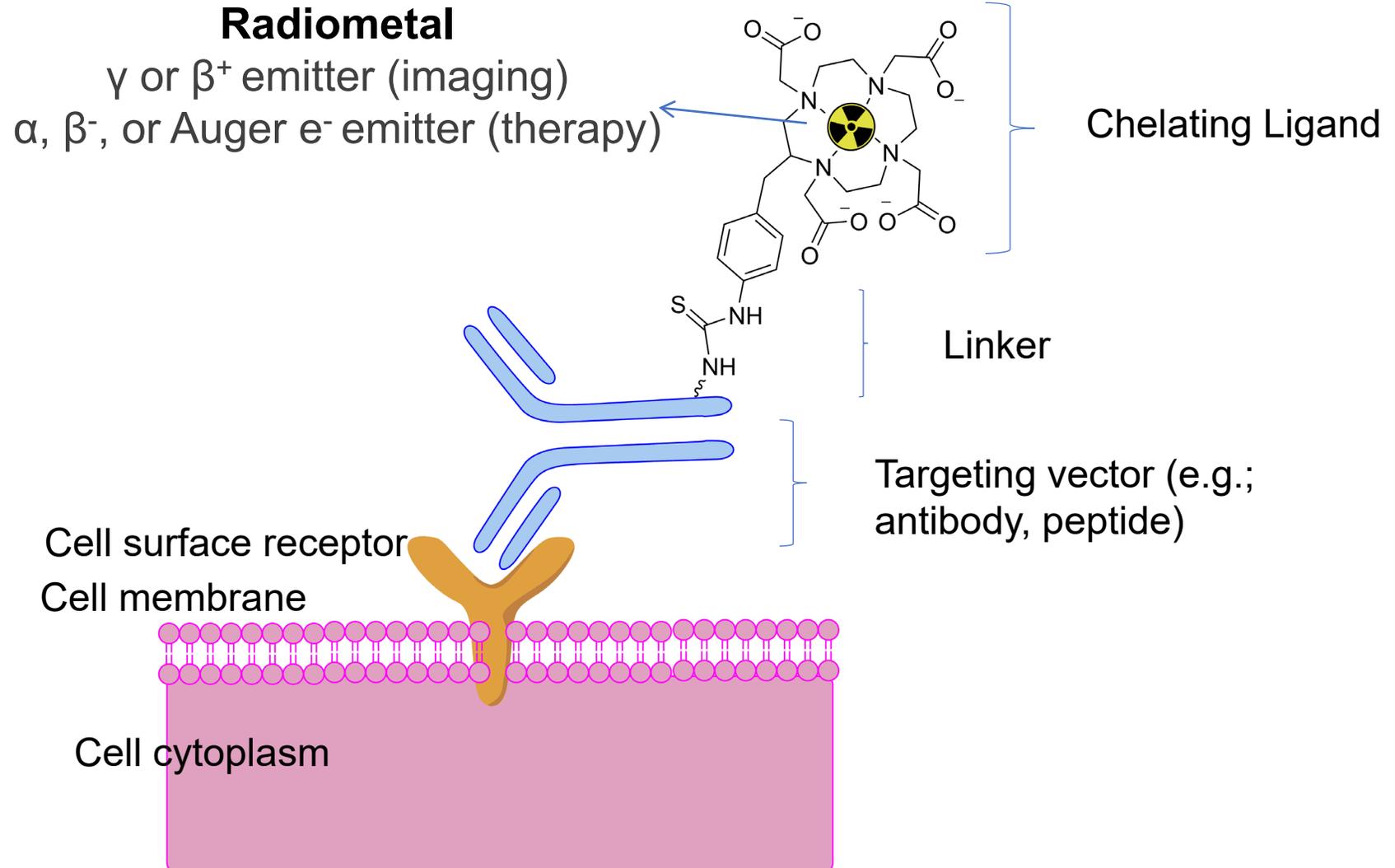


Production and purification of ^{225}Ra and ^{225}Ac at TRIUMF's Isotope Separation On-line (ISOL) facility and subsequent radiolabeling studies with α -emitter ^{225}Ac

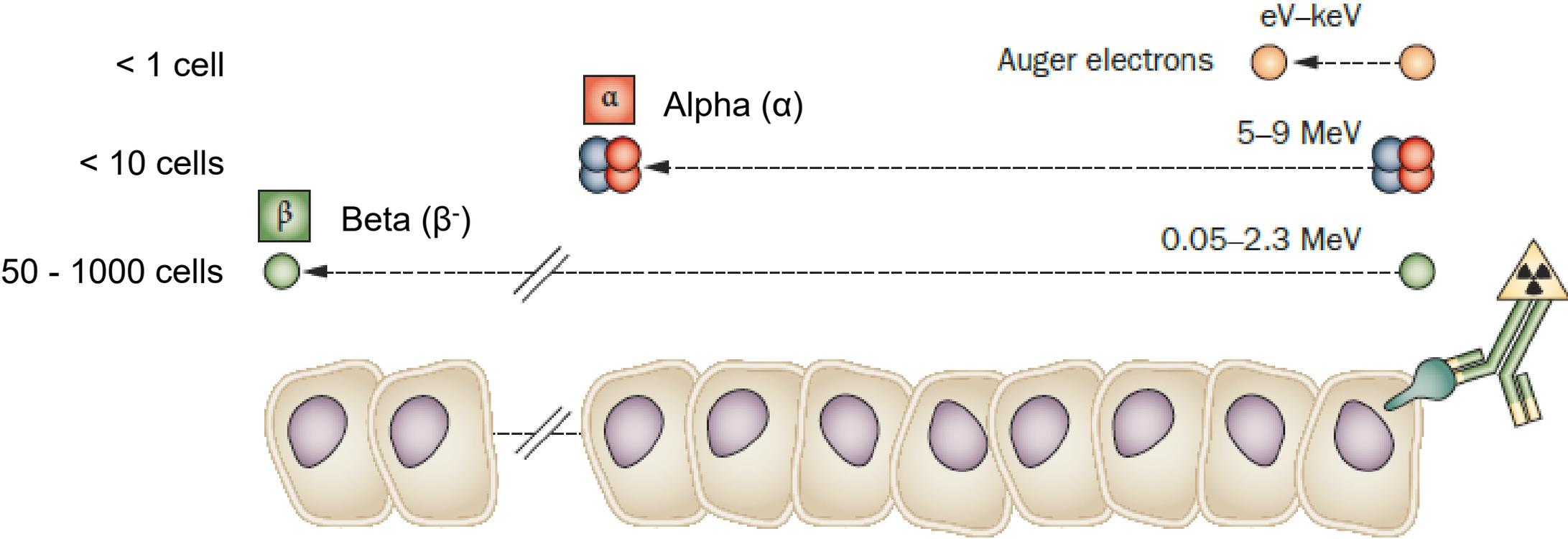
C. F. Ramogida^{1,2}, A. K. H. Robertson^{1,3}, P. Kunz⁶, C. Zhang⁴, U. Jermilova¹, J. Lassen⁶, I. Bratanovic¹, V. Brown¹, C. Rodriguez-Rodriguez⁵, L. Southcott¹, V. Radchenko¹, F. Bénard⁴, C. Orvig⁷, P. Schaffer¹

¹Life Sciences, TRIUMF – Vancouver, Canada; ²Chemistry, Simon Fraser University – Burnaby, Canada; ³Physics & Astronomy, University of British Columbia – Vancouver, Canada; ⁴Molecular Oncology, BC Cancer Agency – Vancouver, Canada; ⁵Centre for Comparative Medicine – Vancouver, Canada; ⁶Accelerator Division, TRIUMF – Vancouver, Canada; ⁷Chemistry, University of British Columbia – Vancouver, Canada

Nuclear Medicine with Radiometals



Targeted Radionuclide Therapy

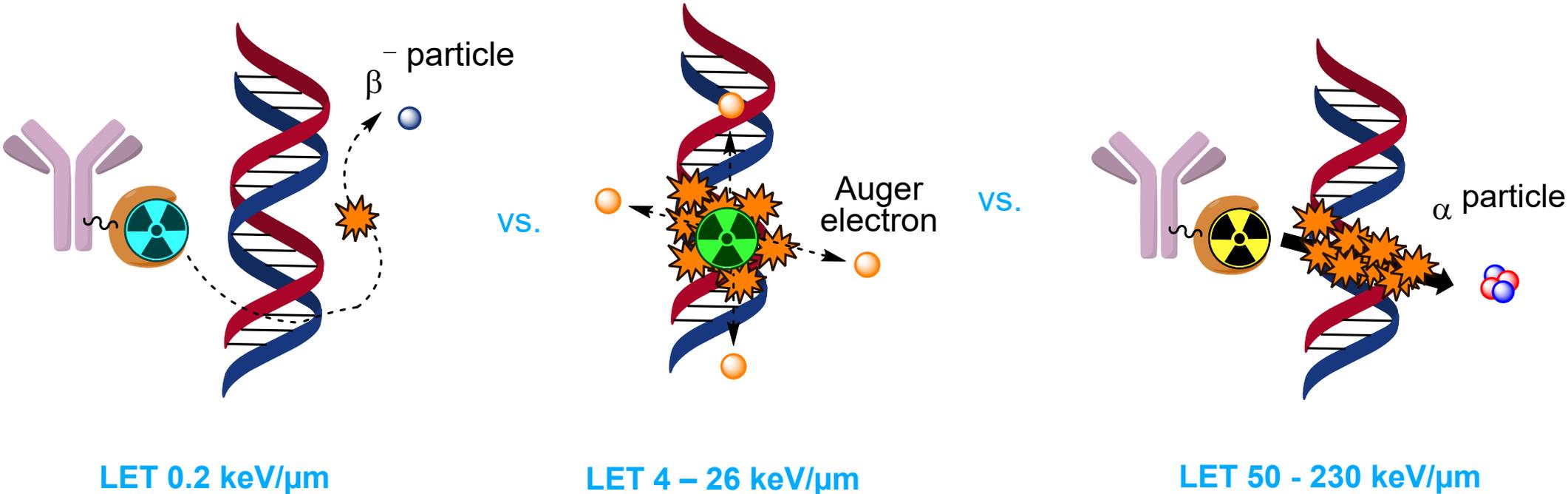


✓ Targeted, site-specific, and non-invasive

M. Miederer, D. Scheinberg, M. McDevitt, *Advanced Drug Delivery Rev.*, **2008**, 60, 1371.; J. Elgqvist, S. Frost, J.-P. Pouget, et al. *Frontiers in Oncology*, **2014**, 3, 324.; M. W. Brechbiel, *Dalton Trans.*, **2007**, 4918.; Y.-S. Kim, M. W. Brechbiel, *Tumor Biol.*, **2012**, 33, 573. J.-P. Pouget, I. Navarro-Teulon, et al. *Nat. Rev. Clin. Oncol.* **2011**, 8, 720.

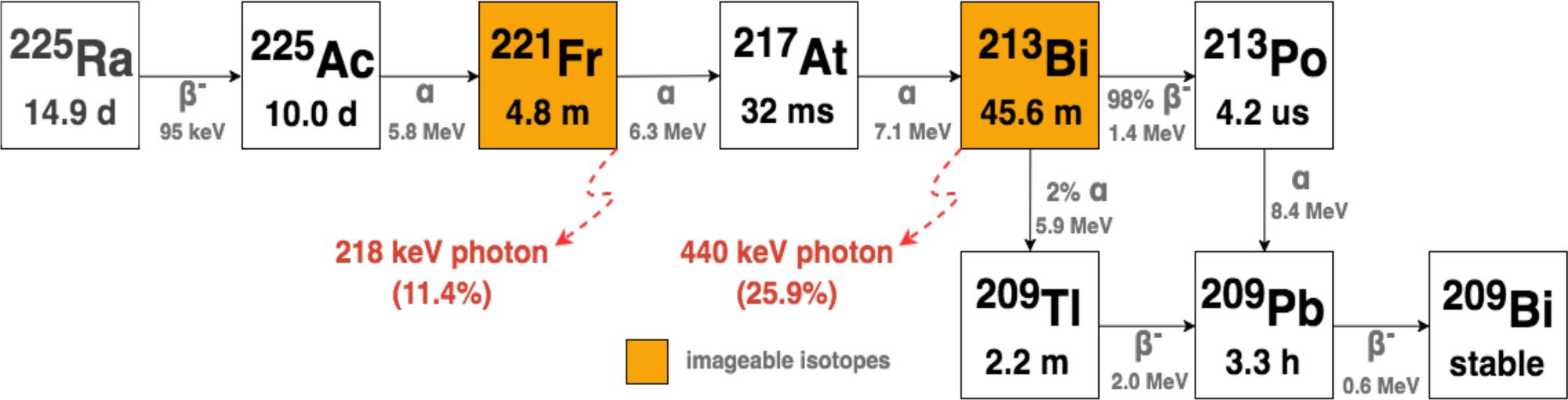
Targeted Alpha-Therapy

α -particles have high LET ($\sim 100 \text{ keV}/\mu\text{m}$) and typical range in tissue of 50 – 100 μm (< 10 cell diameters)



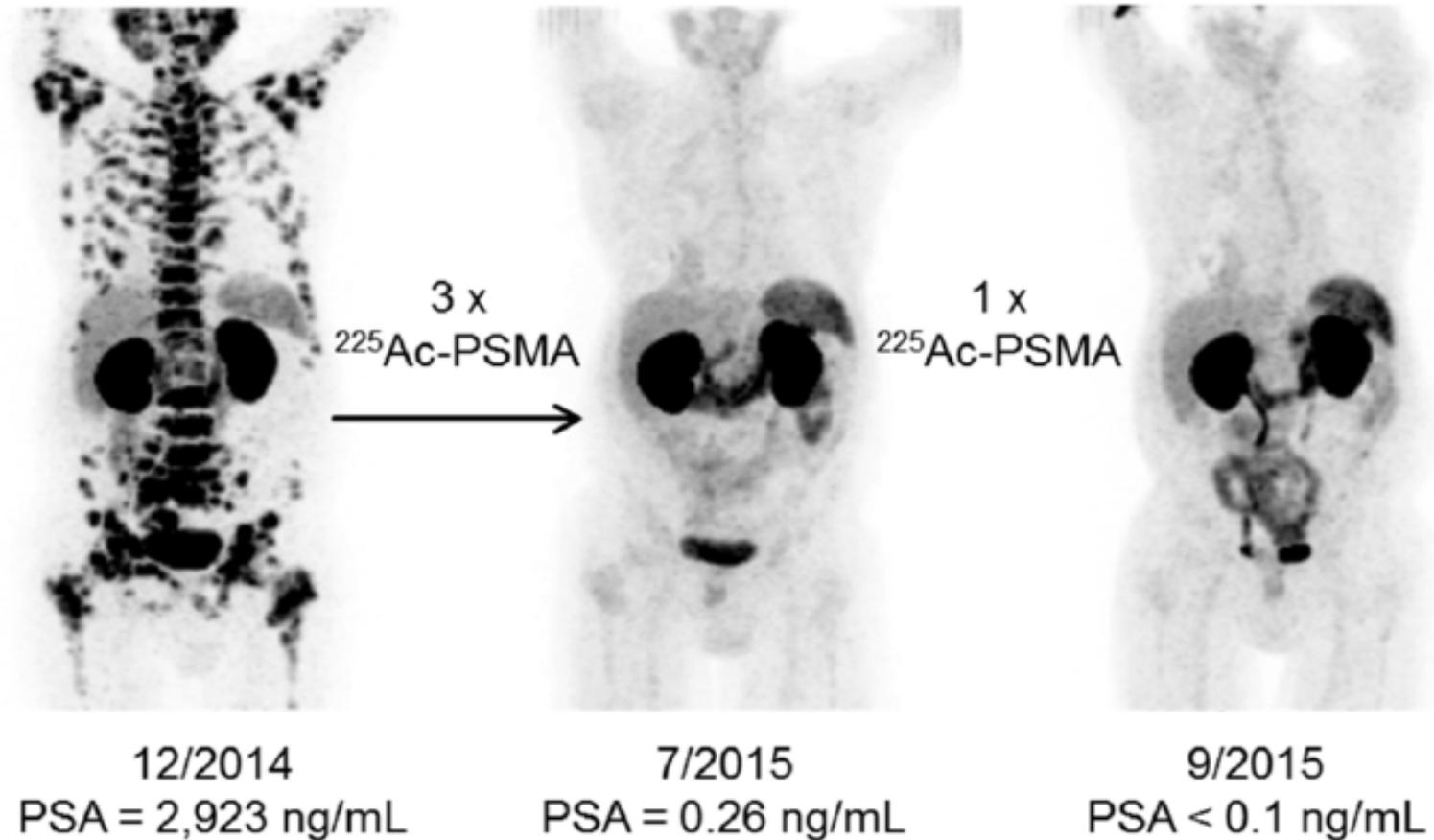
Targeted Alpha-Therapy with Actinium-225 (^{225}Ac)

Actinium-225 (^{225}Ac) has a relatively long half-life ($t_{1/2} = 10 \text{ d}$) followed by **four** fast alpha decays



Targeted Alpha-Therapy with ^{225}Ac

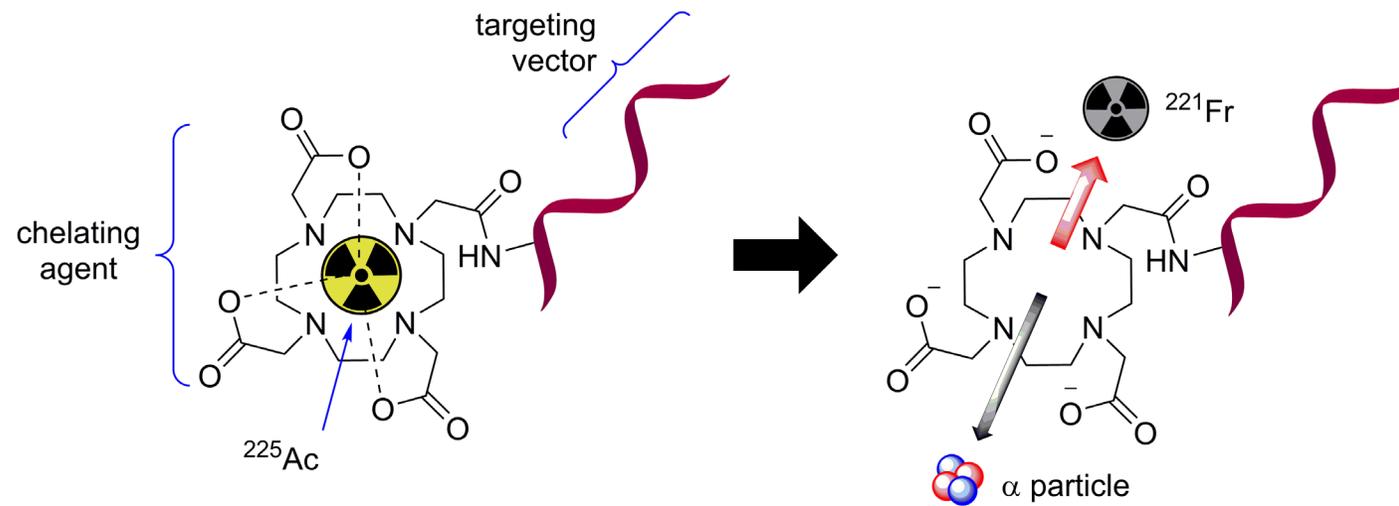
^{225}Ac labeled prostate specific membrane antigen (PSMA) has shown remarkable therapeutic response in patients – **complete remission**



PET images of the ^{68}Ga -labeled analogue

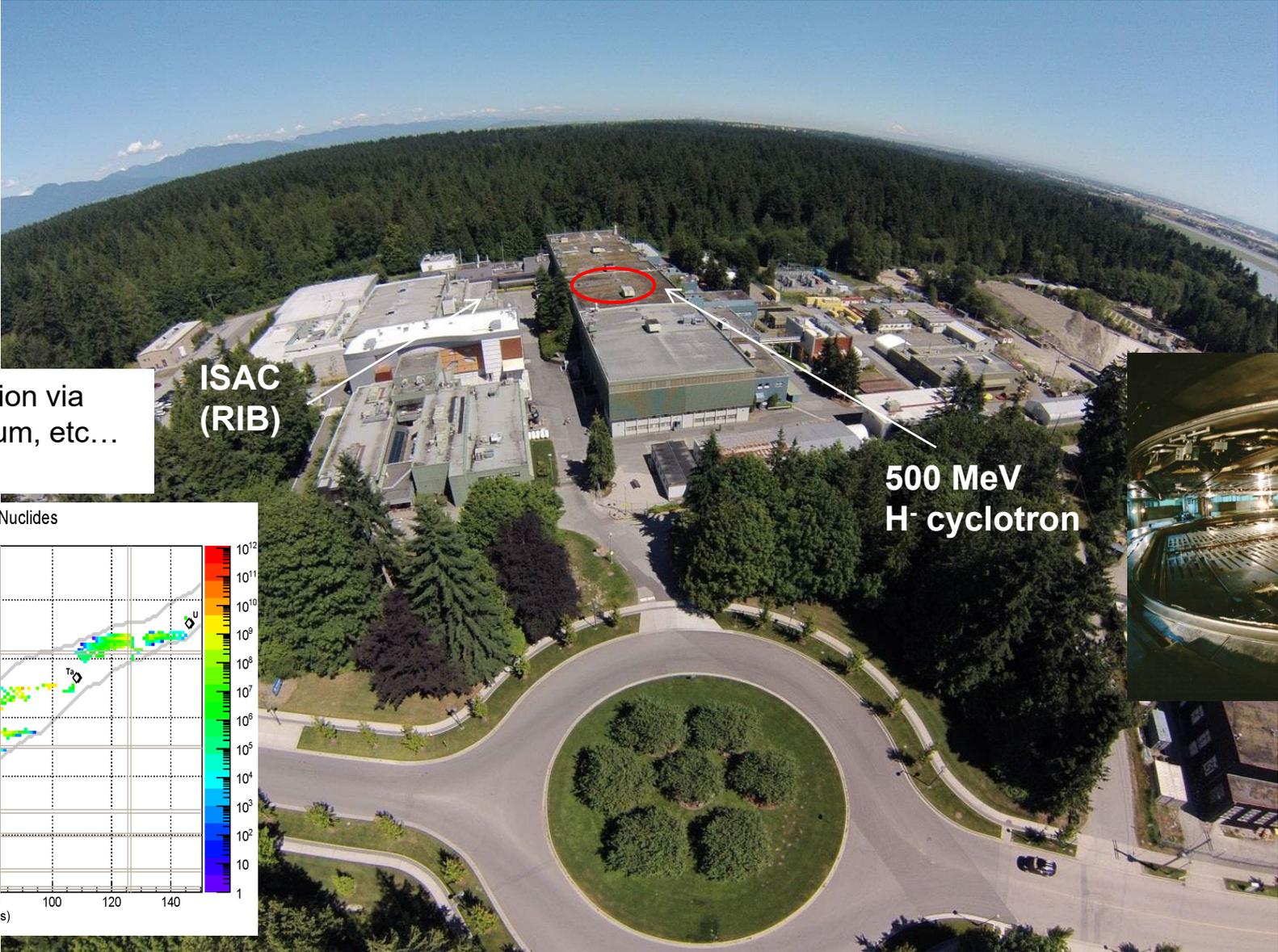
Targeted Alpha-Therapy with ^{225}Ac : Current Challenges

- Current world-wide production = **1.7 Ci/yr** (63 GBq/yr) – enough for < 2000 patients
- No non-radioactive surrogate – chemistry is virtually unexplored
- ^{225}Ac chelation and retention of daughters in vivo remains a challenge



Daughter isotopes are released from chelating agent due to **100 keV recoil energy** associated with α emission

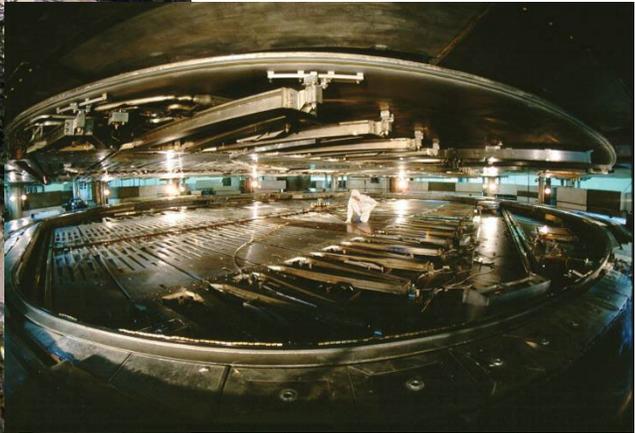
TRIUMF – Canada’s Particle Accelerator Centre



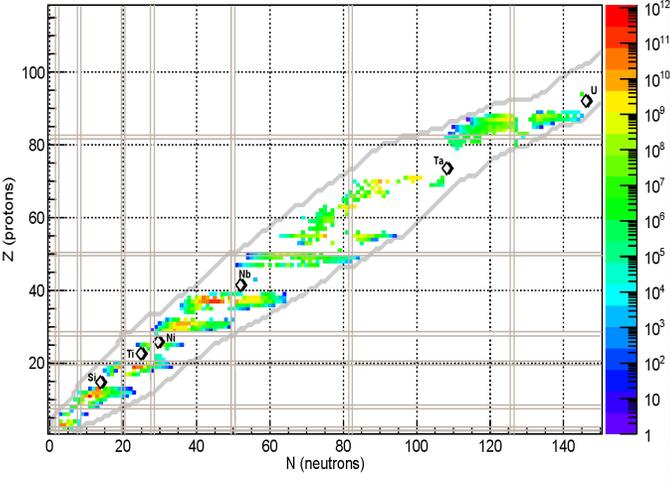
Isotope production via spallation of uranium, etc... targets

ISAC (RIB)

500 MeV H⁻ cyclotron

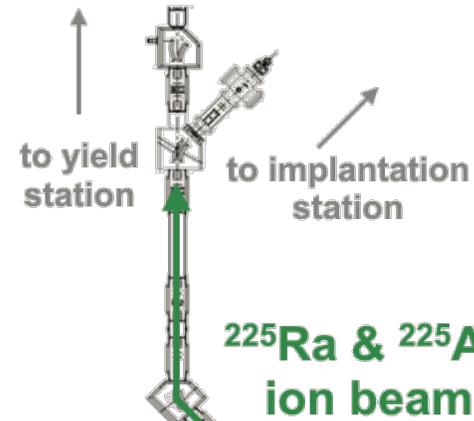
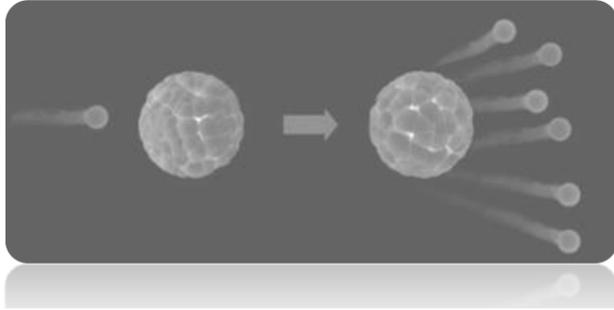


Yield Chart of Nuclides



Medical Isotope Production at TRIUMF's ISAC ISOL facility

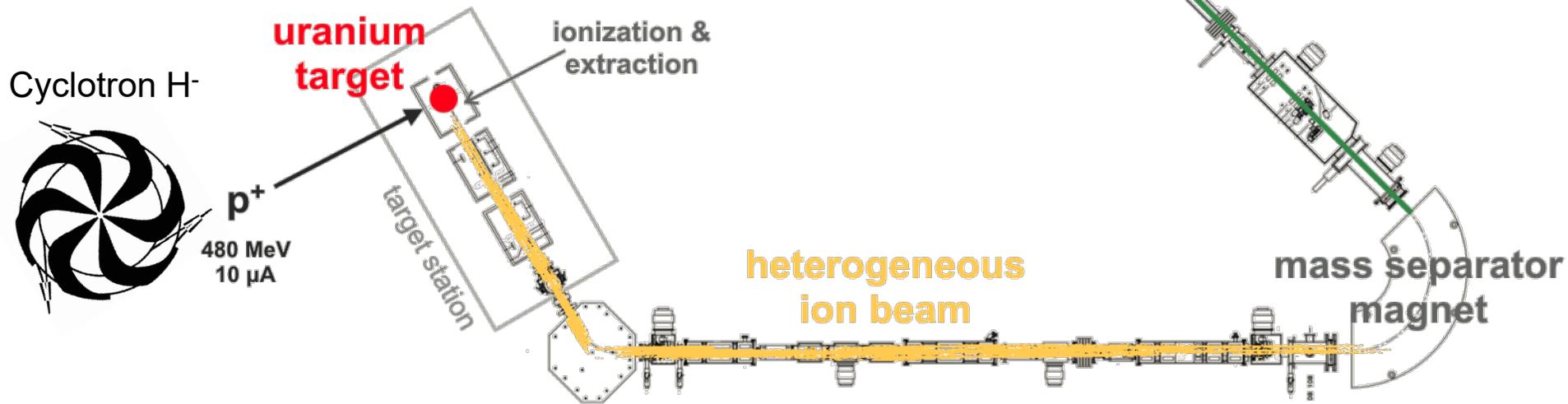
Isotope Separator and Accelerator (ISAC)
Isotope Separation On-line (ISOL)



Andrew Robertson



Dr. Peter Kunz

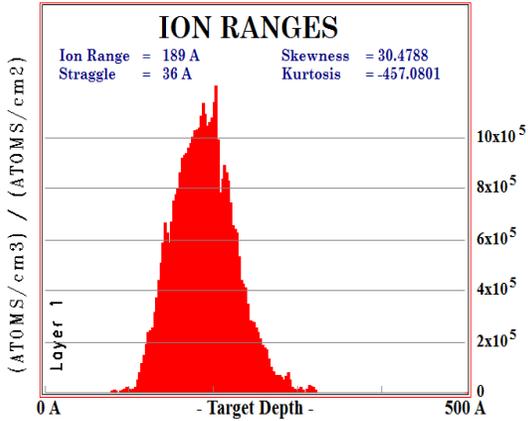
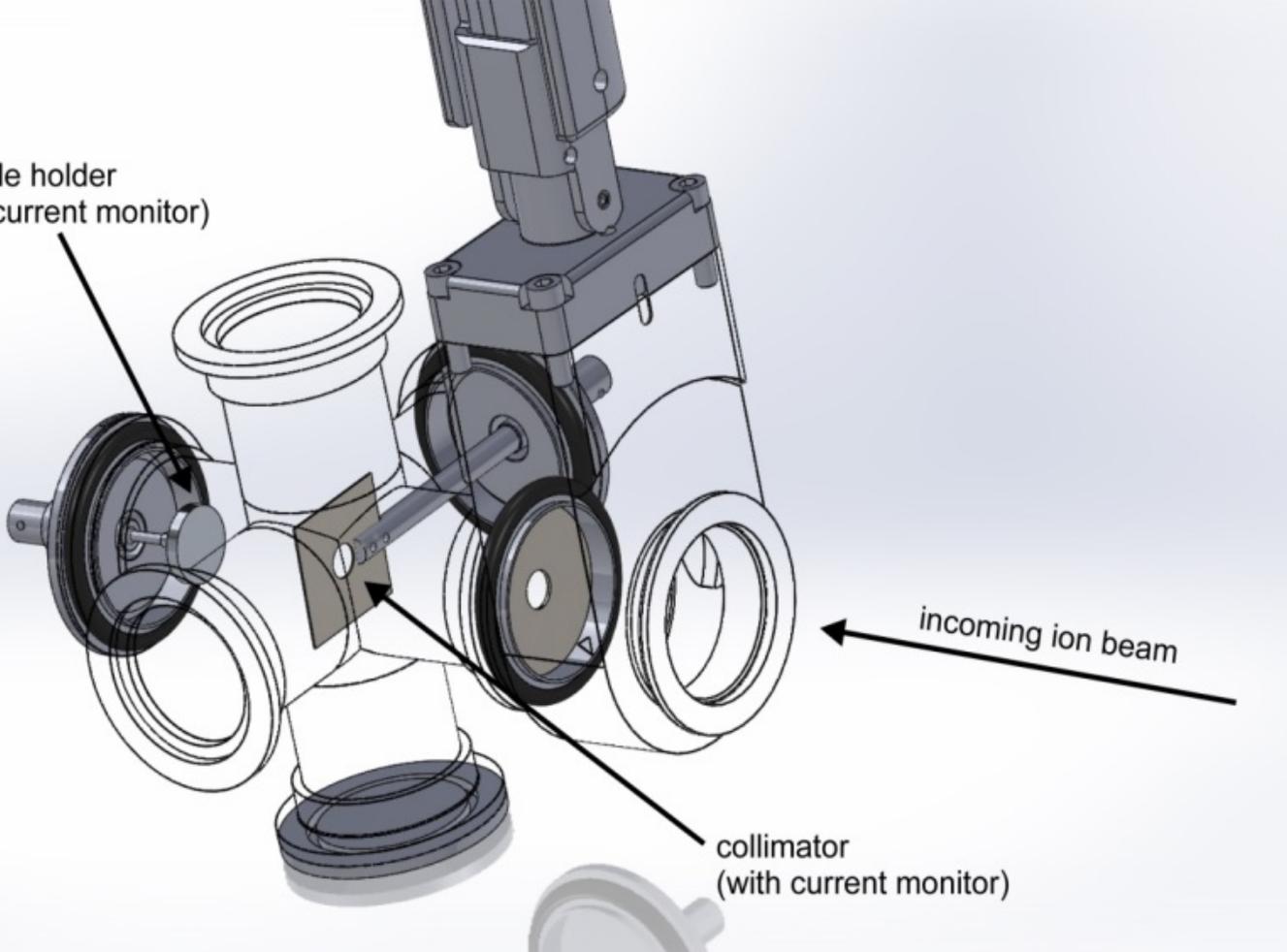


Implantation Station – Ion Collector



Al SEM sample stage

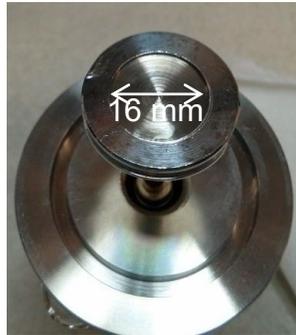
Sample holder
(with current monitor)



Dr. Peter Kunz

Target Dissolution

$^{225}\text{Ra}/^{225}\text{Ac}$ etched off
Al stage using 0.1 M
HCl

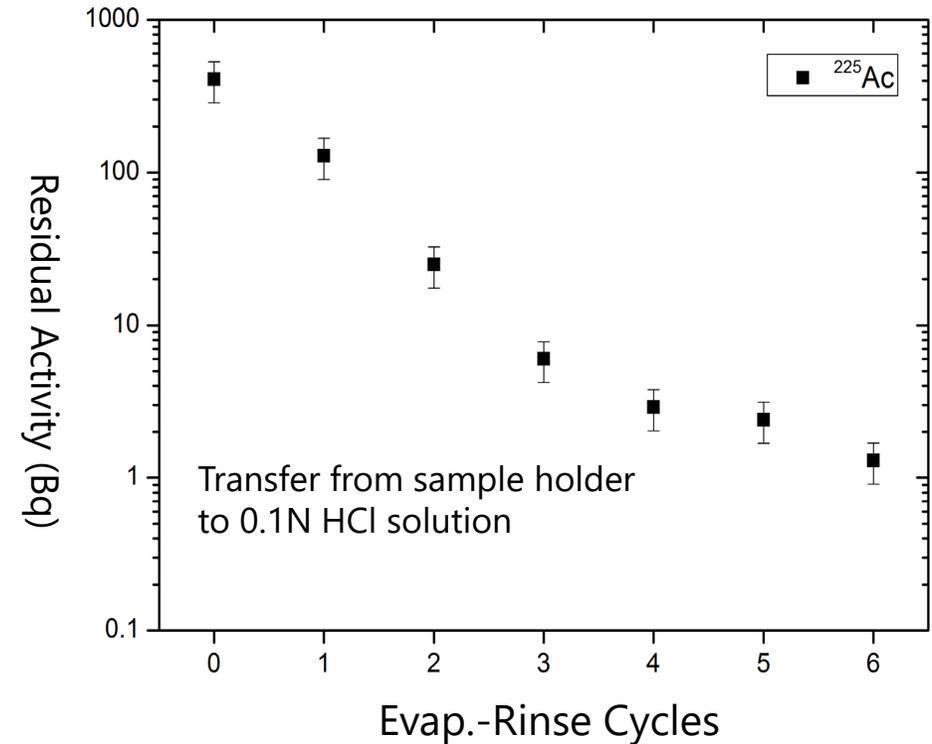
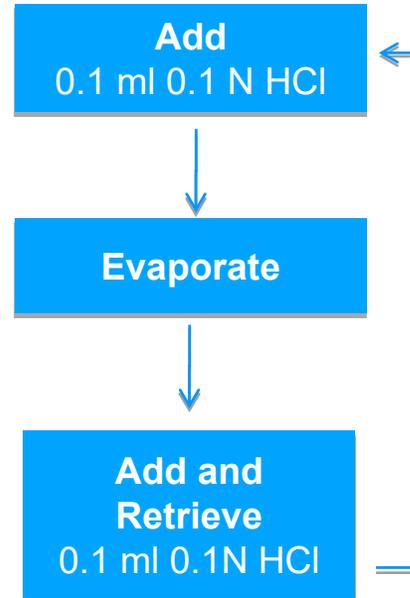


Al target stage

Activity Produced:

^{225}Ra (1.1 – 7.5 MBq)

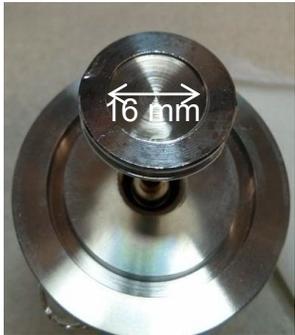
^{225}Ac (1.4 – 18.0 MBq)



Efficiency of activity transfer was first studied using low activity (<1 kBq) samples and quantified via **alpha spectroscopy**

Target Dissolution

$^{225}\text{Ra}/^{225}\text{Ac}$ etched off
Al stage using 0.1 M
HCl

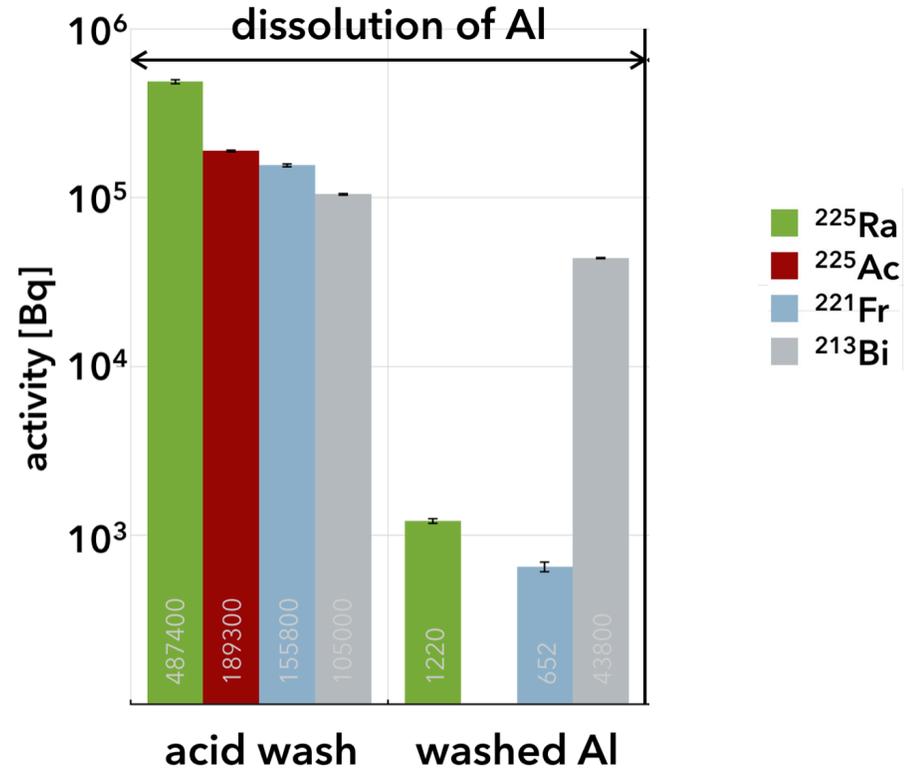


Al target stage

Activity Produced:

^{225}Ra (1.1 – 7.5 MBq)

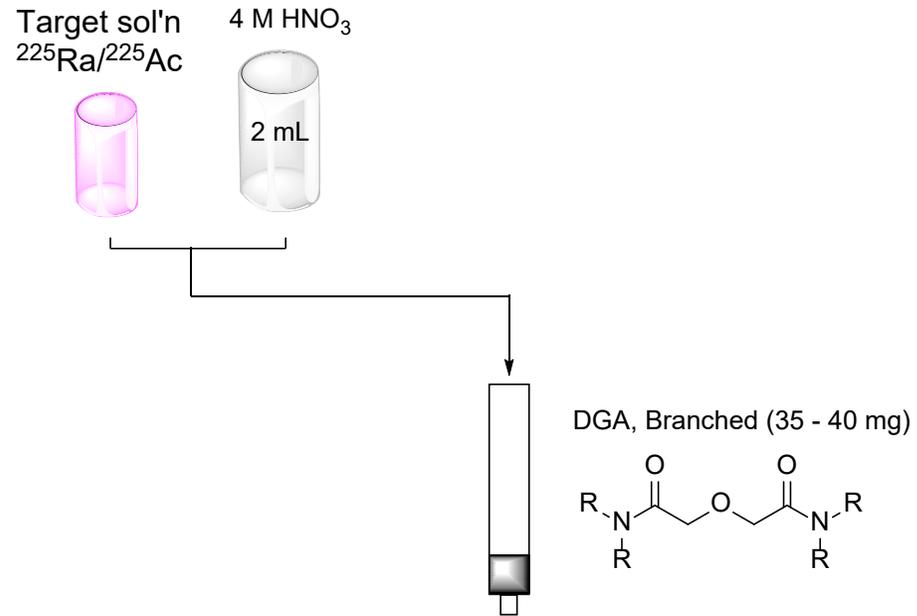
^{225}Ac (1.4 – 18.0 MBq)



> 99% of all implanted $^{225}\text{Ra}/^{225}\text{Ac}$ activity* was retrieved from SEM stage, quantified using **HPGe gamma spectroscopy**

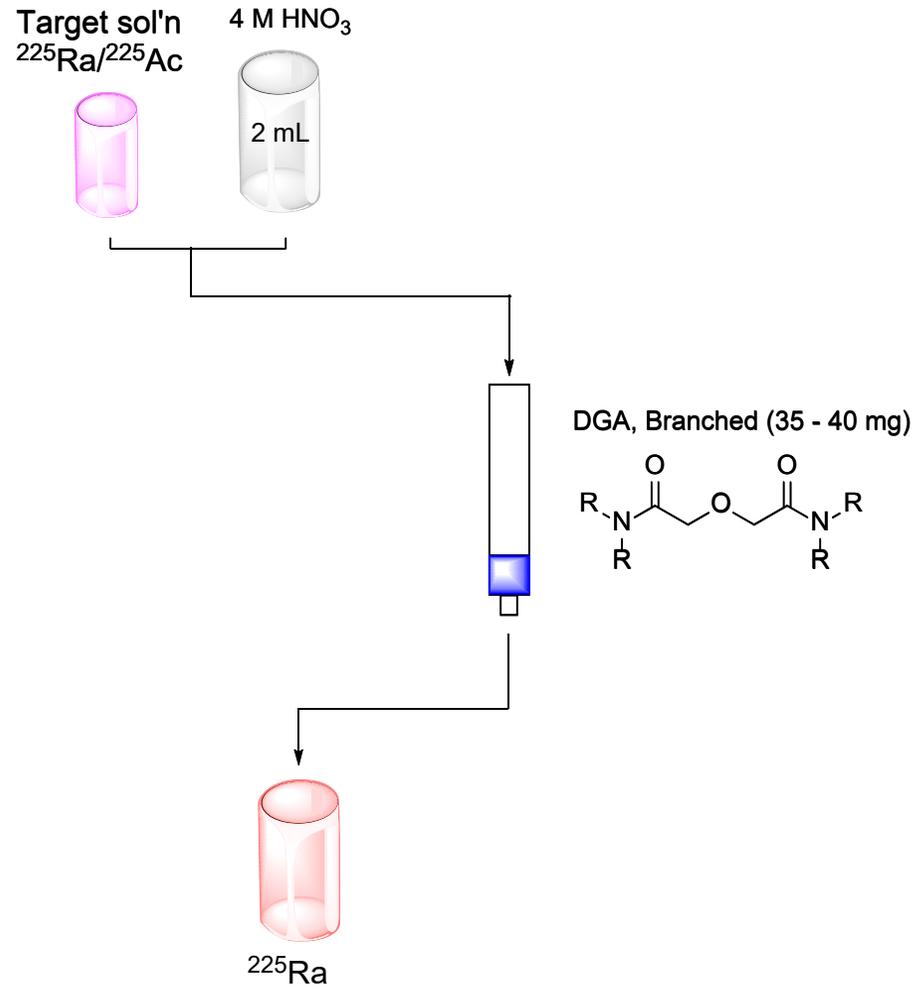
Radiochemical Separation

Step 1: Load



Radiochemical Separation

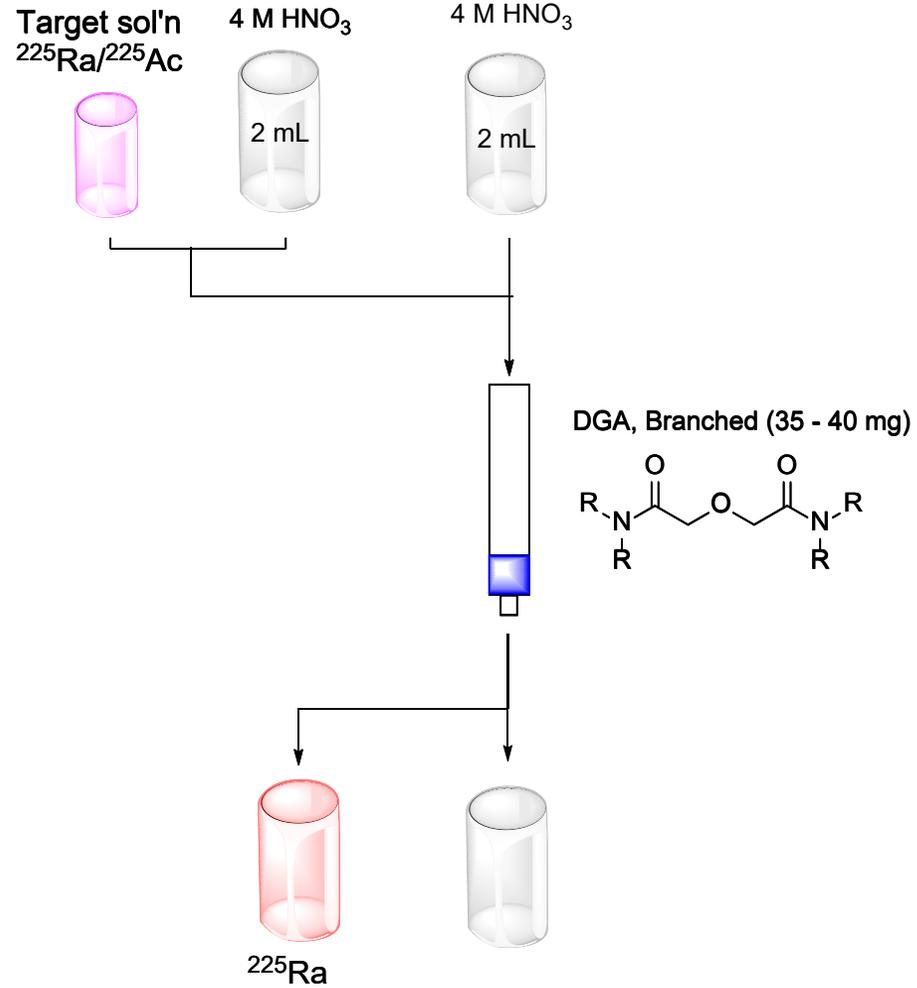
Step 1: Load



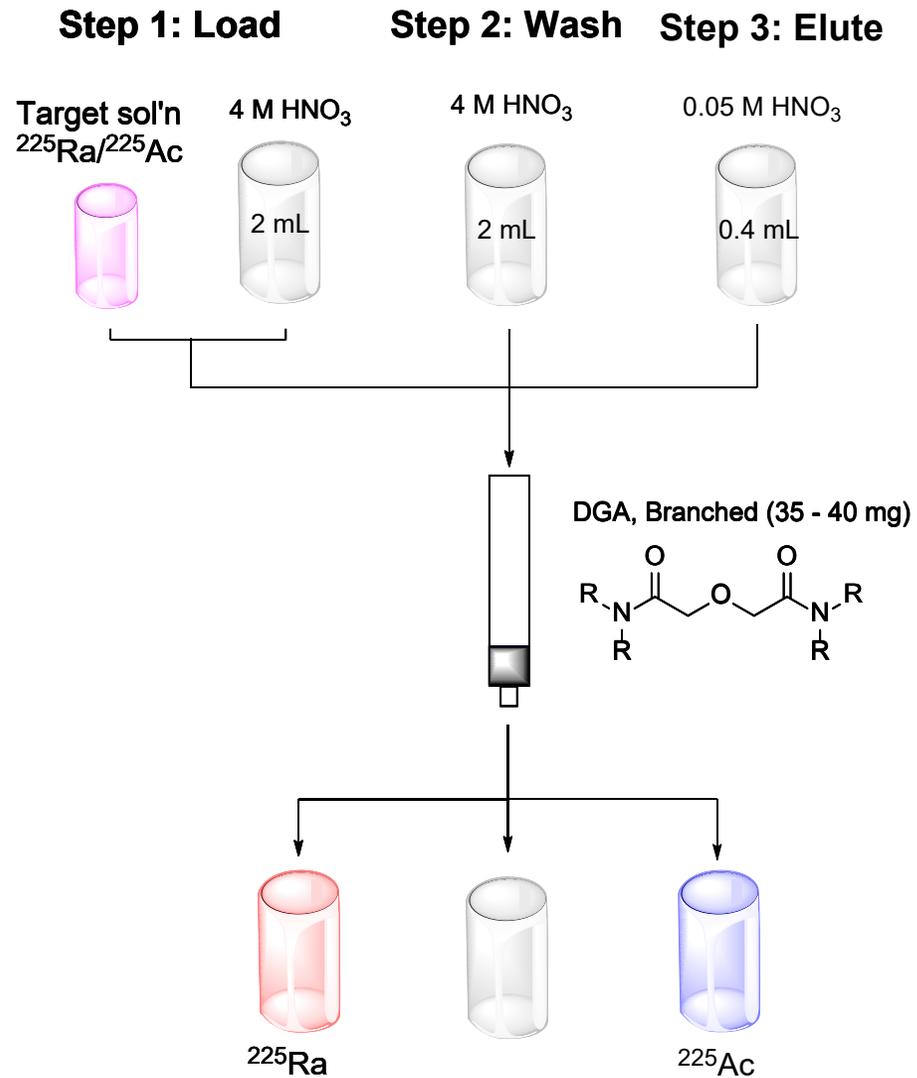
Radiochemical Separation

Step 1: Load

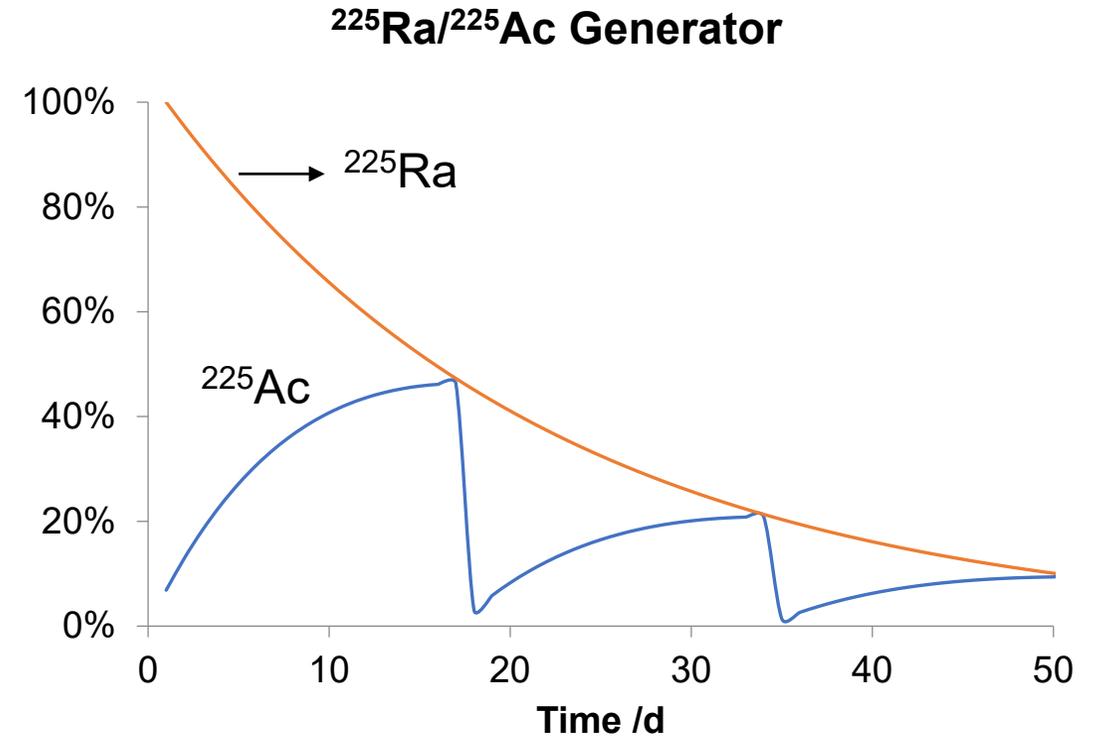
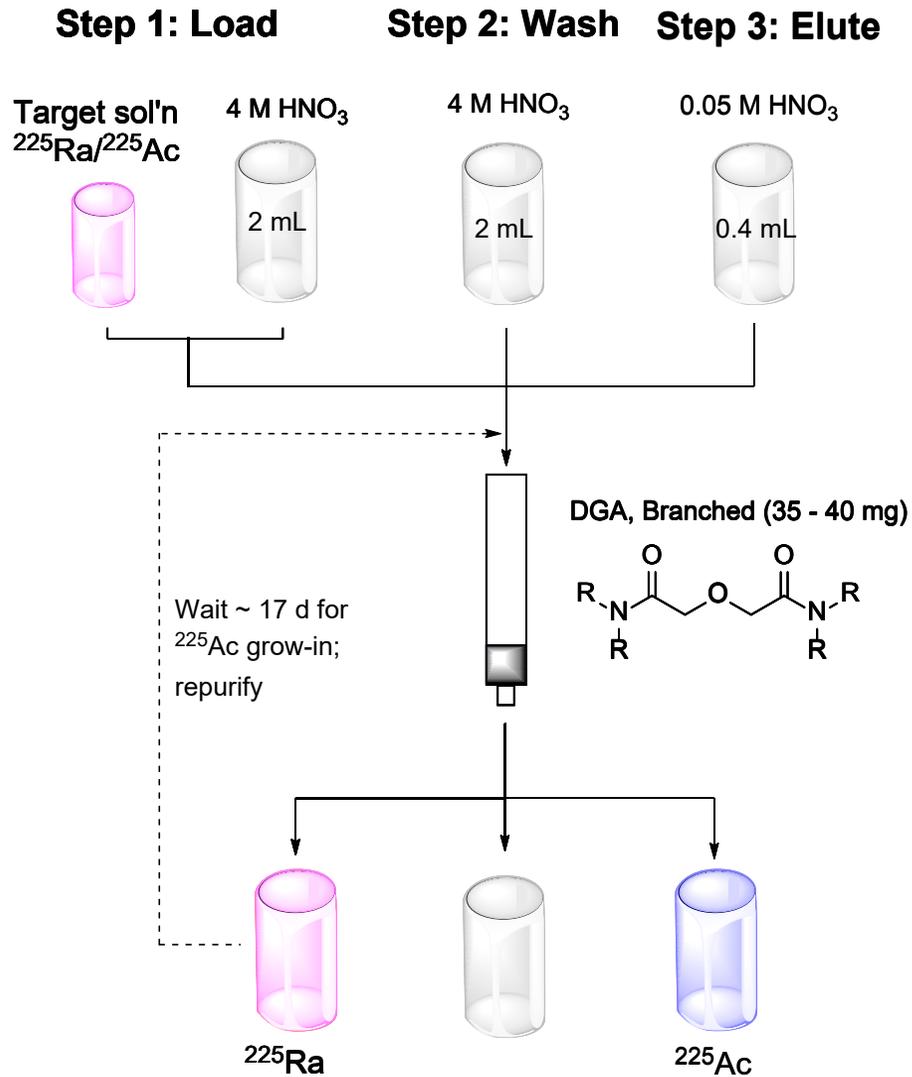
Step 2: Wash



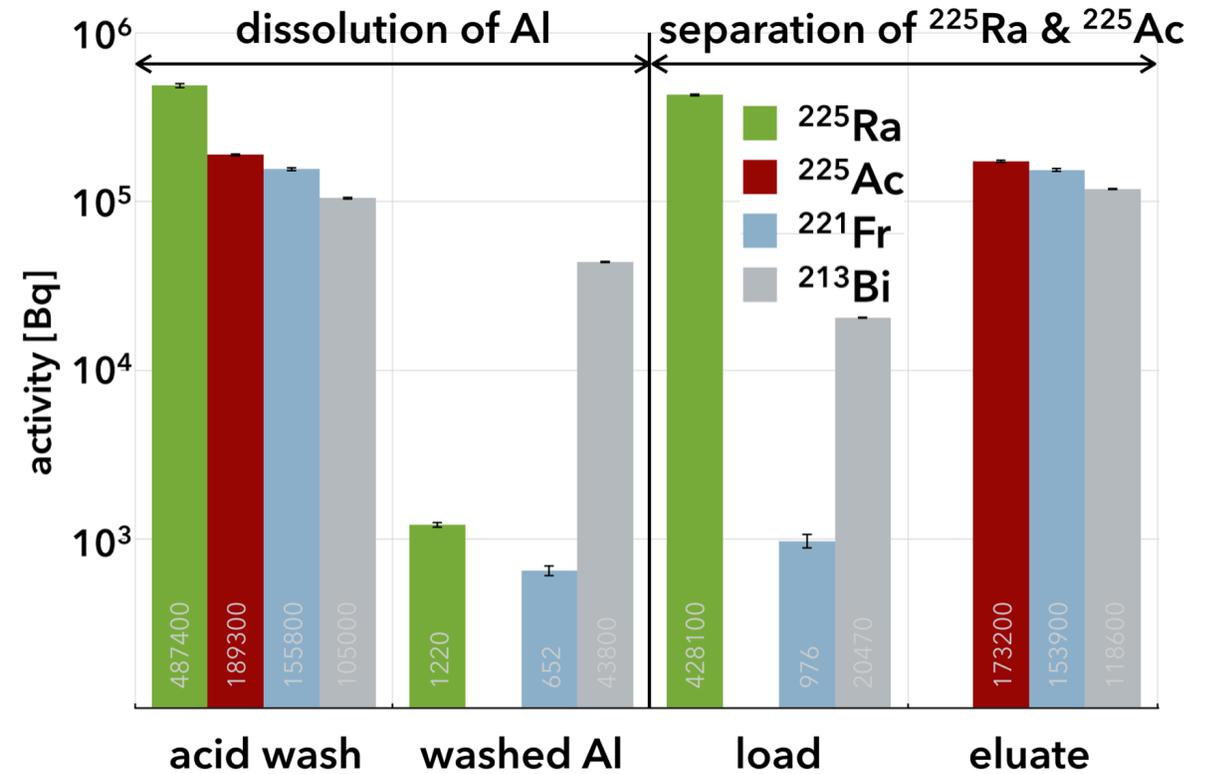
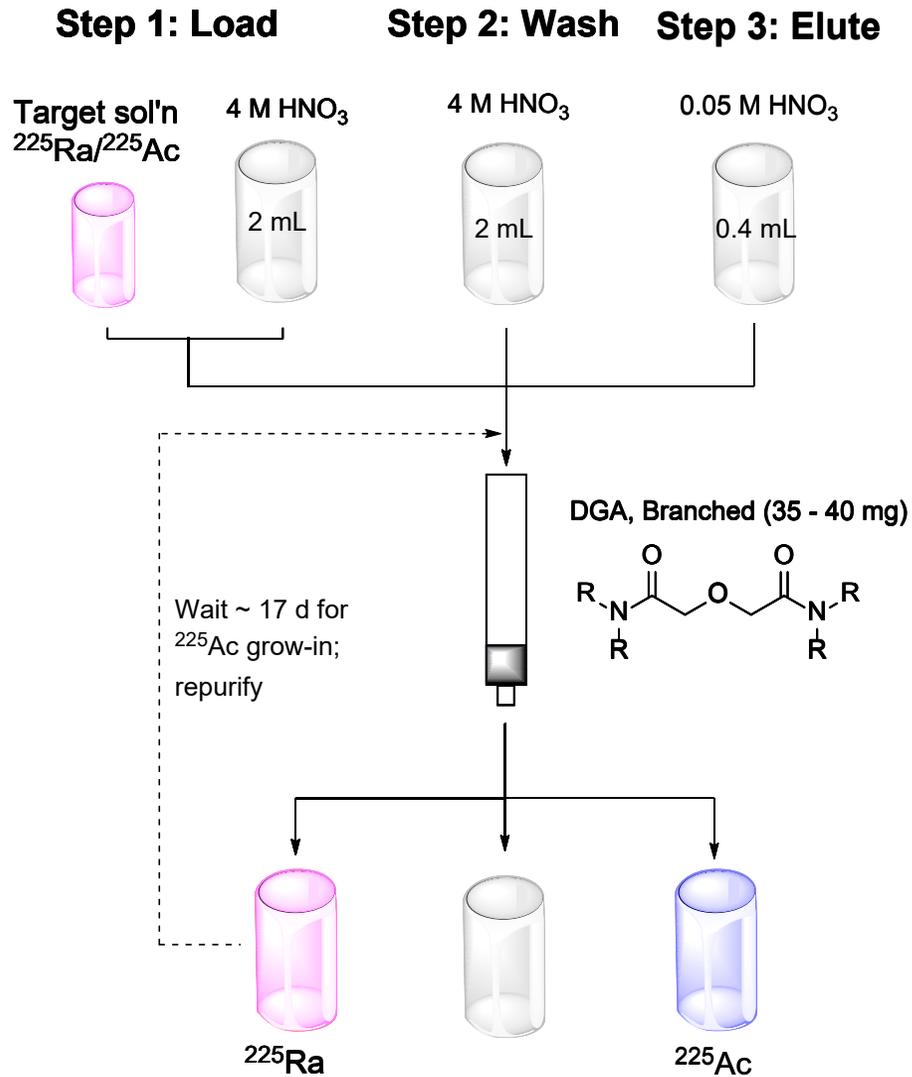
Radiochemical Separation



Radiochemical Separation



Radiochemical Separation



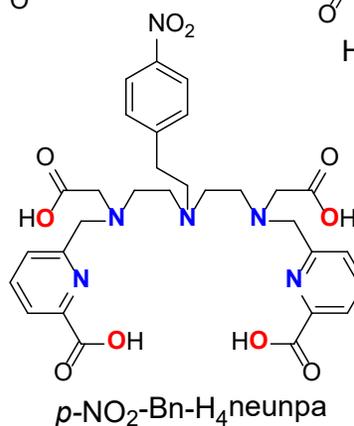
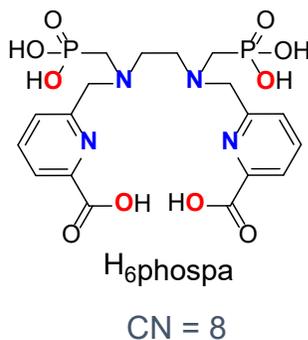
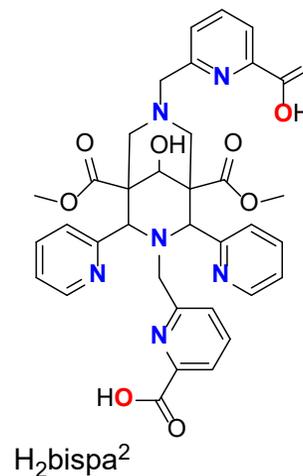
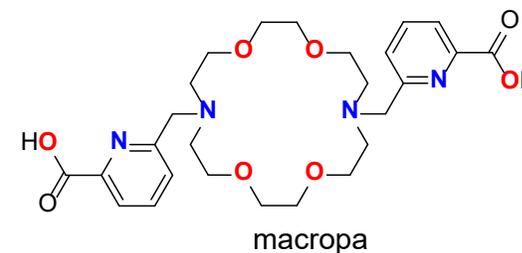
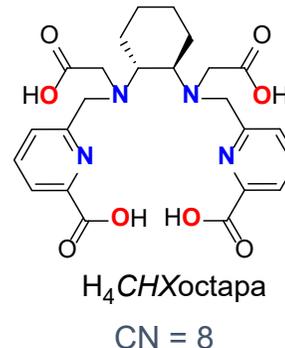
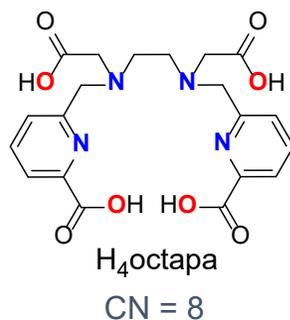
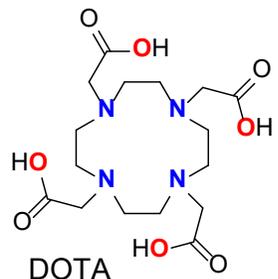
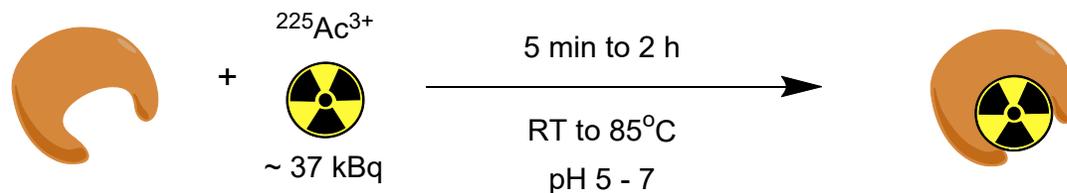
Summary of A = 225 Production at ISOL

Run		Implantation			RIB Yields [ions/s]		Activity Produced [MBq] ^c	
#	Date	Duration [h]	EE ^a	LIS ^b	²²⁵ Ra	²²⁵ Ac	²²⁵ Ra	²²⁵ Ac
1	Dec '15	13.3	Shorted	X	3.2×10^7	3.8×10^6	0.19	0.16
2	Apr '16	44.8	Shorted	On	4.0×10^6	1.0×10^7	0.99	1.40
3	May '16	48.9					1.13	1.35
4	Aug '16	21.6	Good	On	1.6×10^8	5.7×10^7	7.1	10.5
5	Dec '16	45.0	Good	On	9.3×10^7	1.3×10^8	6.8	18.0
6	Apr '17	80.7	Shorted	X	9.0×10^7	2.8×10^6	7.5	1.7

^aEE = extraction electrode; ^bLIS = Laser ionisation source; ^cquantified by HPGe γ -spec

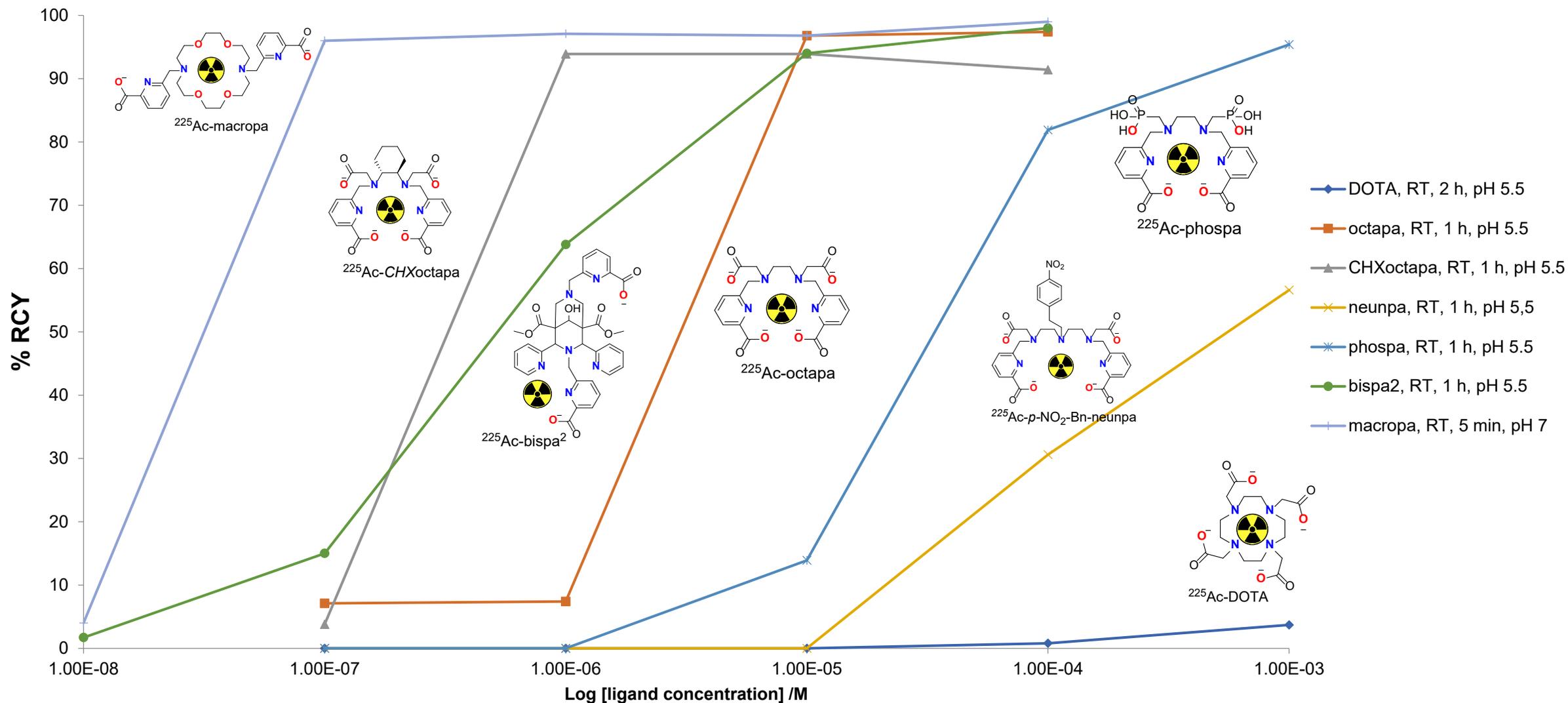
^{225}Ac Radiolabeling & Chelation Studies

Small library of chelating ligands tested against the current “gold standard”



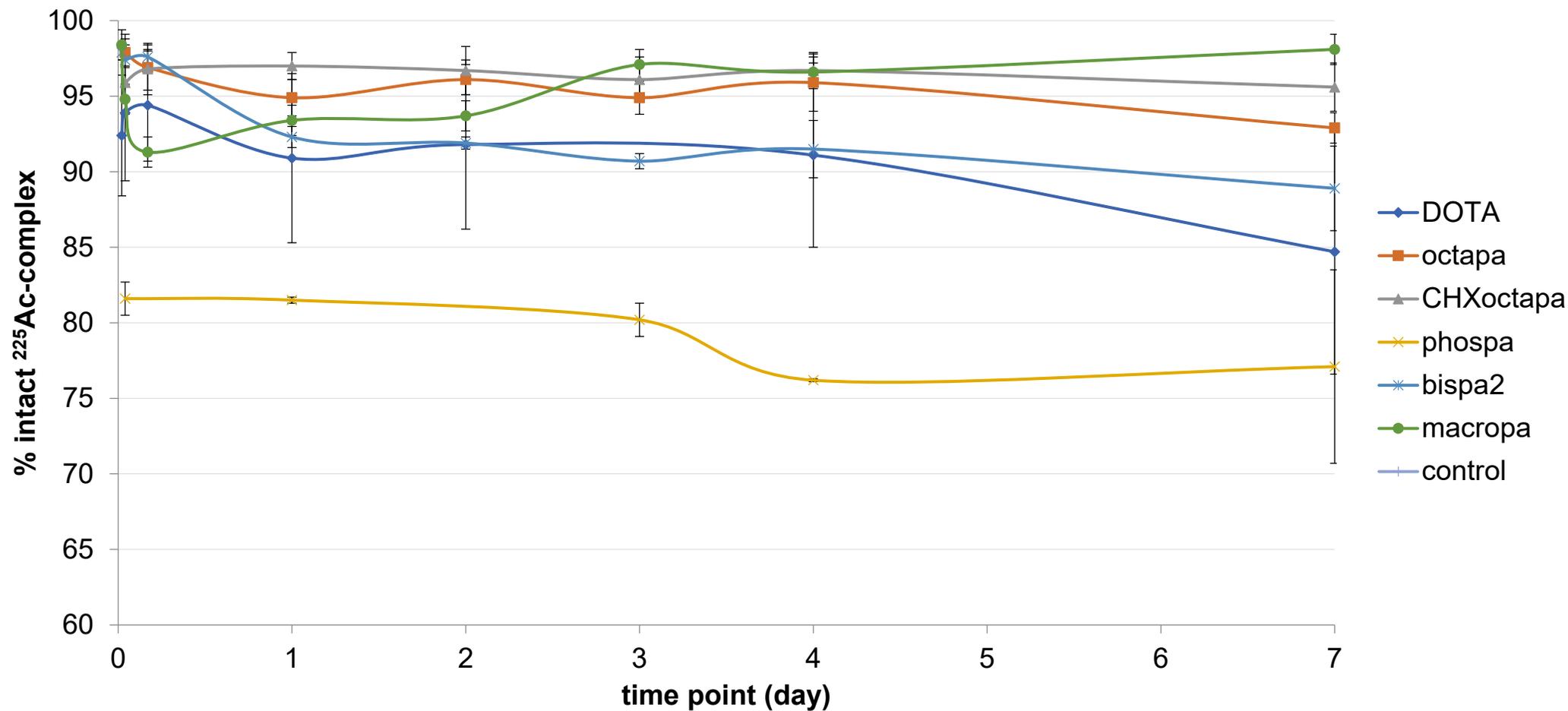
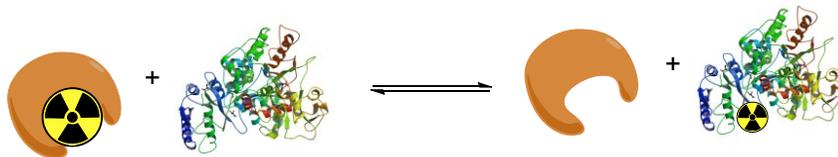
CN = coordination number

^{225}Ac Radiolabeling & Chelation Studies



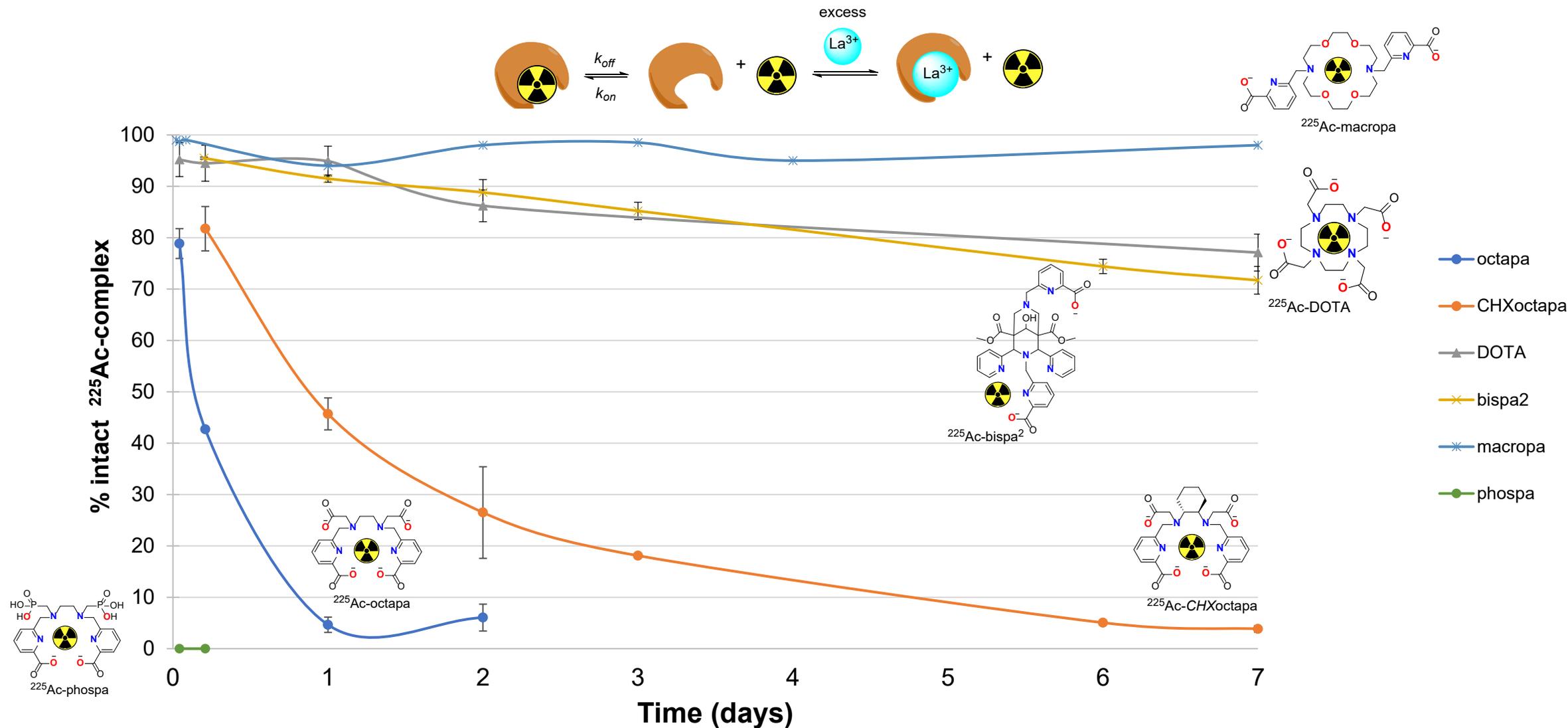
^{225}Ac -Complex Stability in Human Serum

Stability of preformed ^{225}Ac -complexes against transchelation to serum proteins



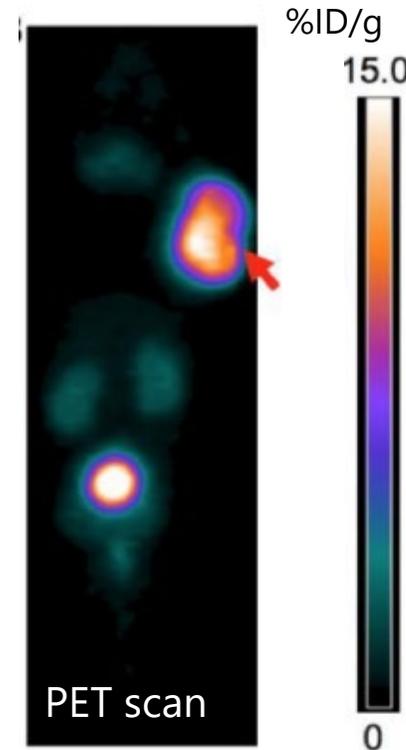
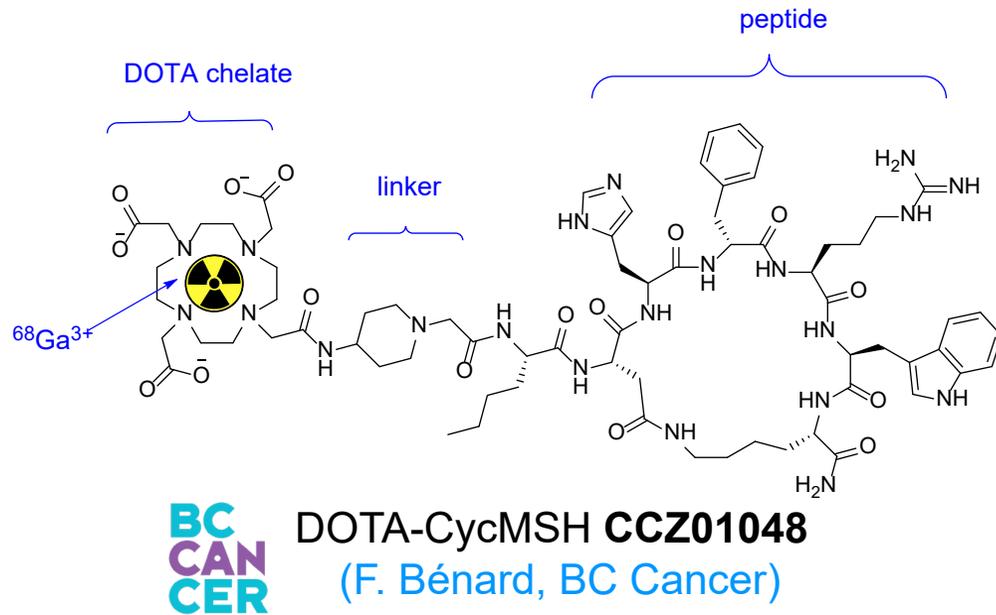
^{225}Ac -Complex Exchange Competition Against La^{3+}

Stability of preformed ^{225}Ac -complexes in 5-fold excess La^{3+} at ambient temperature



Efforts Towards Targeted Delivery: ^{225}Ac -DOTA-CycMSH

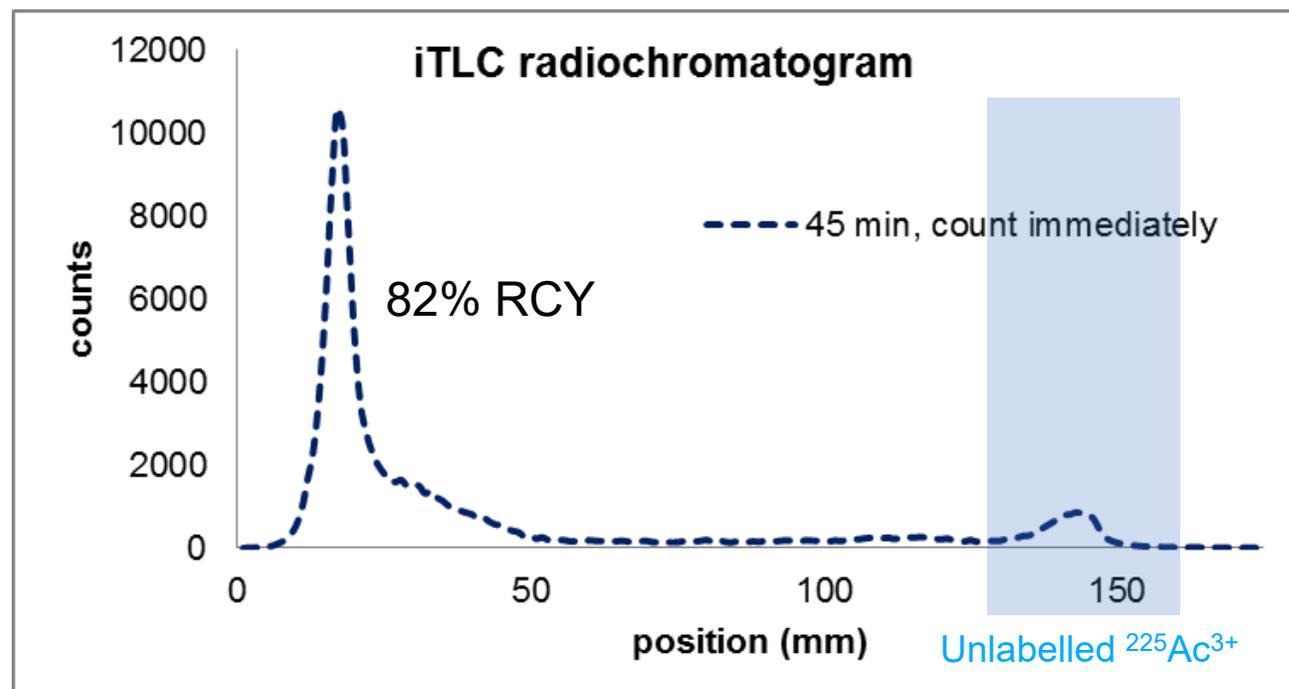
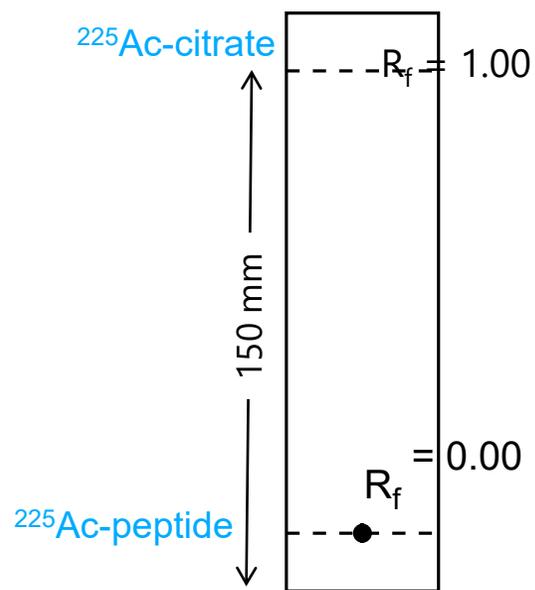
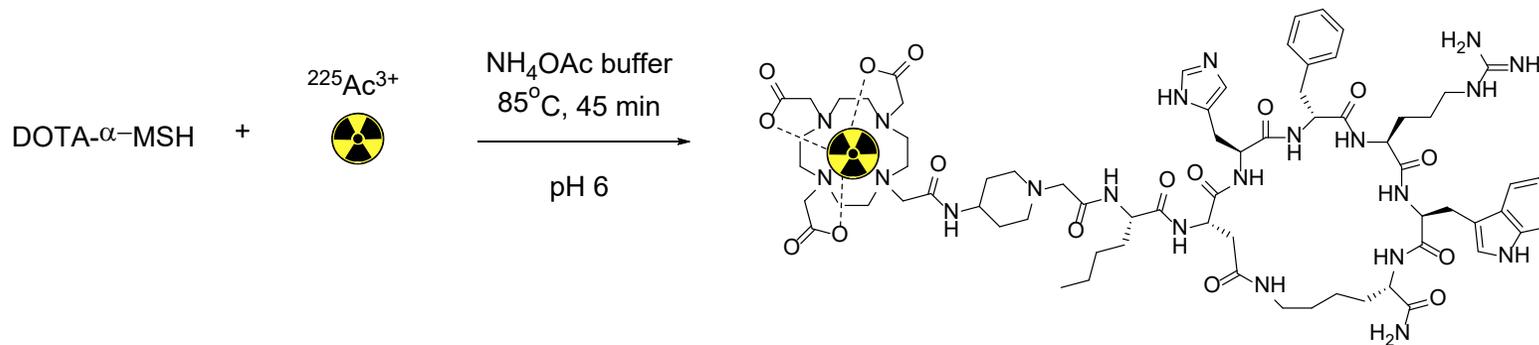
Background: α -Melanoma-stimulating hormone peptide shows high affinity for the melanocortin 1 receptor (MC1R) which is highly expressed in majority of melanomas (skin cancer)



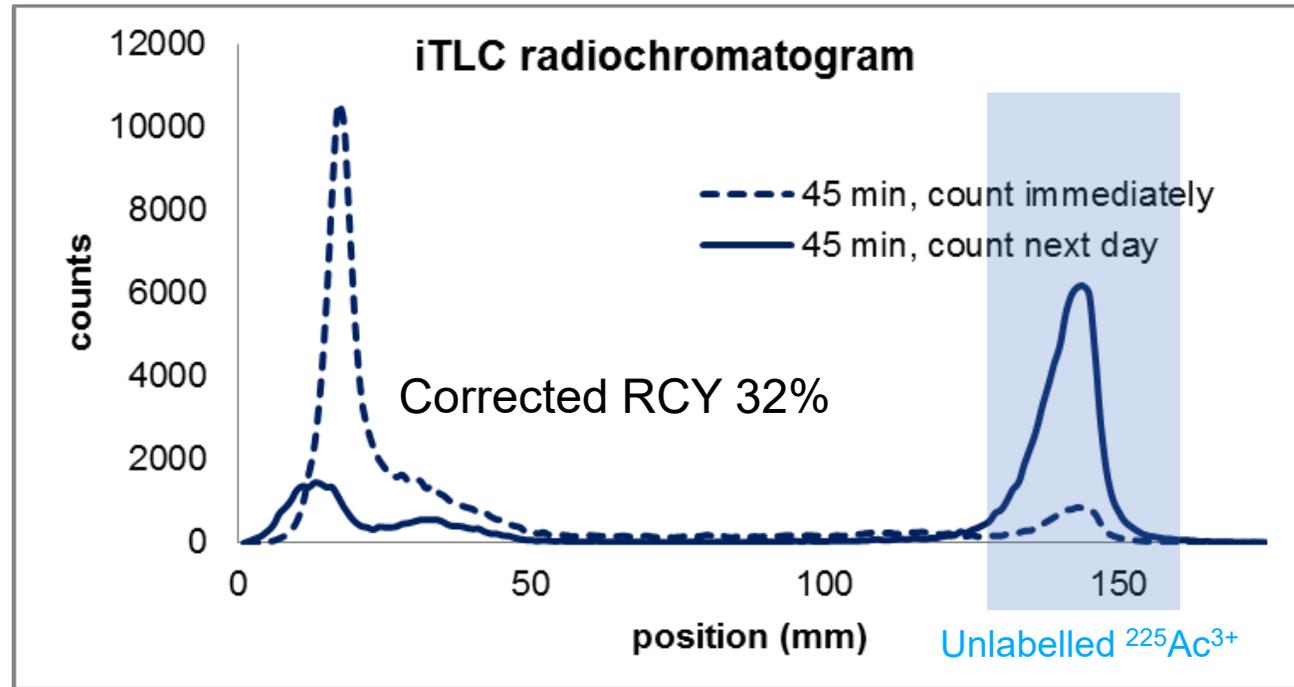
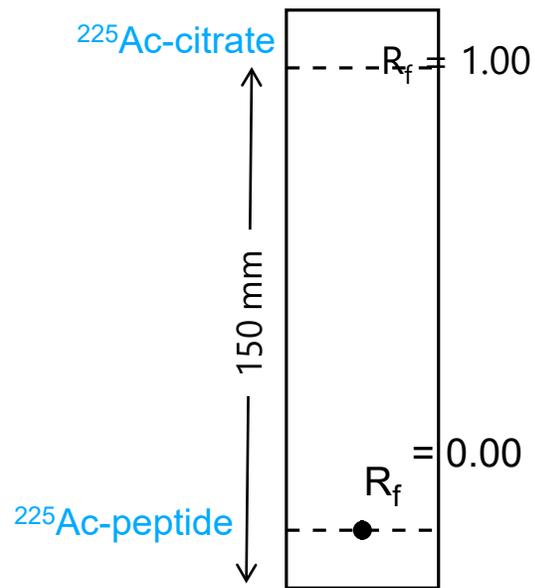
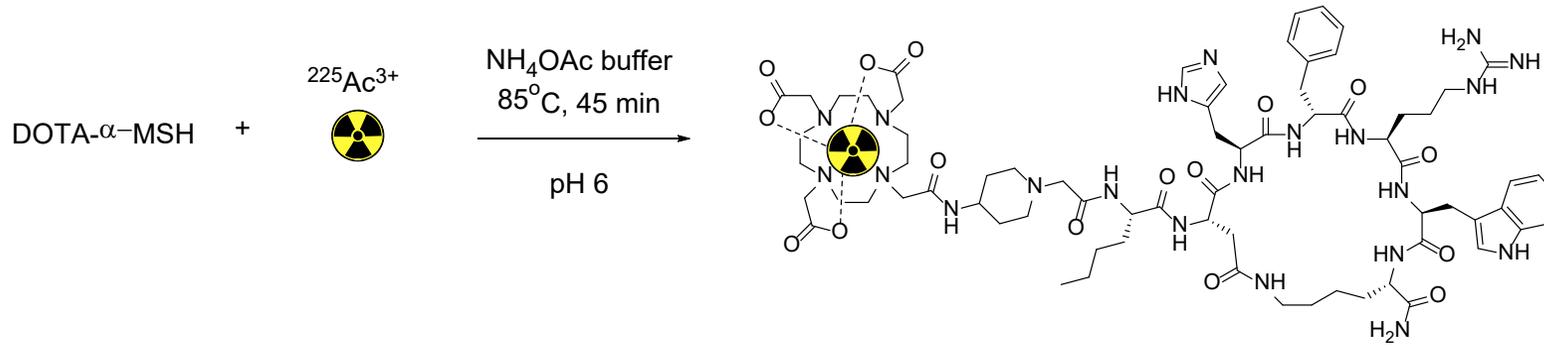
- ✓ High receptor binding affinity
- ✓ High tumour uptake and tumour to non-target tissue ratios
- ✓ Rapid internalization of tracer

PET image of ^{68}Ga -CCZ01048 (S.A. ~ 200 MBq/nmol) at 2 h p.i. in mice bearing B16F10 tumours

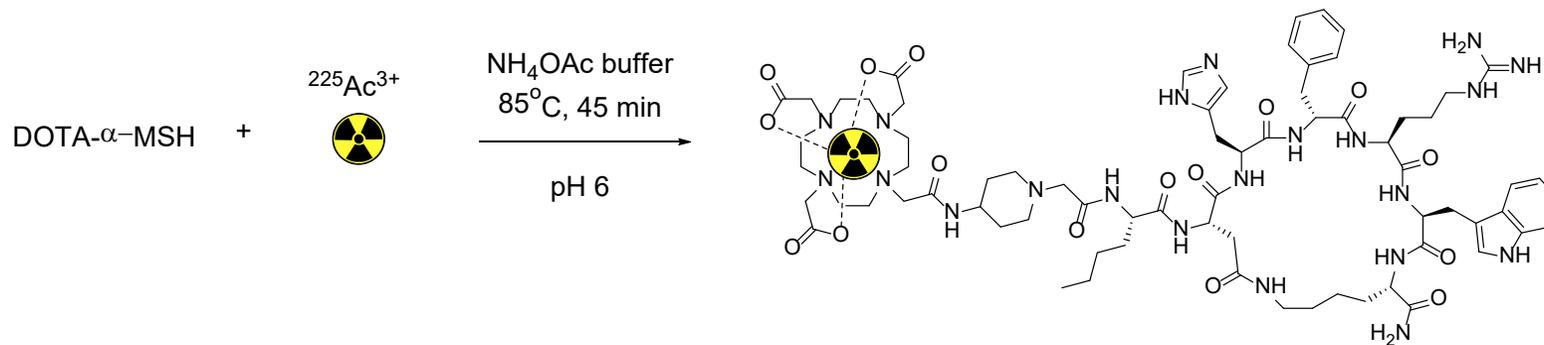
^{225}Ac Radiolabeling of DOTA-CycMSH



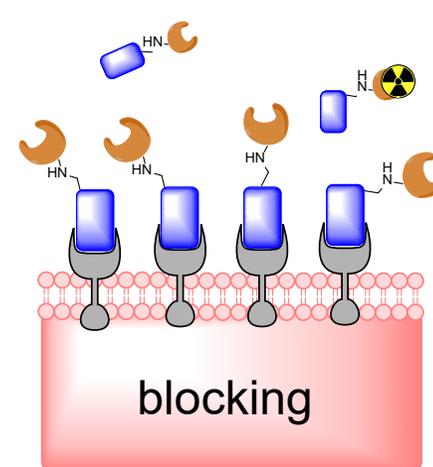
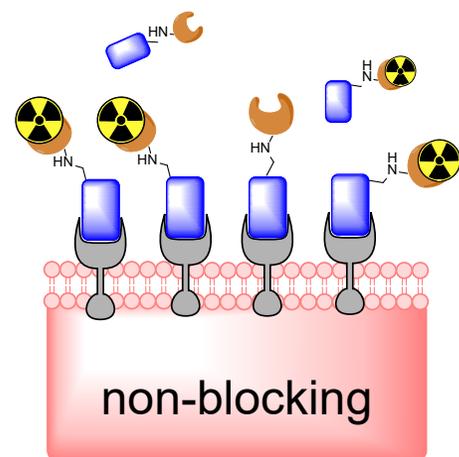
^{225}Ac Radiolabeling of DOTA-CycMSH



^{225}Ac Radiolabeling of DOTA-CycMSH



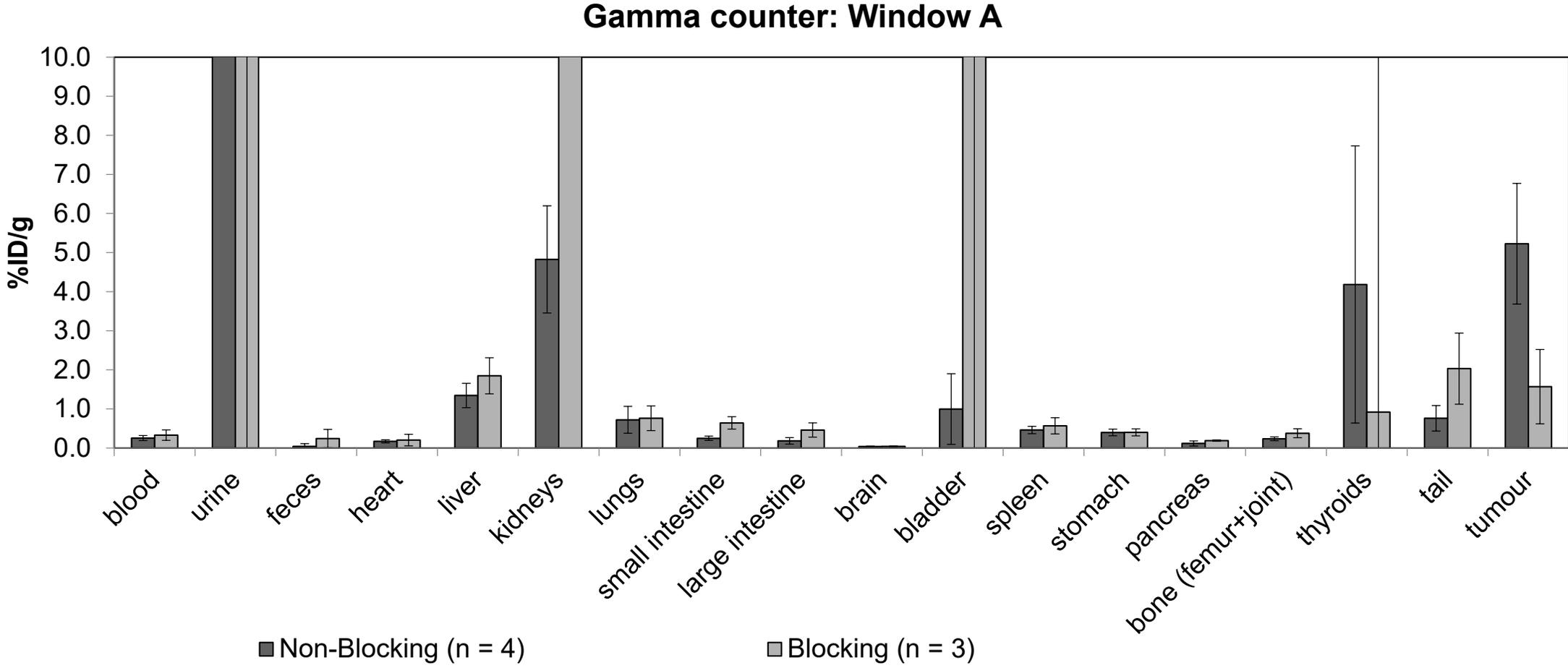
Experiment	Molar Activity (kBq/nmol)	Total injected peptide (nmol)	Total injected activity (kBq)	Unlabeled:labeled peptide ratio
Non-blocking	> 200	~ 0.1	~ 20	~2,440:1
Blocking	1.6	~14	~ 22	~305,000:1



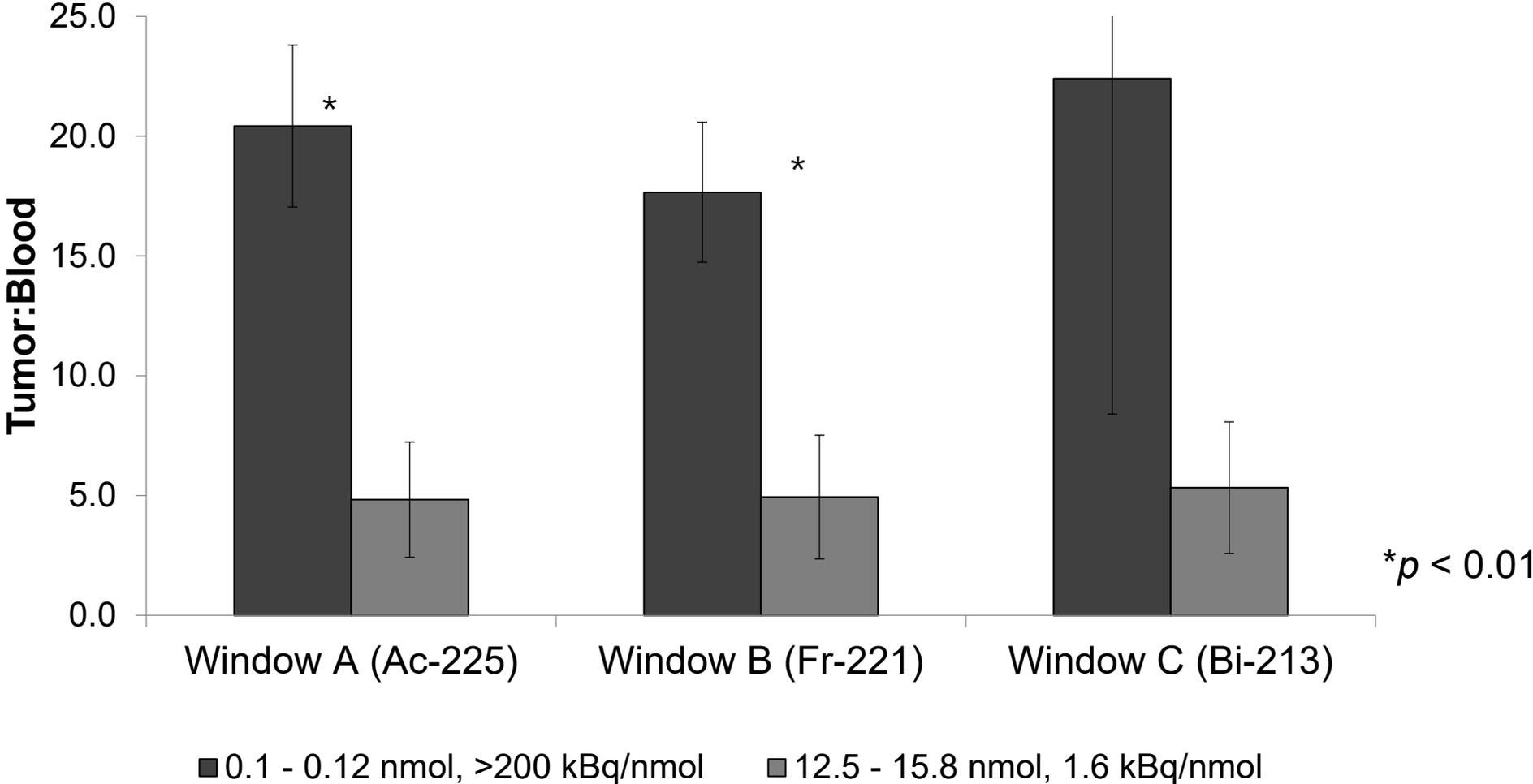
Note: ^{225}Ac -CCZ01048 was purified via RP-HPLC (for non-blocking study only) to remove excess unlabeled CCZ01048, and C18 sep-pak to remove free $^{225}\text{Ac}^{3+}$

In Vivo Biodistribution of ^{225}Ac -DOTA-CycMSH

Purified radiotracer injected via tail vein into mice bearing melanoma tumours (B16F10 cells); organs harvested at **2 h p.i.**



In Vivo Biodistribution of ²²⁵Ac-DOTA-CycMSH



Window A = ²²⁵Ac energy (60-120 keV); Window B = ²²¹Fr energy (180-260 keV); Window C = ²¹³Bi energy (400-480 keV)

Conclusions & Future Work

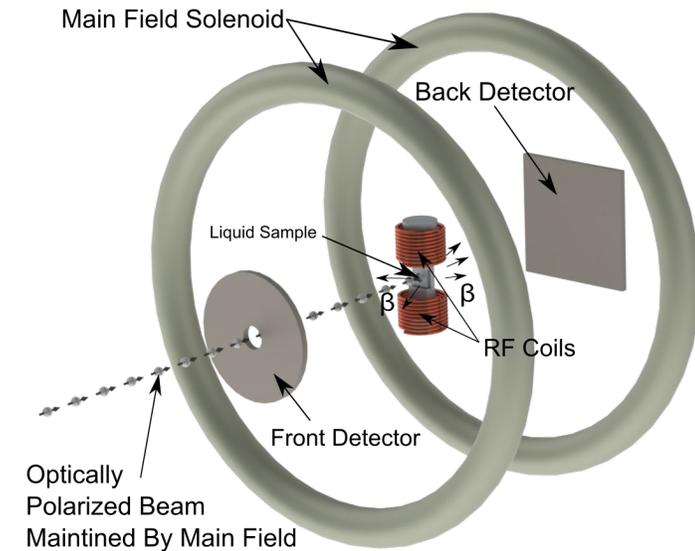
- **MBq quantities** of ^{225}Ra (1.1 – 7.5 MBq) & ^{225}Ac (1.4 – 18.0 MBq) can be produced via the ISOL technique by irradiation of UC_x targets → isotopically **pure ^{225}Ac product**
- Simple, one-step purification of ^{225}Ac yields product of high radionuclidic purity, while ^{225}Ra can be stored and used as a generator
- Isolated ^{225}Ac enables preclinical radiolabeling, in vitro, and in vivo studies with a variety of novel chelating ligands and bioconjugates
- Medical Isotope Production via ISOL has shifted towards production of other exotic and medically relevant isotopes
 - **A = 224** | ^{212}Pb via ^{224}Ra (10^8 ions/s)
 - **A = 165** | ^{165}Er via ^{165}Tm (10^{10} ions/s)

Future Work

- Designing more effective ^{225}Ac -radiopharmaceuticals: Elucidating the coordination environment of Ac-complexes using β -NMR



β -NMR with liquid samples - Dr. Monika Stachura (TRIUMF)



ISOL will provide access to ^{230}Ac , ^{234}Ac \rightarrow suitable for β NMR measurement

Acknowledgments

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Una Jermilova (co-op, UBC)

Lily Southcott (co-op, McMaster)

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UBC Chemistry

Prof. Chris Orvig

Sarah Spreckelmeyer

Thomas Kostelnik

Lily Li

Orvig group

BC Cancer

Prof. François Bénard

Chengcheng Zhang

Gemma Dias

Julie Rousseau

Nadine Colpo

Cornell

Prof. Justin Wilson

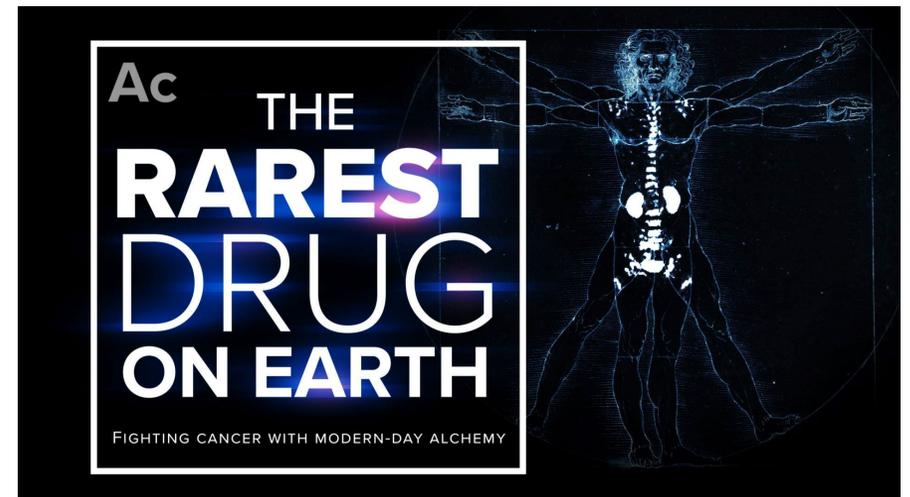
Nikki Thiele

U. Heidelberg

Prof. Peter Comba

Katharina Rück

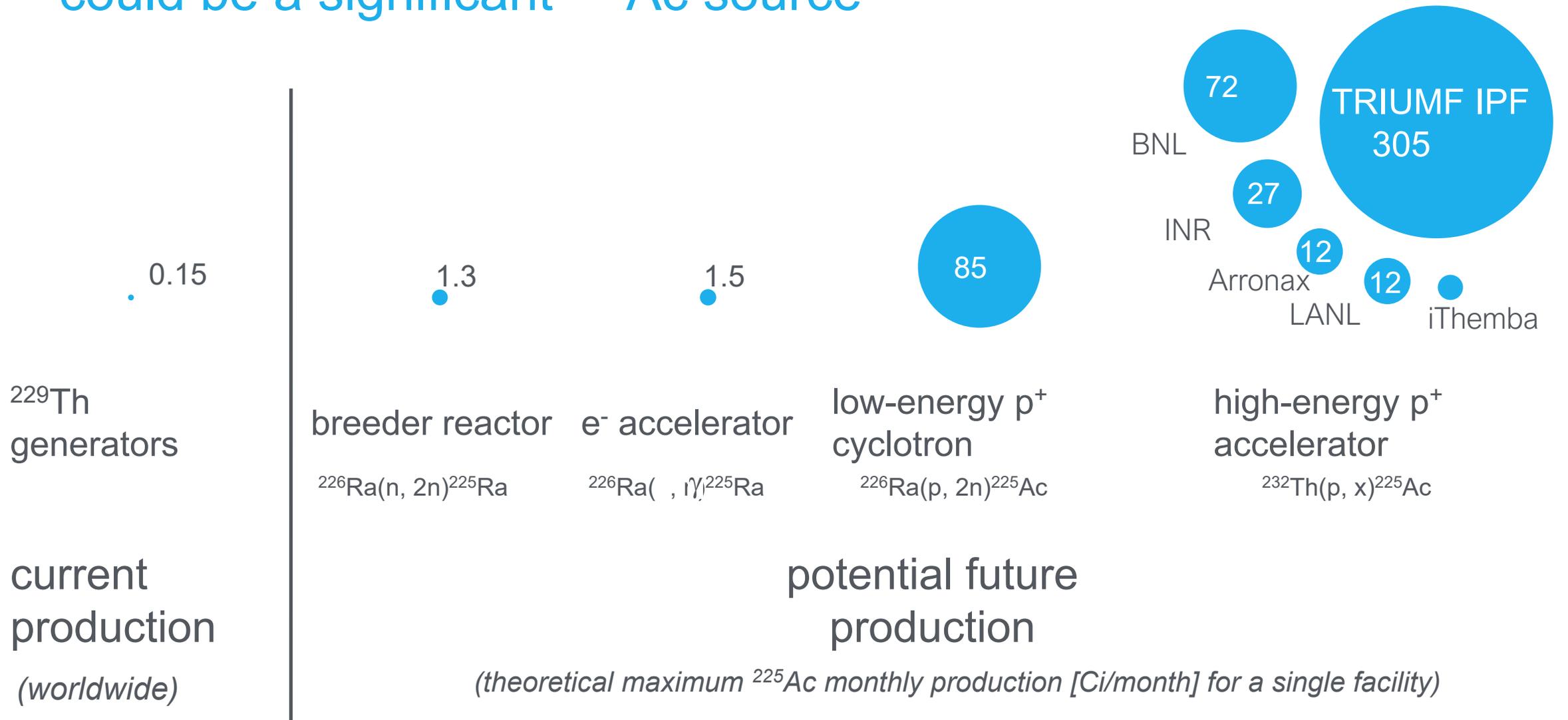
**10 min documentary highlighting
TRIUMF’s efforts to produce ^{225}Ac**



rarestdrug.com



TRIUMF's 500 MeV Isotope Production Facility could be a significant ^{225}Ac source



Robertson, et al., "Development of ^{225}Ac Radiopharmaceuticals: TRIUMF Perspectives and Experiences," *Curr. Radiopharm.*,

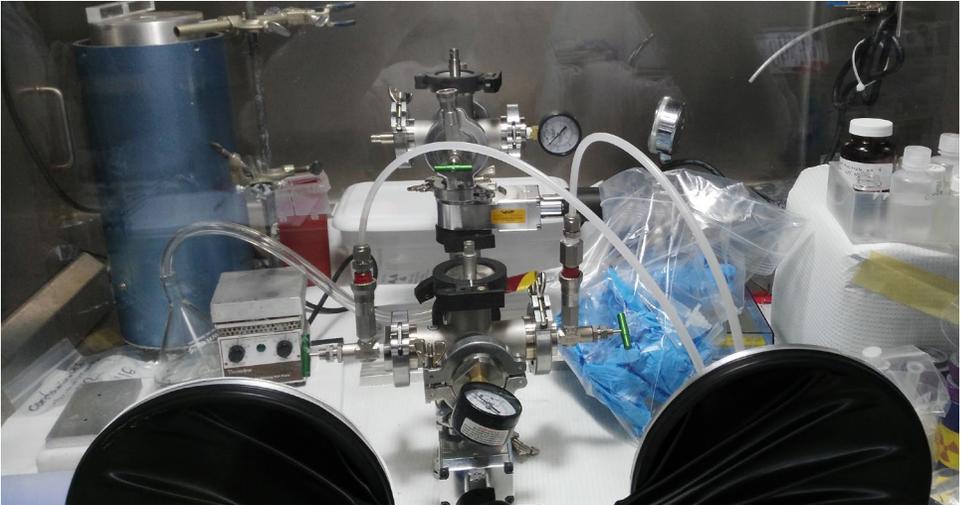
^{225}Ac must be purified from thorium and many other elements

elements with isotopes in thorium target 1 week after EOB

1 IA 1A	2 IIA 2A																	13 IIIA 3A	14 IVA 4A	15 VA 5A	16 VIA 6A	17 VIIA 7A	18 VIIIA 8A	
	4 Be Beryllium																							
11 Na Sodium	12 Mg Magnesium	3 IIIB 3B	4 IVB 4B	5 VB 5B	6 VIB 6B	7 VIIB 7B	8 VIII 8	9 VIII 9	10 VIII 10	11 IB 1B	12 IIB 2B			15 P Phosphorus	16 S Sulfur								18 Ar Argon	
19 K Potassium	20 Ca Calcium	21 Sc Scandium		23 V Vanadium	24 Cr Chromium	25 Mn Manganese	26 Fe Iron	27 Co Cobalt	28 Ni Nickel	29 Cu Copper	30 Zn Zinc	31 Ga Gallium	32 Ge Germanium	33 As Arsenic	34 Se Selenium	35 Br Bromine	36 Kr Krypton							
37 Rb Rubidium	38 Sr Strontium	39 Y Yttrium	40 Zr Zirconium	41 Nb Niobium	42 Mo Molybdenum	43 Tc Technetium	44 Ru Ruthenium	45 Rh Rhodium	46 Pd Palladium	47 Ag Silver	48 Cd Cadmium	49 In Indium	50 Sn Tin	51 Sb Antimony	52 Te Tellurium	53 I Iodine	54 Xe Xenon							
55 Cs Cesium	56 Ba Barium	57-71	72 Hf Hafnium	73 Ta Tantalum	74 W Tungsten	75 Re Rhenium	76 Os Osmium	77 Ir Iridium	78 Pt Platinum	79 Au Gold	80 Hg Mercury	81 Tl Thallium	82 Pb Lead	83 Bi Bismuth	84 Po Polonium	85 At Astatine	86 Rn Radon							
	88 Ra Radium	89-103																						
Lanthanide Series	57 La Lanthanum	58 Ce Cerium	59 Pr Praseodymium	60 Nd Neodymium	61 Pm Promethium	62 Sm Samarium	63 Eu Europium	64 Gd Gadolinium	65 Tb Terbium	66 Dy Dysprosium	67 Ho Holmium	68 Er Erbium	69 Tm Thulium	70 Yb Ytterbium	71 Lu Lutetium									
Actinide Series	89 Ac Actinium	90 Th Thorium	91 Pa Protactinium	92 U Uranium																				

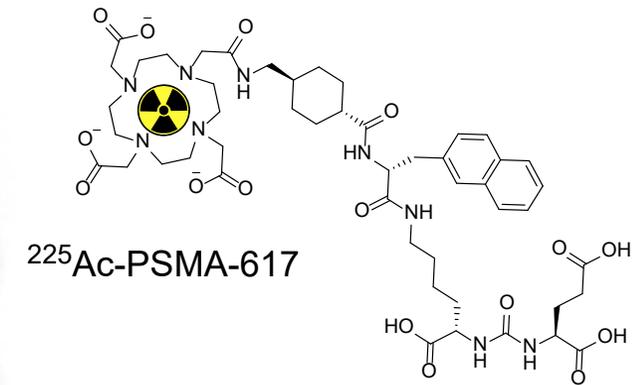
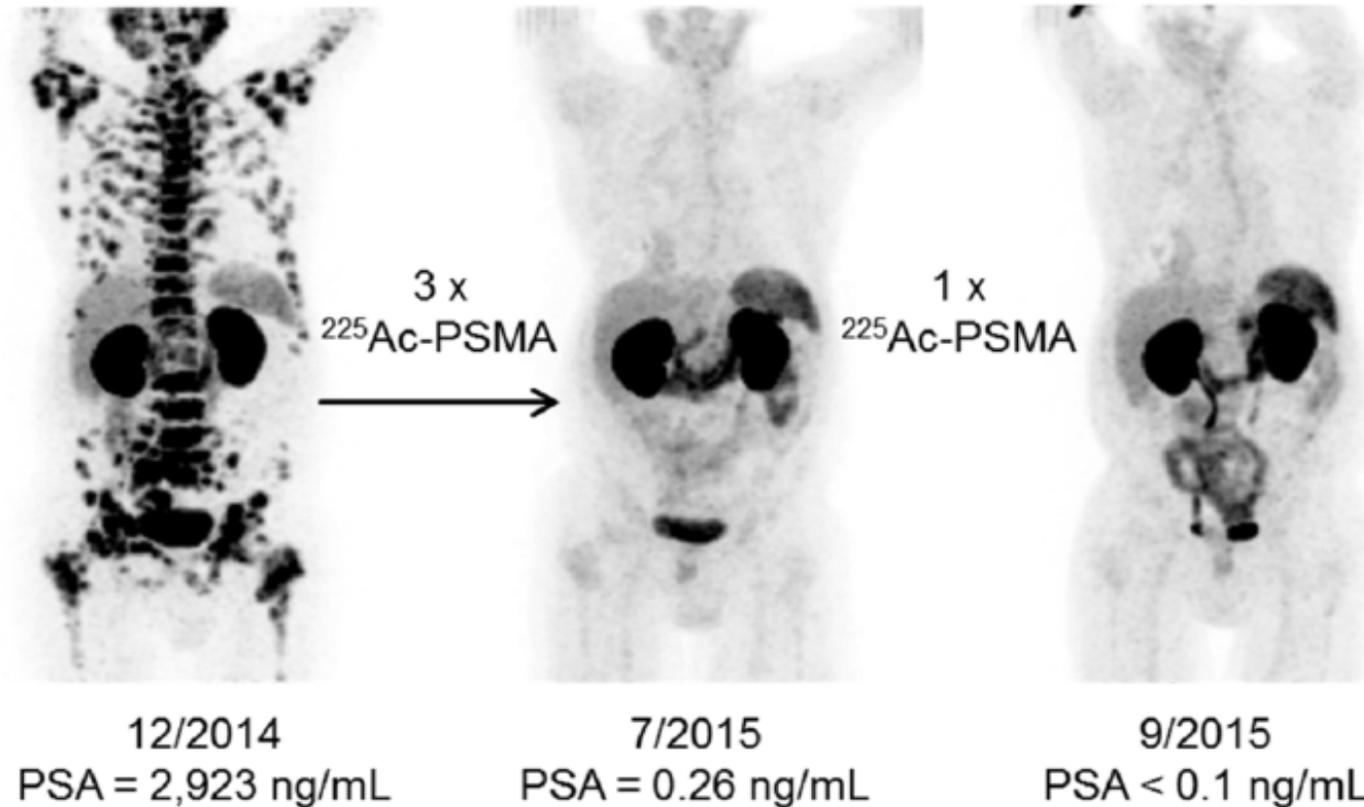
- challenging purification chemistry
- complex radiation hazards

Target Removal



Targeted Alpha-Therapy with ^{225}Ac

^{225}Ac labeled prostate specific membrane antigen (PSMA) has shown remarkable therapeutic response in patients – **complete remission**



PET images of the ^{68}Ga -labeled analogue