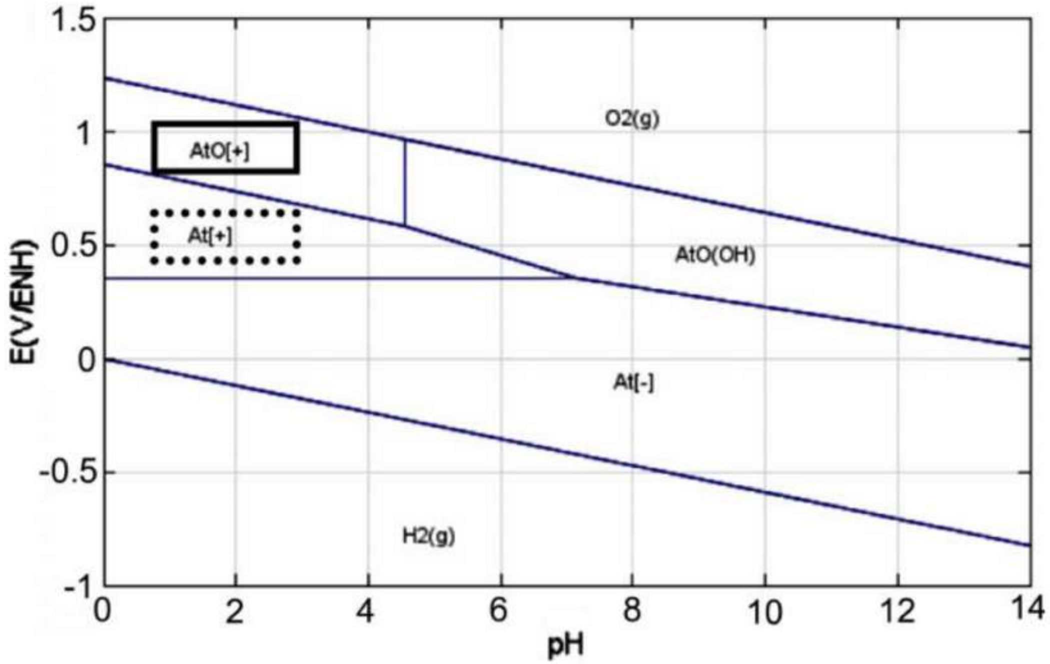
Inorganica Chimica Acta

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

ELSEVIER

Determination of stability constants between complexing agents and At(I) and At(III) species present at ultra-trace concentrations

J. Champion[a], C. Alliot[b], S. Huclier[a], D. Deniaud[c], Z. Asfari[d], G. Montavon[a,*]



Champion, J. et al. *Inorganica Chim. Acta* **2009**, *362* (8), 2654-2661.

PCCP

PAPER

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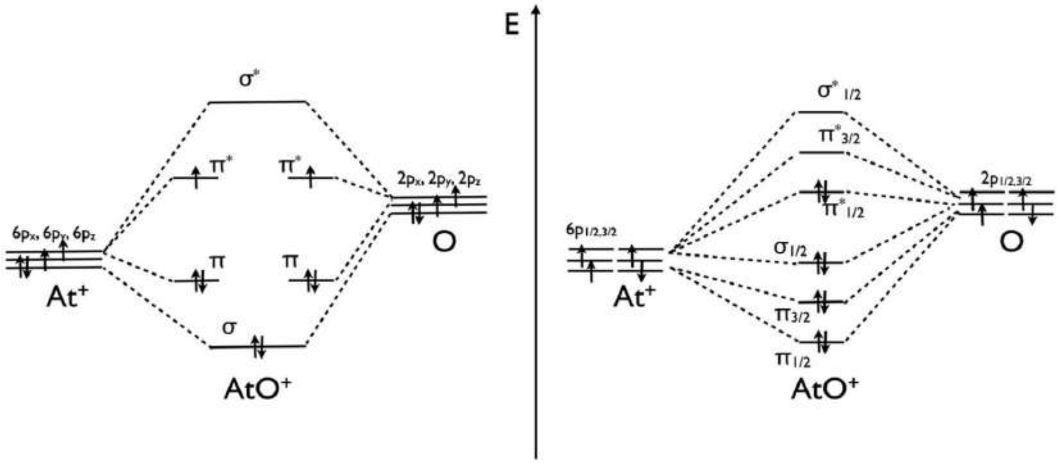
Cite this: *Phys. Chem. Chem. Phys.*, 2014, 16, 9238

Electronic structure investigation of the evanescent AtO^+ ion†

André Severo Pereira Gomes,*[a] Florent Réal,[a] Nicolas Galland,[b] Celestino Angeli,[c] Renzo Cimiraglia[c] and Valérie Vallet[a]

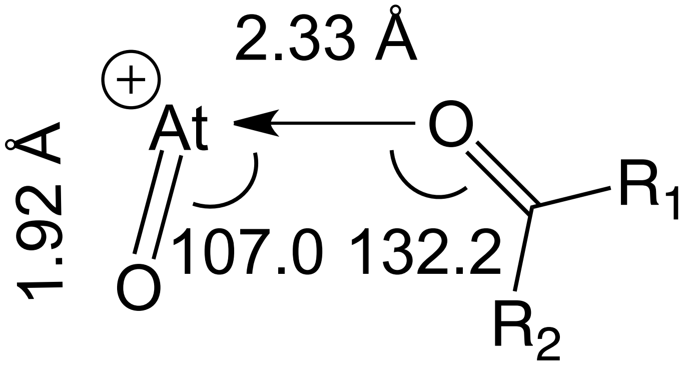


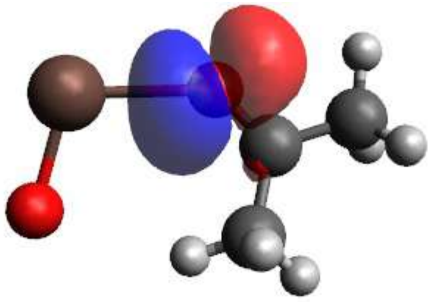
Spin-Orbit
Off

Spin-Orbit
On

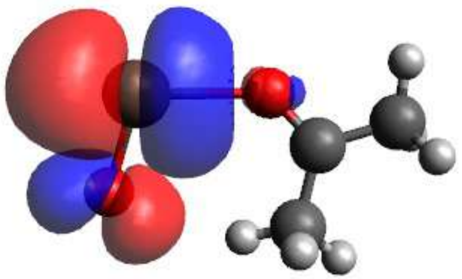
Severo Pereira Gomes, A. et al. *Phys.Chem.Chem.Phys.* **2014**, *16*, 9238-9248.

O Lone Pair Interaction with AtO^+ π*



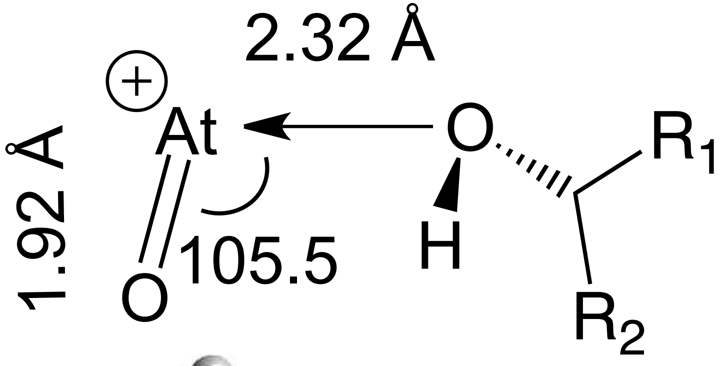


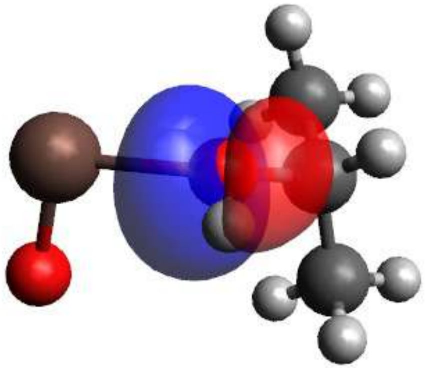
NBO Donor O sp^2
Occ. = 1.67 e^-



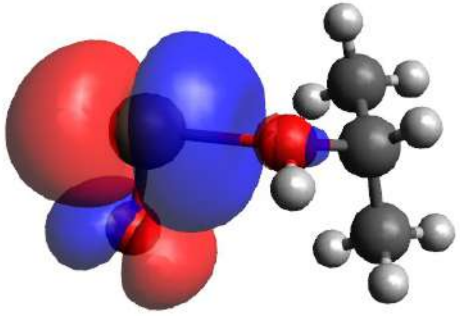
NBO Acceptor AtO^+ π*
Occ. = 0.29 e^-

$\Delta G = -47.2$ kcal/mol





NBO Donor O sp^3
Occ. = 1.78 e^-

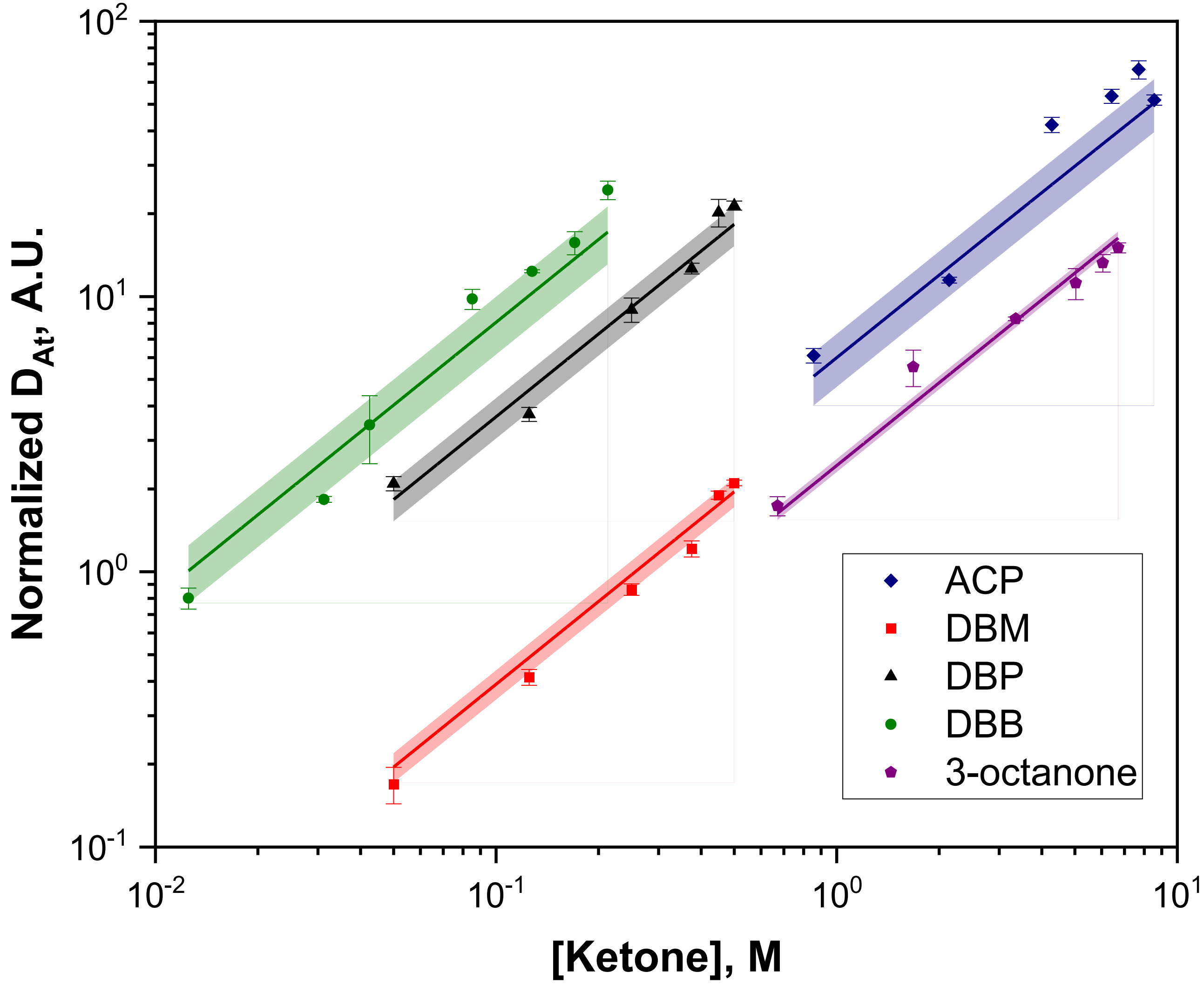


NBO Acceptor AtO^+ π*
Occ. = 0.24 e^-

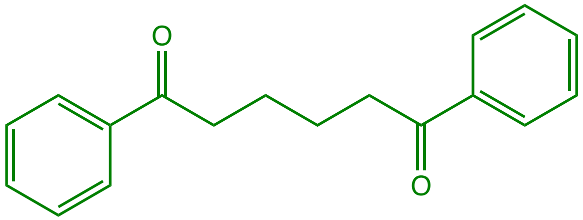
$\Delta G = -42.6$ kcal/mol

Burns, J. D. et al. *Chem. Commun.* **2020**, *56* (63), 9004.

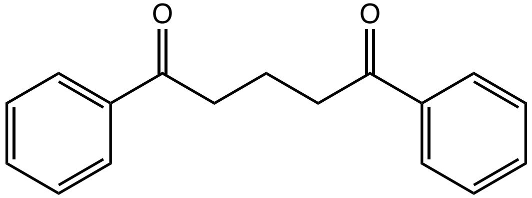
^{211}At Extraction Speciation



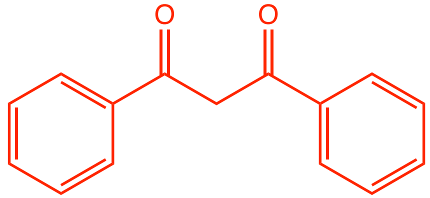
Burns, J. D. et al. *Inorg. Chem.* **in review**.



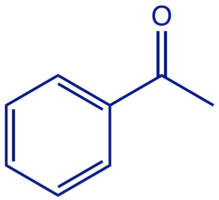
1,4-Dibenzoylbutane



1,3-Dibenzoylpropane



Dibenzoylmethane



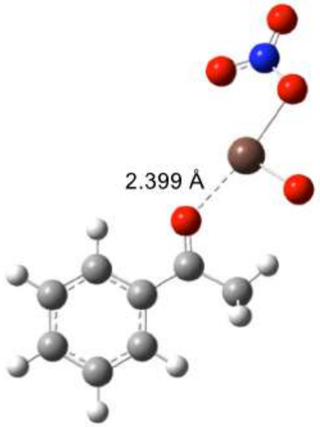
acetophenone

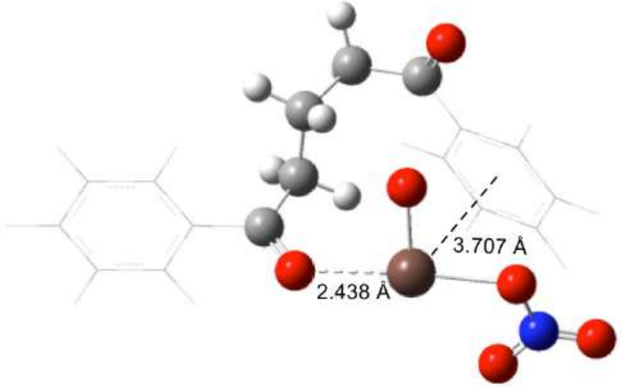
3-octanone

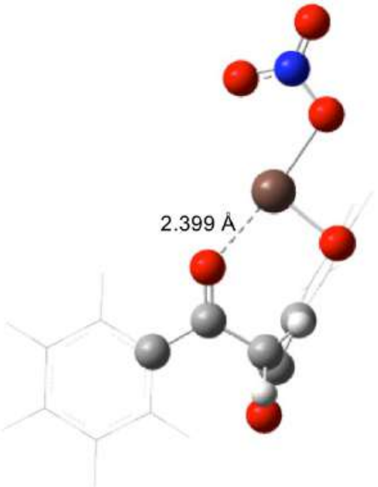
^{211}At Extraction Speciation Cont.

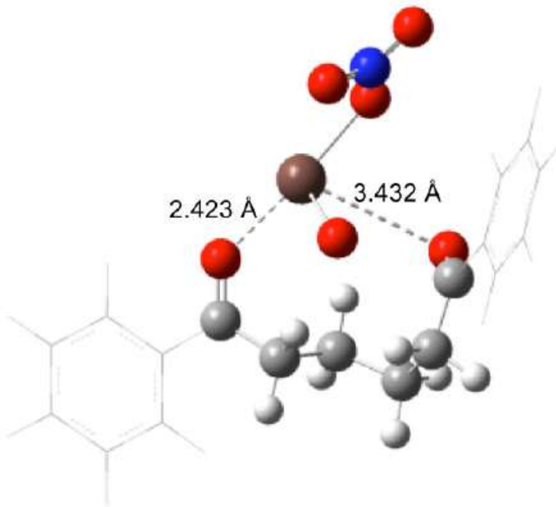
Monodentate

Bidentate





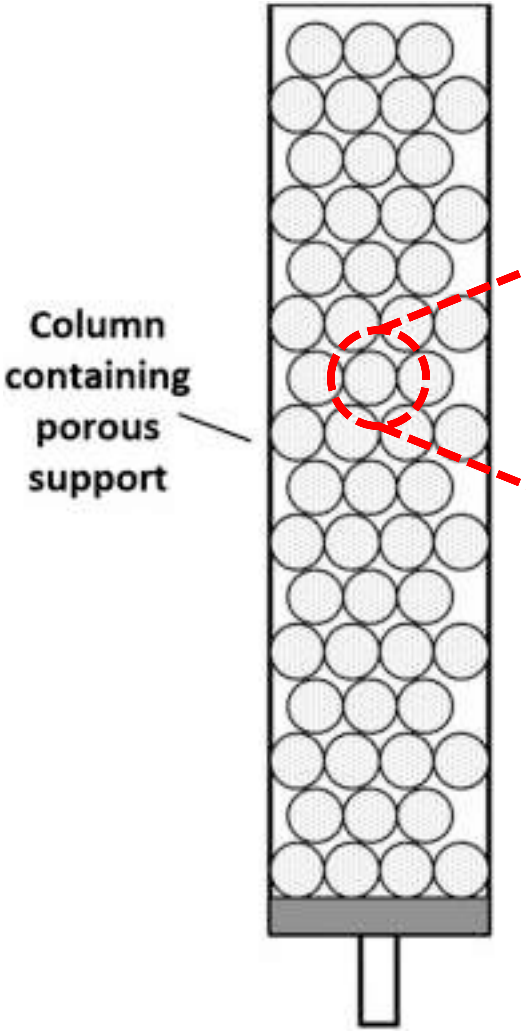


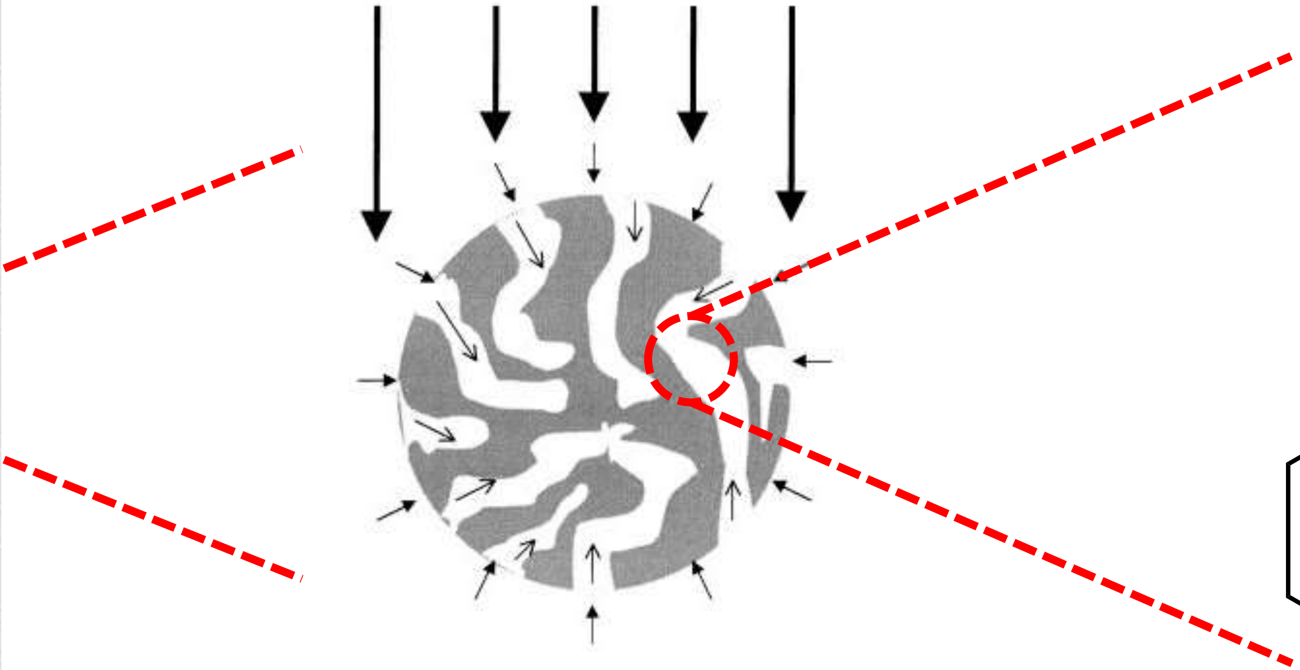


Solvent	Mode	ΔG(sol) / kcal•mol^{-1}	E_d / kcal•mol^{-1}
3-octanone	Mono	-11.91	4.21
acetophenone	Mono	-13.56	1.00
dibenzoylmethane	Mono	-12.06	3.23
1,3-dibenzoylpropane	Mono	-15.58	0.71
	Bi O O	-11.27	4.29
	Bi O phenyl	-14.32	7.99
1,4-dibenzoylbutane	Mono	-11.58	3.20
	Bi O O	-19.04	4.52
	Bi O phenyl	-17.86	4.39

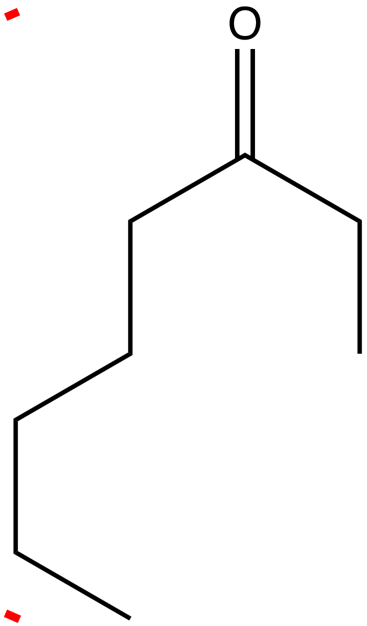
Burns, J. D. et al. *Inorg. Chem.* **in review**.

Extraction Chromatography





Amberchrom® CG300
Support: styrene-divinylbenzene
Particle Size: 50–100 µm
Pore Size: 0.7 mL/g pore volume
300 Å mean pore size
Surface Area: 700 m^2/g

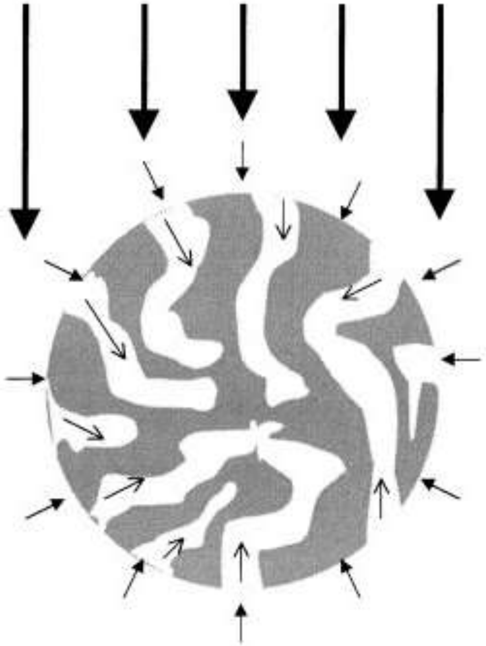


3-octanone

FDA UNII: 79173B4107

fdasis.nlm.nih.gov/srs/unii/79173b4107

Characterization of Impregnated Resin



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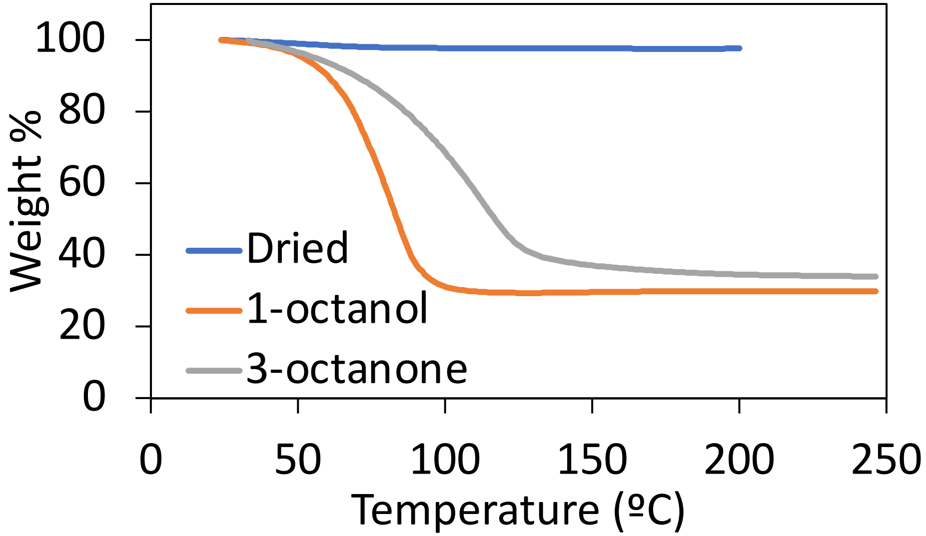
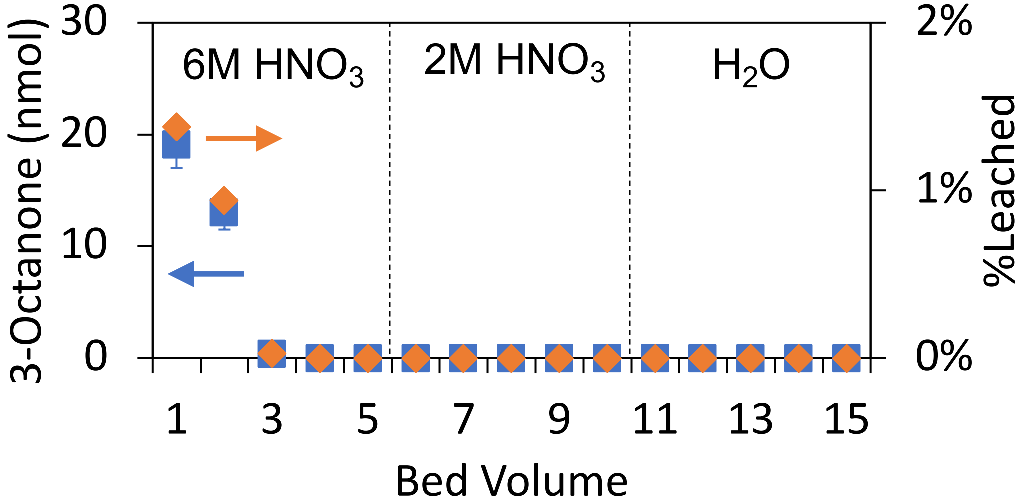
J. D. Burns *et al.*, *Sep. Purif. Technol.* **2021**, *256*, 117794 .

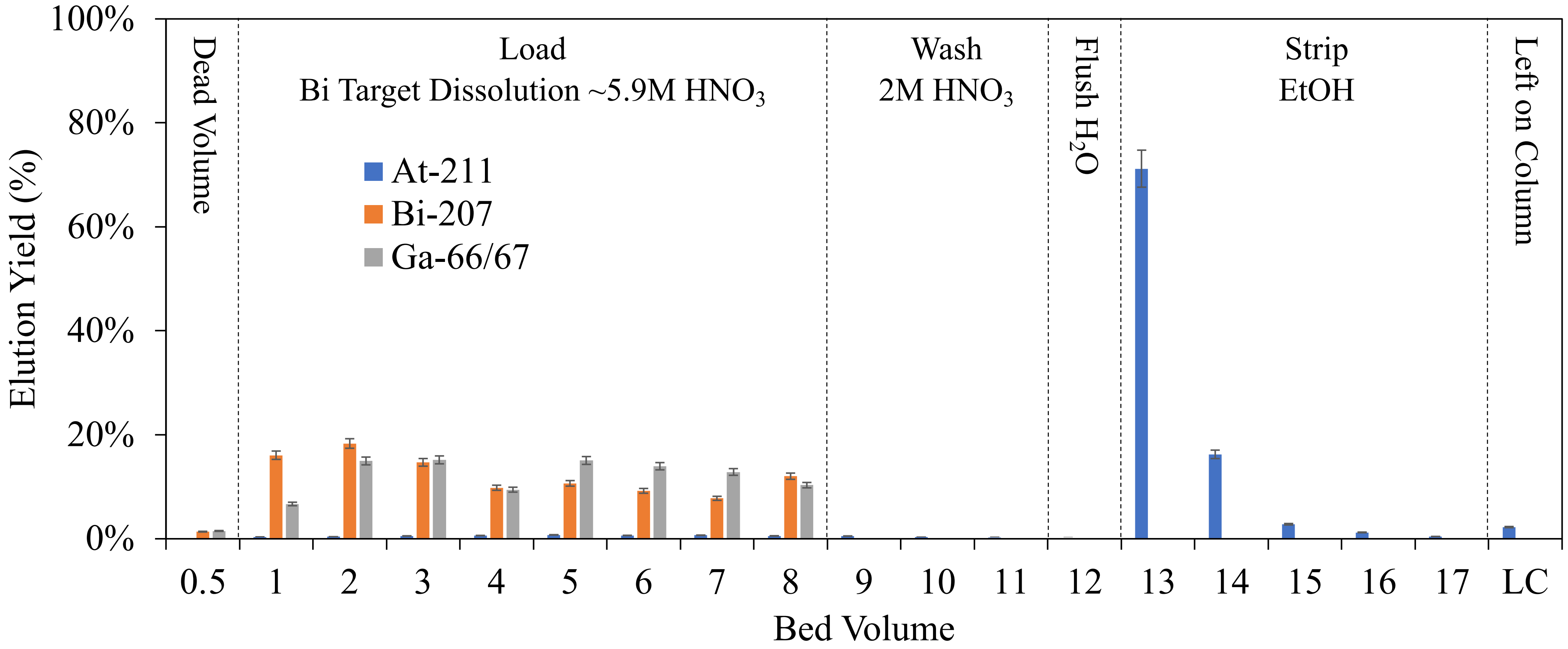




At-211 Separation: Extraction Chromatography

Oct=O on Amberchrom® CG300
Bed Volume = 0.5 mL
Bed Height = 12.99 mm

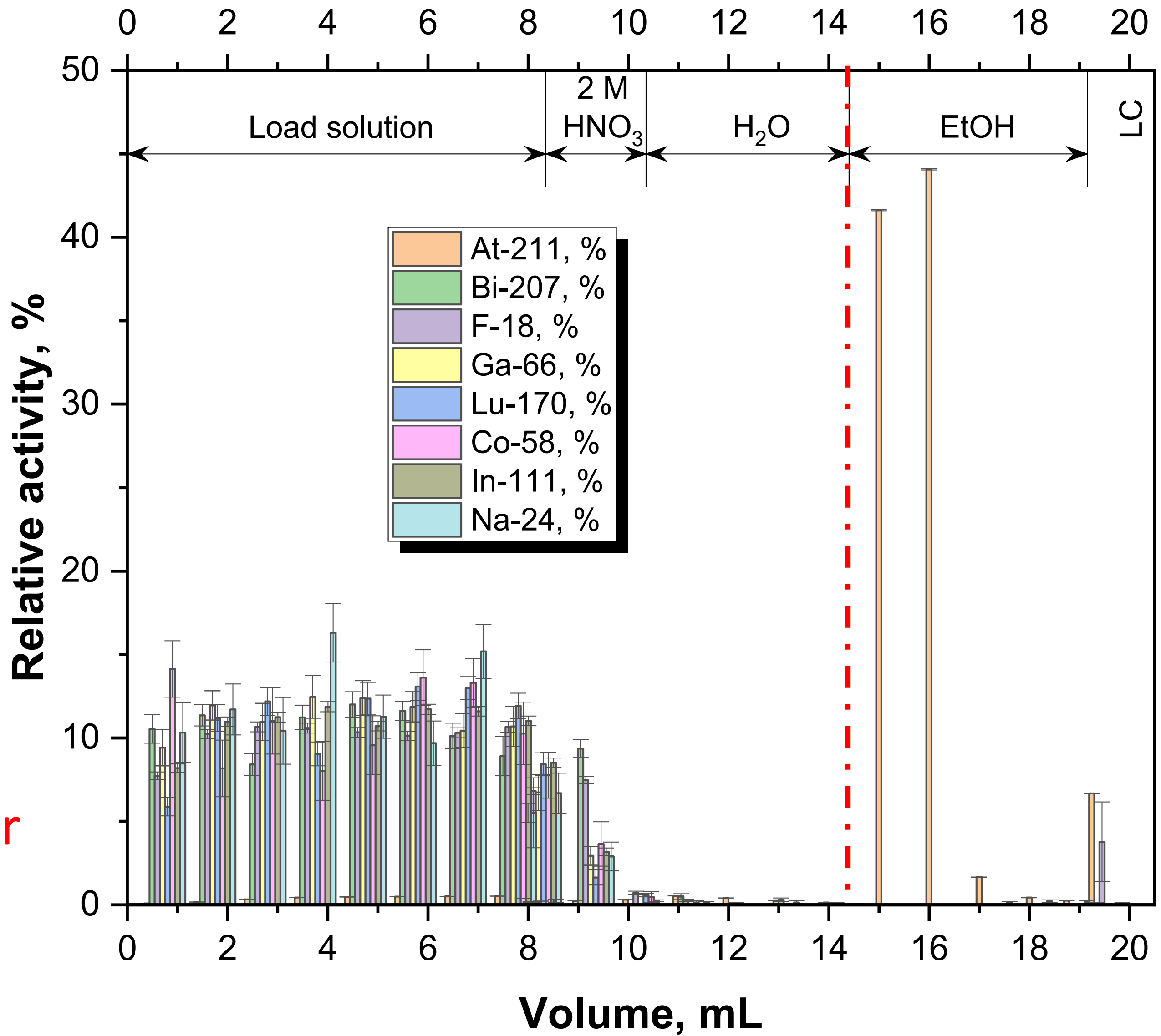
ID = 7 mm
9.8 mCi ^{211}At
1.7 M Bi^{3+}



J. D. Burns *et al.*, *Sep. Purif. Technol.* **2021**, *256*, 117794 .

Cartridge Column Loading

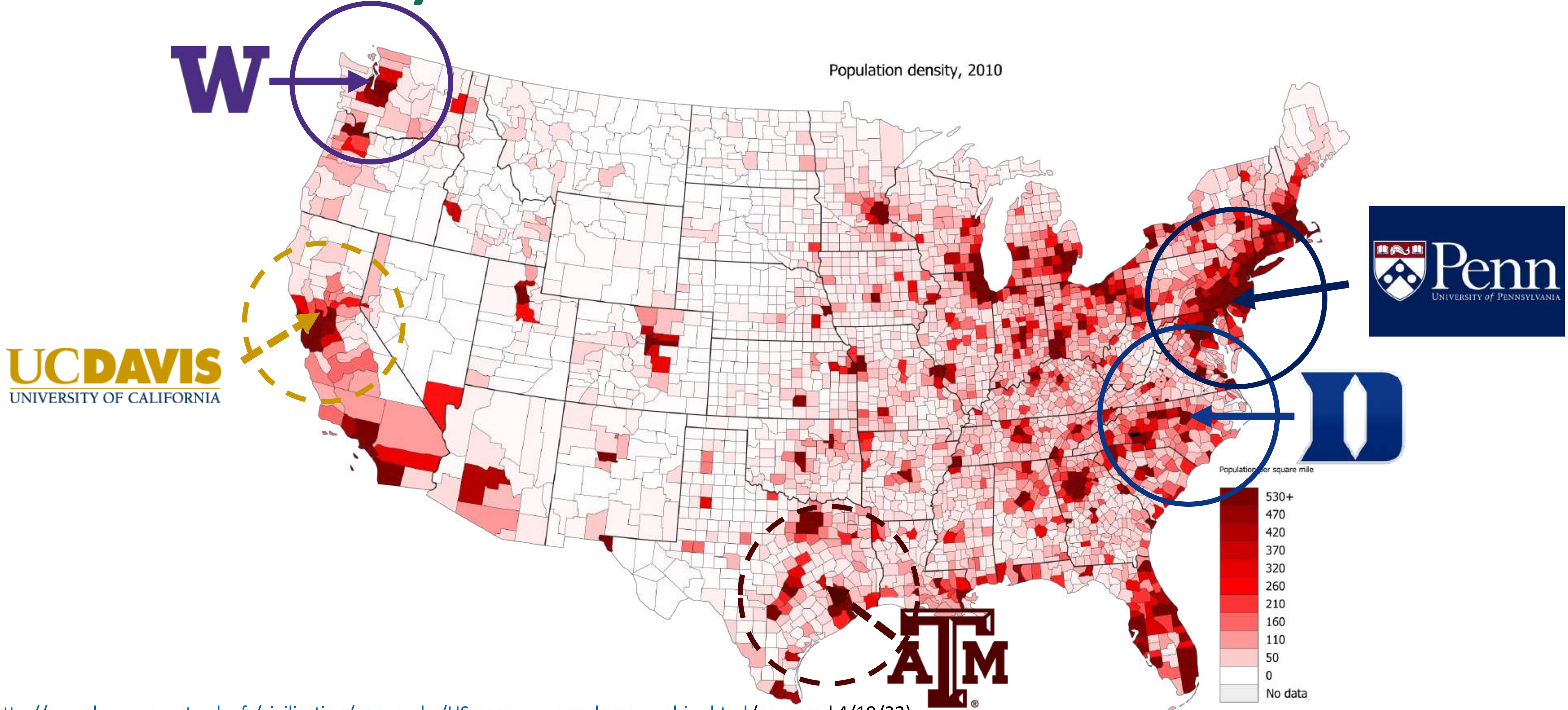
- 3-octanone impregnated on Amberchrom® CG300
- ID = 7 mm
- Bed Volume = 0.5 mL
- Bed Height = 12.99 mm
- ~60 mCi ^{211}At
- ~0.5 M Bi^{3+}
- **<20 min to recover ^{211}At**



Free liquid removed from cartridge and held for 3.5 & 34 h between Wash and Strip

Tereshatov, E. E.; et al. *Chem. Eng. J.* **2022**, *442*, 136176.

3.5 h Proximity from ^{211}At Production Sites in US



http://ecpmlangues.u-strasbg.fr/civilization/geography/US-census-maps-demographics.html (accessed 4/19/22)

Summary

- Targeted Radionuclide Therapy, specifically Targeted Alpha Therapy, is a very promising emerging approach to cancer treatment.
- Next to ^{223}Ra, ^{225}Ac and ^{211}At are two of the most promising TAT radionuclides.
- The main challenges for both are:
  - Limited supply
  - Limited understanding of chemical properties.

Acknowledgements ^{211}At

- Texas A&M Cyclotron Institute Staff
- Radiological Safety Program Staff
- DOE Isotope Program DE-SC0020958
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- NNSA DE-NA0003841
- Los Alamos National Laboratory
- TAMU: Bright Chair, T3 Grant, NLO

Isotope Program
U.S. Department of Energy

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Thank you!

Questions?

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