

Cyclotron-Based Production of Metallic Radionuclides for Medical Application

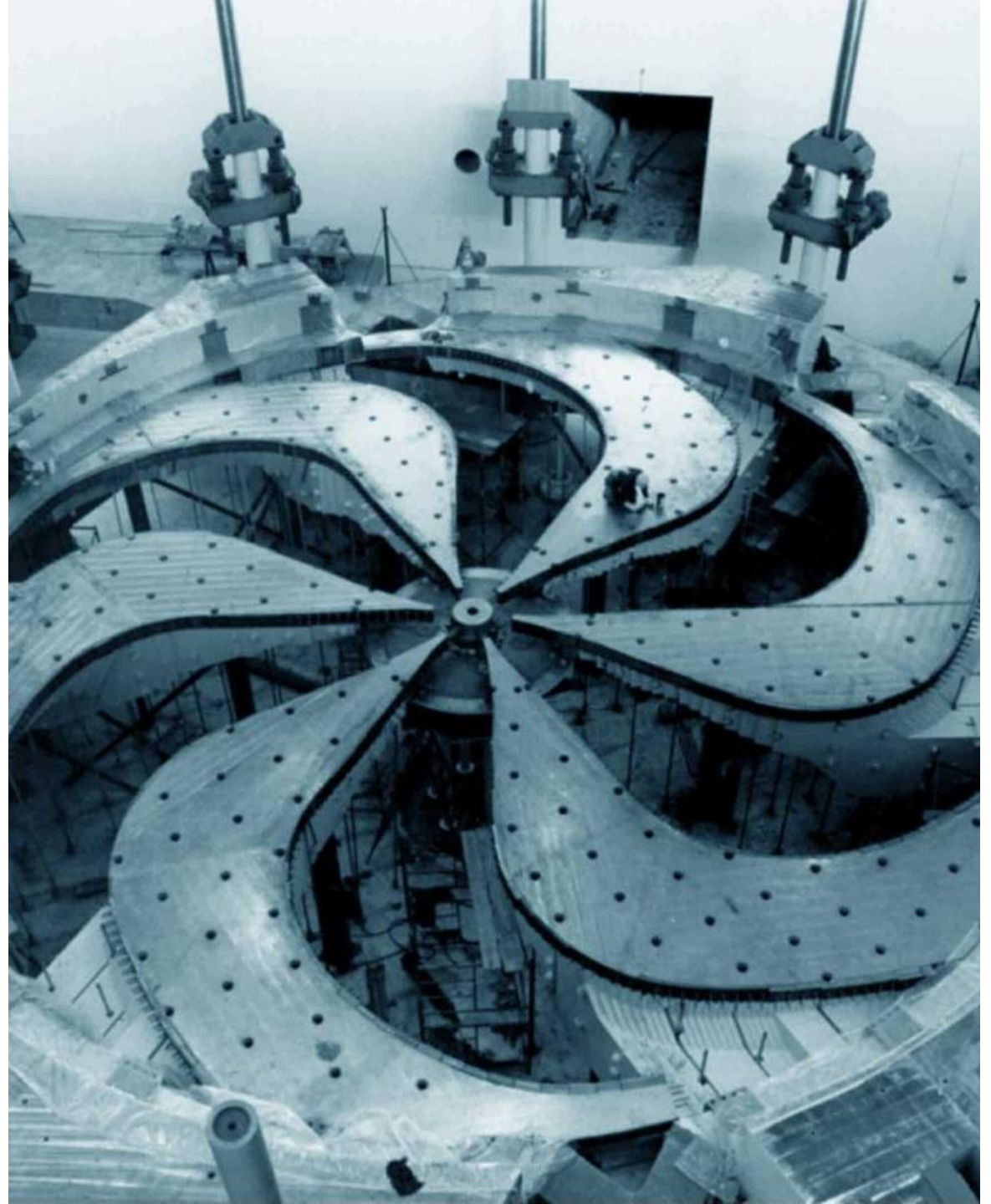
Paul Schaffer, PhD

Associate Laboratory Director, Life Sciences

TRIUMF

May 1st, 2018

2018-05-01



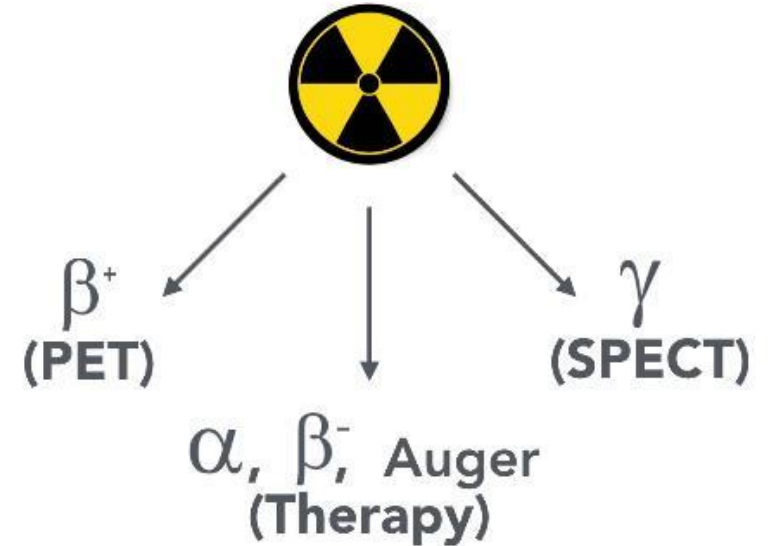
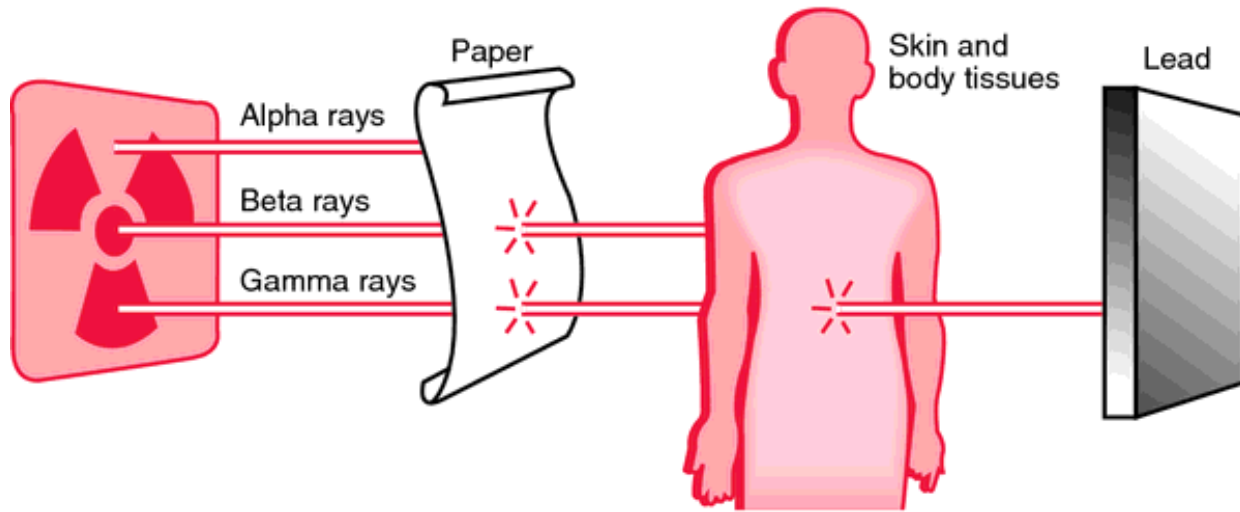
Disclosure

- I am a full-time employee of TRIUMF
- TRIUMF is part owner of a spin-off company called ARTMS Products, Inc.
- I am compensated by ARTMS Products, Inc. and currently serve as Chief Technology Officer
- I am a listed inventor on patents in technology licensed to ARTMS
- To avoid bias, I will present updates on competing technologies and describe the benefits and drawbacks of each

Overview

- Introduction:
 - Isotopes, Isotope Production, Medical Imaging and Radionuclide Therapy
- R&D Summary of:
 - Solid Targets for Accelerator Production of Isotopes
 - Liquid Targets for Accelerator Production of Metallic Radionuclides
 - Therapeutic Isotope Production
- Summary and Conclusions

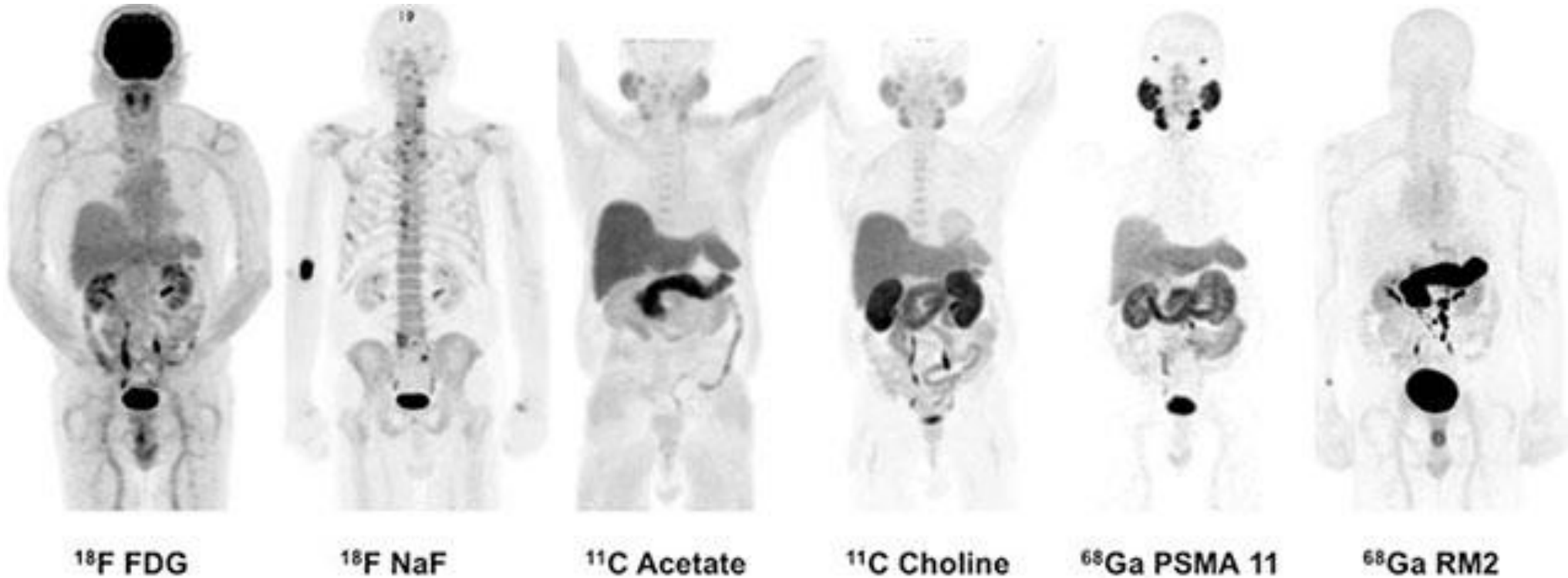
Isotopes in Medicine



Considerations:

- Emission type/intended application
- Radiological properties: half-life, branching ratio(s)
- Chemical properties: compatibility with radiopharmaceutical process

Isotopes enable functional imaging....



83-year-old man with biochemically recurrent prostate cancer

A. Iagaru, et al. J. Nucl. Med. 2016;57(4):557-62

...and an understanding of our biology at the molecular level

Metallic Isotopes in Medicine

PET Isotopes (Short Half-Life) / SPECT Isotopes (Long Half-Life)

E
Element Denotes an element with isotopes suitable for both PET and SPECT

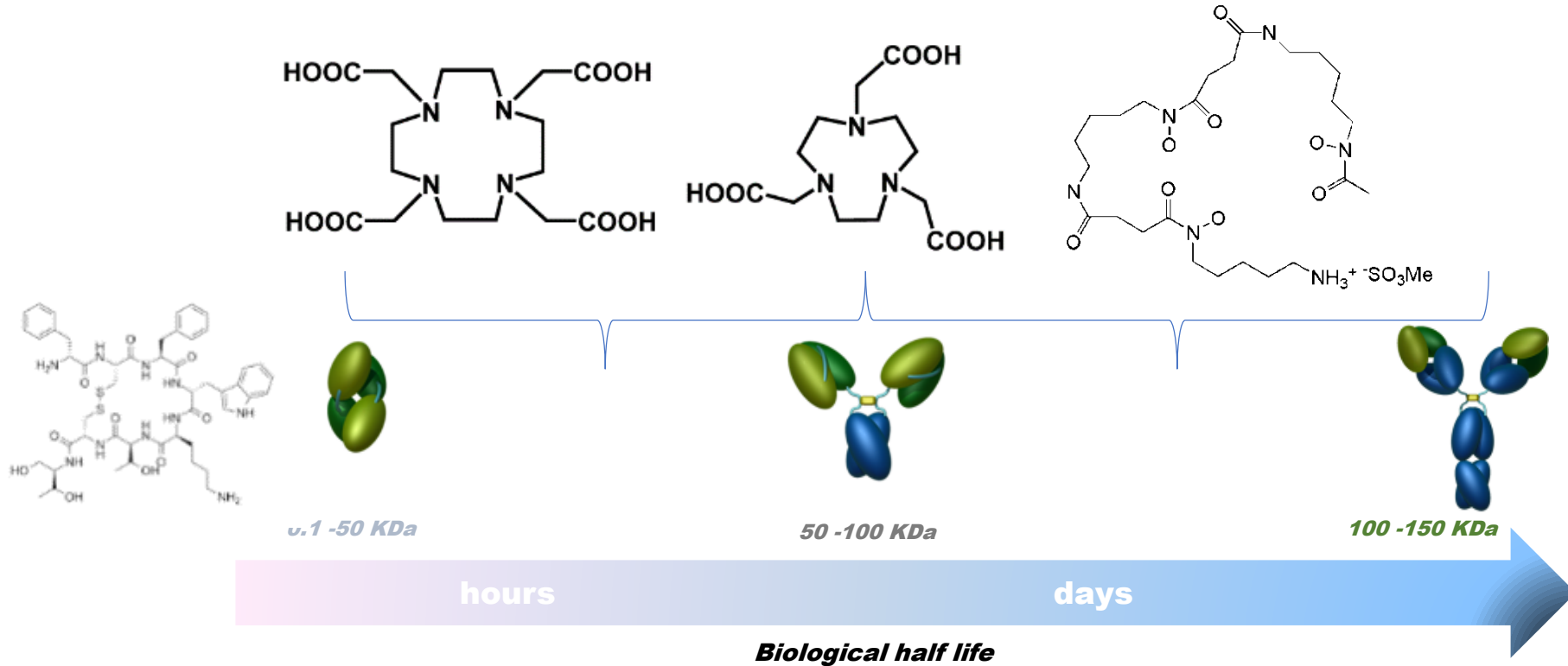
E
Element Denotes an element with multiple isotopes with different physical half-lives

1 H Hydrogen																	2 He Helium						
3 Li Lithium	4 Be Beryllium																	5 B Boron	6 C Carbon	7 N Nitrogen	8 O Oxygen	9 F Fluorine	10 Ne Neon
11 Na Sodium	12 Mg Magnesium																	13 Al Aluminum	14 Si Silicon	15 P Phosphorus	16 S Sulfur	17 Cl Chlorine	18 Ar Argon
19 K Potassium	20 Ca Calcium	21 Sc Scandium	22 Ti Titanium	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	57-70 Lanthanides	71 Lu* Lutetium	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					
87 Fr Francium	88 Ra Radium	89-102 Actinides	103 Lr Lawrencium	104 Rf Rutherfordium	105 Db Dubnium	106 Sg Seaborgium	107 Bh Bohrium	108 Hs Hassium	109 Mt Meitnerium	110 Ds Darmstadtium	111 Rg Roentgenium	112 Cn Copernicium	113 Uut Ununtrium	114 Fl Flerovium	115 Uup Ununpentium	116 Lv Livermorium	117 Uus Ununseptium	118 Uuo Ununoctium					

*Isotopes typically used for radiotherapy with which SPECT is also possible but not common — e.g., ^{177}Lu , ^{105}Rh , ^{186}Re , etc. — have been omitted.

Isotope toolkit

	^{64}Cu	^{86}Y	$^{99\text{m}}\text{Tc}$	^{119}Sb	
	$t_{1/2}$ 12.7 h	$t_{1/2}$ 14.7 h	$t_{1/2}$ 6.01 h	$t_{1/2}$ 38.2 h	
^{213}Bi	^{68}Ga	^{44}Sc	^{90}Nb	^{89}Zr	^{225}Ac
$t_{1/2}$ 0.76 h	$t_{1/2}$ 1.13 h	$t_{1/2}$ 3.97 h	$t_{1/2}$ 14.6 h	$t_{1/2}$ 78.4 h	$t_{1/2}$ 238.1 h



Diagnostic Radionuclides

- **For SPECT**

γ -emitters (100 – 250 keV)

^{99m}Tc , **(steady use)**

^{123}I **(increasing)**

^{201}Tl , ^{67}Ga **(declining)**

- **For PET**

β^+ emitters (511 keV photons)

^{11}C , ^{13}N , ^{15}O , ^{18}F , ^{82}Sr (^{82}Rb), ^{64}Cu **(increasing use)**

^{68}Ge (^{68}Ga) **(rapidly increasing use)**

Therapeutic Radionuclides

- β^- -emitters (^{32}P , ^{90}Y , ^{131}I , ^{153}Sm , ^{177}Lu)

- α -emitter (^{211}At , ^{223}Ra , ^{225}Ac)

- Auger electron emitters (^{111}In , ^{125}I , ^{119}Sb)

- X-ray emitter (^{103}Pd)

(increasing significance)

Generation 1: Simple: salts, diffusion-based, non-specific imaging

$^{99m}\text{TcO}_4$, $^{99m}\text{TcMDP}$, $^{18}\text{F}^-$ (bone), colloid (liver)

Generation 2: Targeted, small molecule, metabolic

$^{99m}\text{TcMIBI}$ (heart), ^{99m}Tc -exametazime/ECD (brain), ^{18}F FDG (tumors)

Generation 3: Targeted, larger molecular weight (peptides, antibodies), binders radiolabeled (^{111}In , ^{68}Ga) octreotide, octreotate, ^{99m}Tc TRODAT, PSMA

Generation 4(?): Theranostic, simultaneous or iso-pharmaceutical imaging/therapy

$[^{223}\text{Ra}]\text{RaCl}_2$ (Xofigo), ^{153}Sm , ^{89}Sr , ^{131}I , $[^{131}\text{I}]\text{Bexxar}$, $[^{90}\text{Y}]\text{Zevalin}$
 ^{225}Ac , ^{212}Pb , ^{213}Bi , ^{212}Bi , ^{211}At ...targeted using Gen 3 vectors

2013 tracer count*:	PET (all) = 622; (humans) = 122
	SPECT (all) = 430; (humans) = 65

* MICAD Database – final year of online catalogue update

Making Isotopes



Reactor



Cyclotrons
(Accelerators)

Making Isotopes



$^{68}\text{Ge}/^{68}\text{Ga}$
(271 d, 68 min)



$^{82}\text{Sr}/^{82}\text{Rb}$
(25.4 d, 1.3 min)

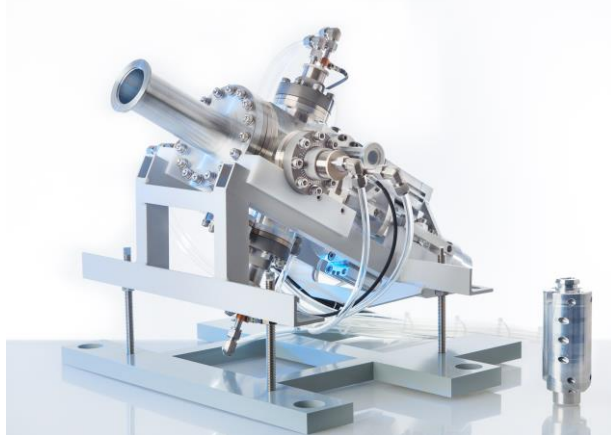


$^{99}\text{Mo}/^{99\text{m}}\text{Tc}$
(66 hr, 6 hr)

- Transportable, easy to use
- Some (^{68}Ga) experiencing wait times, difficult and expensive to purchase

Life Sciences at TRIUMF

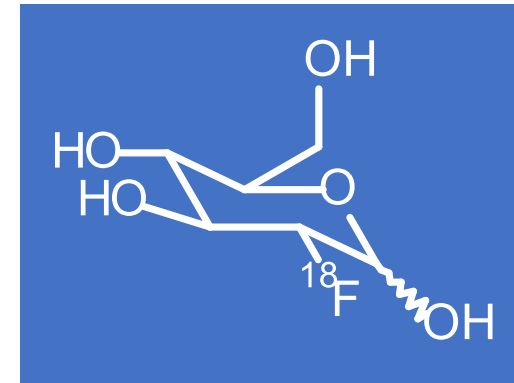
Applied Ion Beams



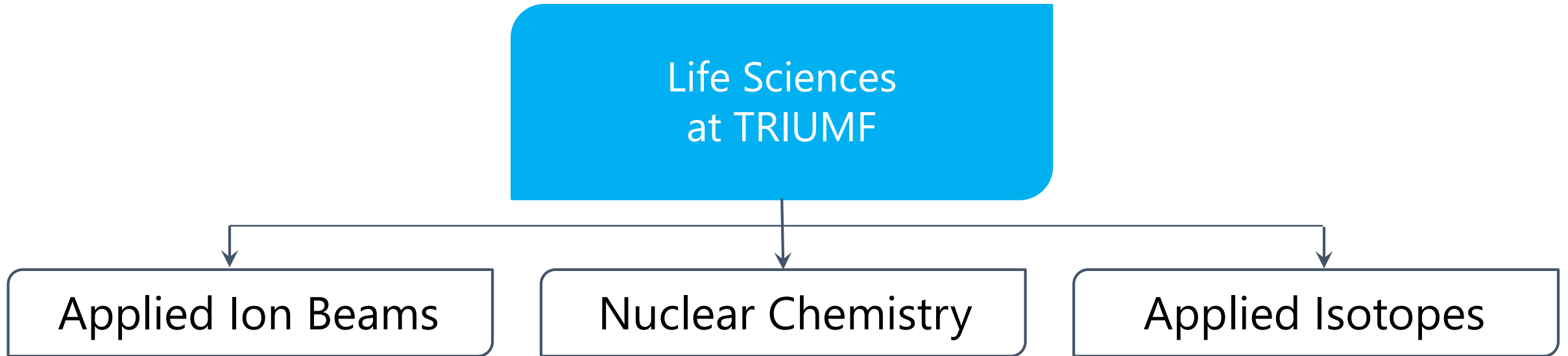
Nuclear Chemistry



Applied Isotopes



TRIUMF Life Sciences focuses on advancing accelerator-based technology for the development of isotopes that can improve life



This talk:

- Solid targets, accelerator production of ^{99m}Tc , ^{89}Zr , ^{68}Ga , ^{64}Cu
- Liquid targets, accelerator production of ^{89}Zr , ^{68}Ga , others
- Therapeutic isotopes

Reactor Supply Model

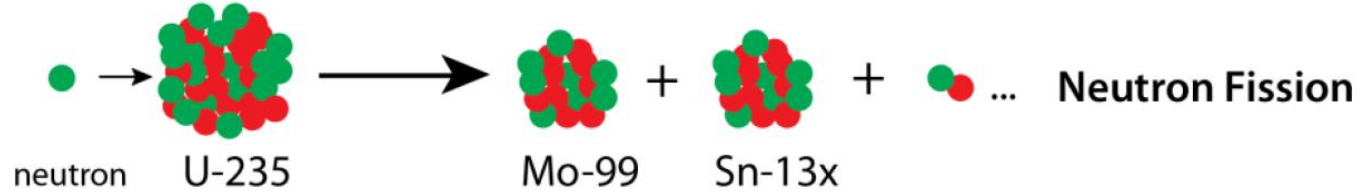
Issues:

- Economics/subsidies
- Politics/misuse
- Social/environmental
- Single point of failure



- Current ^{99}Mo demand: 9,000 6d Ci/wk
- Require 35% buffer capacity for supply stability
- No fewer than 9 producers, 6 processors currently on-line
 - 2 more producers, 1 additional processor expected on-line within 2 years
- Current ^{99}Mo production capacity: ~17,300 6d Ci/wk
 - Additional ~2500 6d Ci/wk capacity coming on-line <2 years
- Challenges continue:
 - Push for full-cost recovery
 - Anti-proliferation - conversion from HEU to LEU
 - 6 of 9 reactors scheduled to end operations within 10 years
 - Some products (^{60}Co , ^{192}Ir , ^{125}I ...) not easily produced by other methods

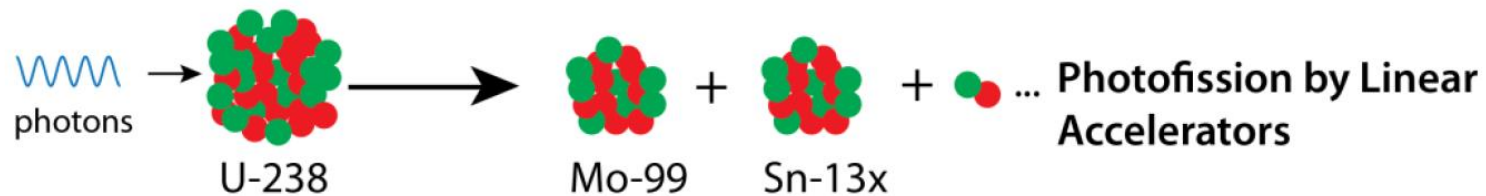
NUCLEAR REACTORS



CYCLOTRONS



LINEAR ACCELERATORS



Accelerator Supply Model

Issues:

- Decentralized production/regulatory
- Complex compared to generator
- Shorter-lived isotopes



Cyclotron

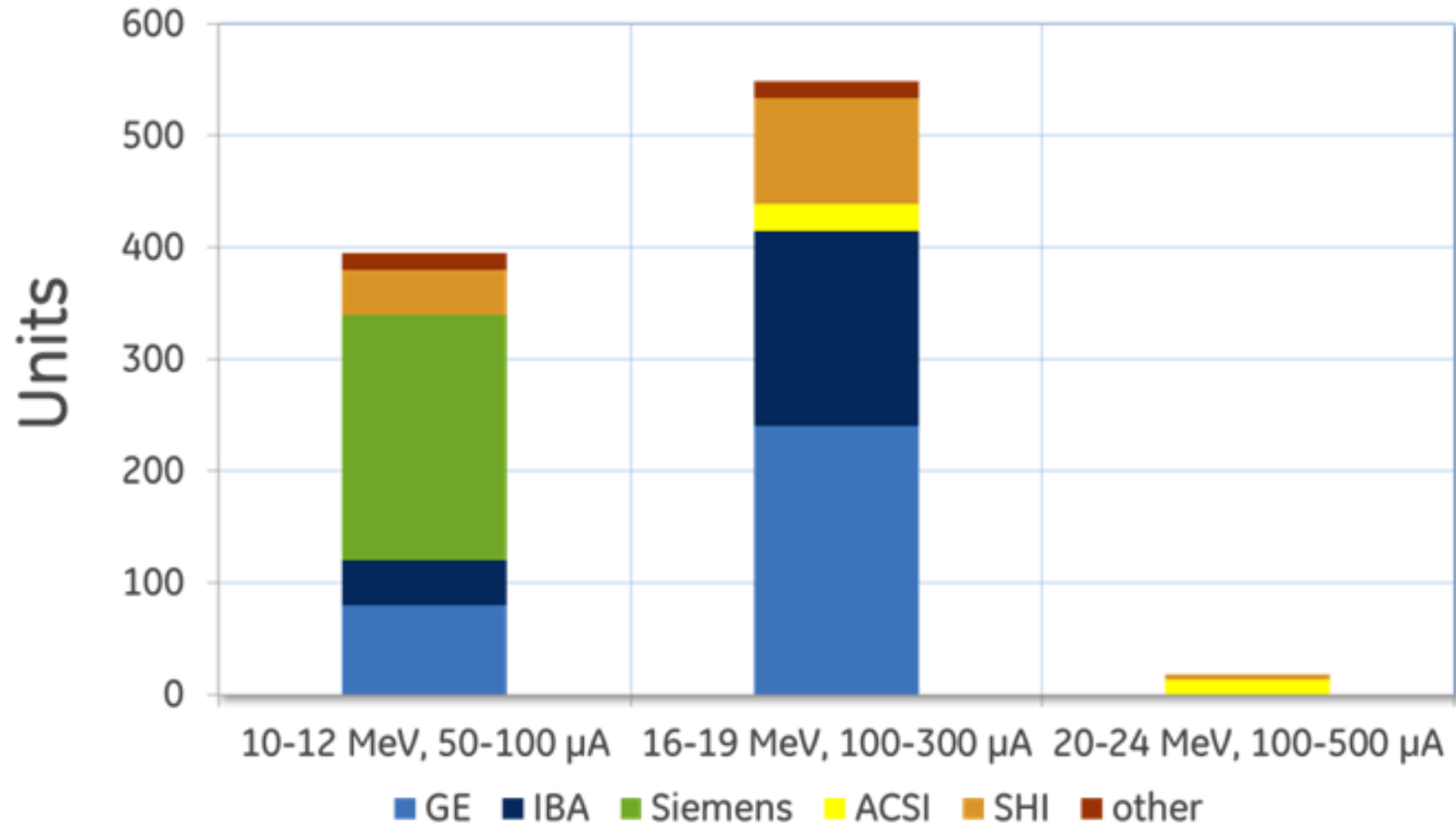


Radiopharmacy

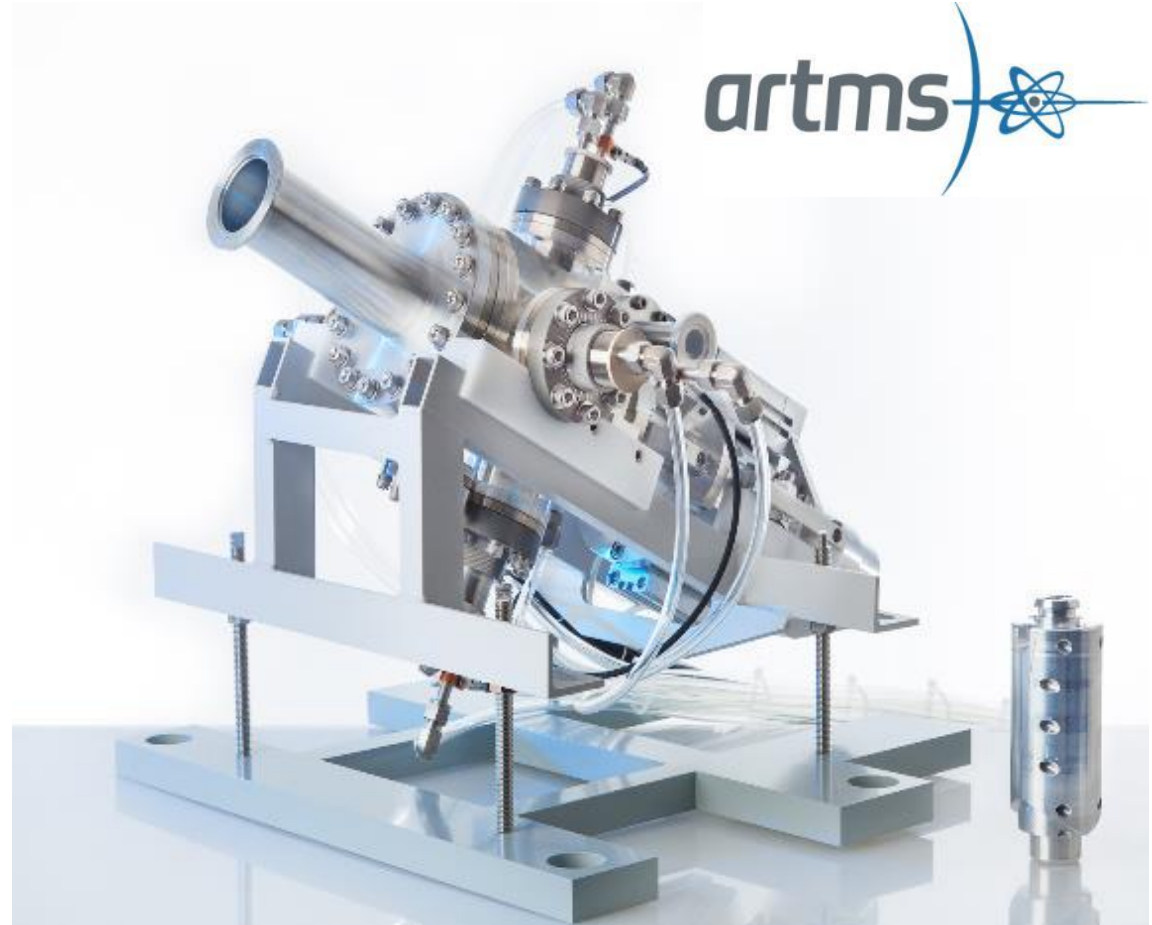
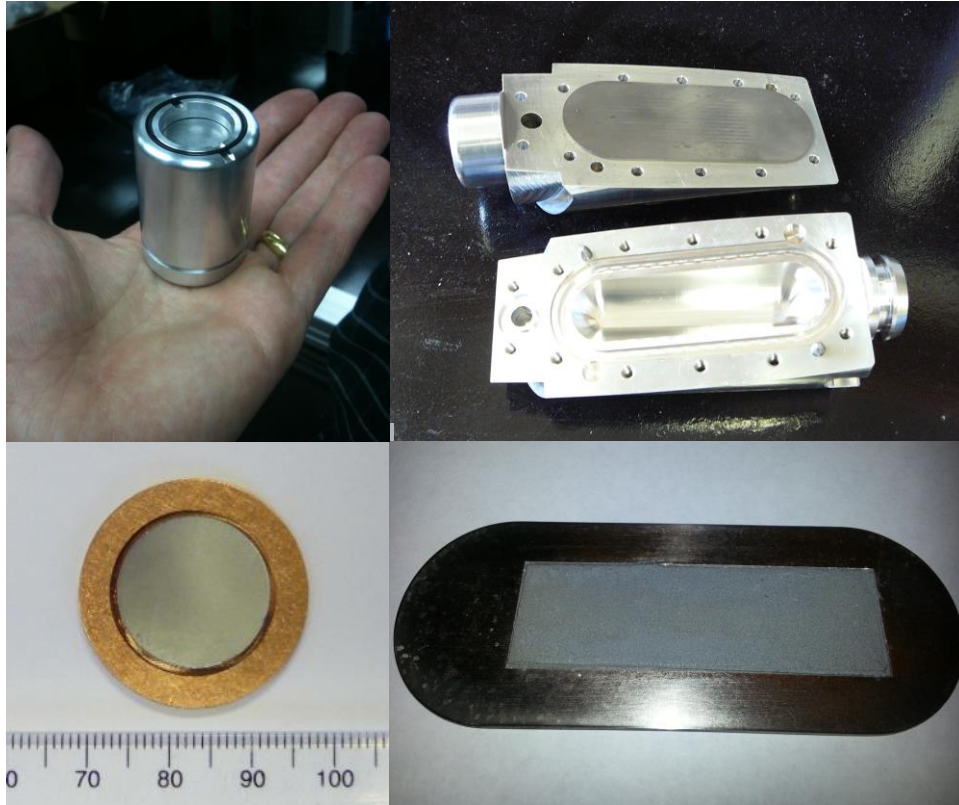


Clinic

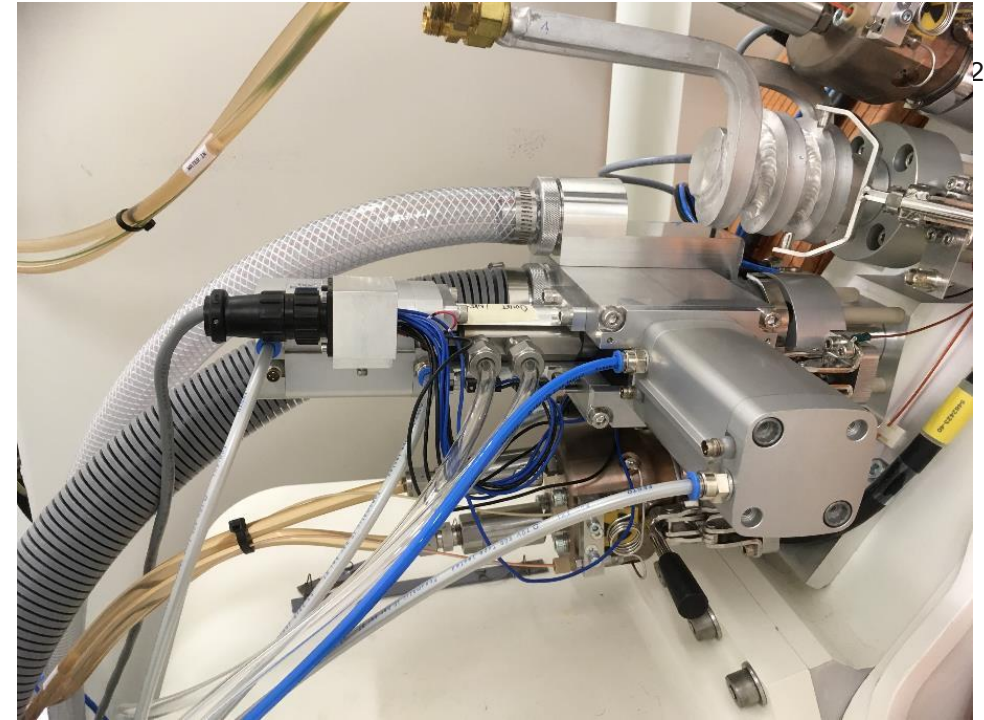
Global Cyclotron Count



P Schaffer, F. Benard, A. Berstein et al. Phys Proc. 2015, 66, 383.



- Production yields of ^{99m}Tc
 - GE **PETTrace** (16.5 MeV, 130 μA): **4.7 Ci** in 6 hrs
 - ACSI **TR19** (18 MeV, 240 μA): **13.9 Ci** in 6 hrs
 - ACSI **TR30** (24 MeV, 450 μA): **~39 Ci** in 6 hrs
- Concurrent ^{18}F production demonstrated successfully
- Purification efficiency: **>93%**
- ^{99}Mo recycling efficiency: **>95%**
- Demonstration of other metals underway
- 60 patient clinical trial completed
- Regulatory filings for Canada, UK underway



ARTMS Target Systems:

Vancouver, London, Hamilton, Canada –
Tc-99m

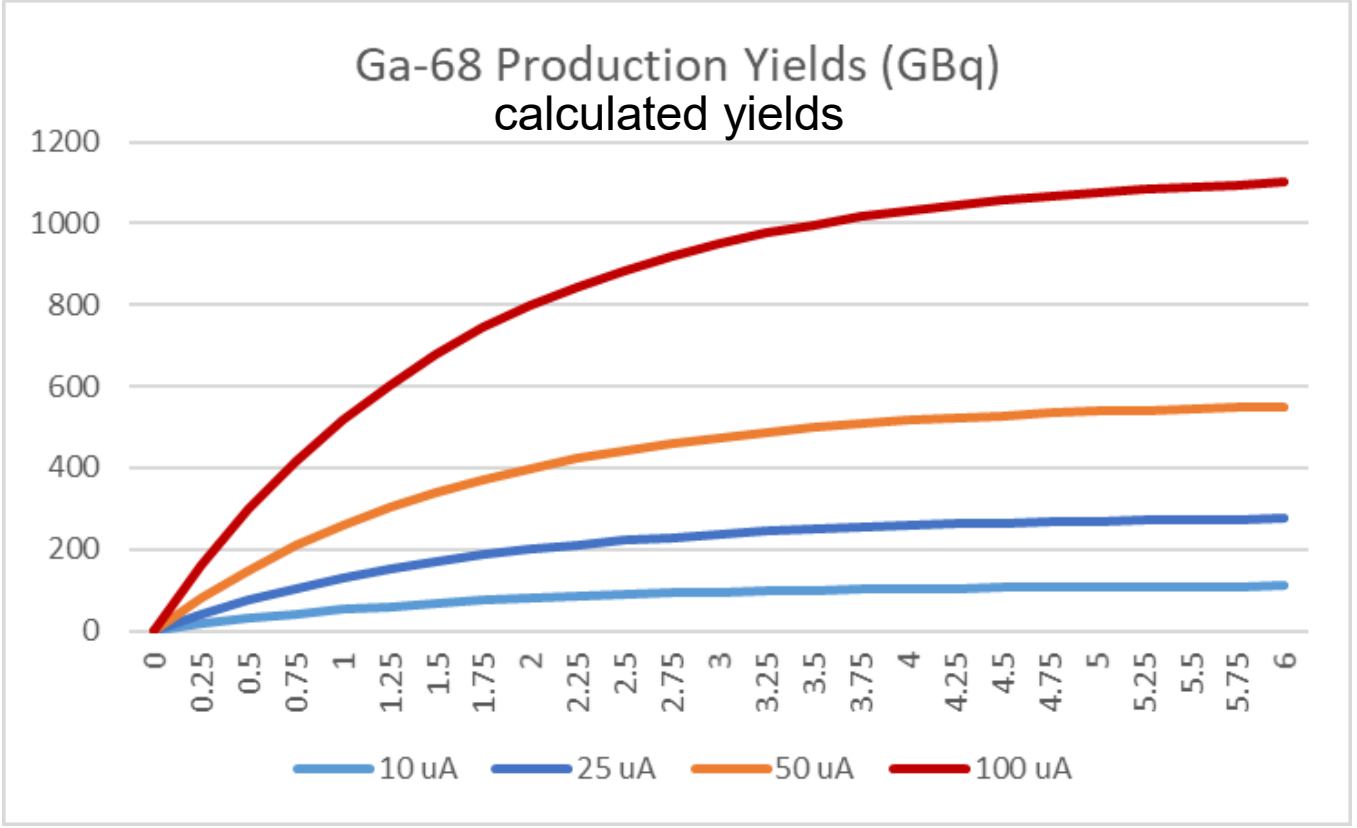
Odense, Denmark – Cu-64

Zurich, Switzerland – Ga-68

Madison, Wisconsin – various

Upcoming: UK – Tc-99m

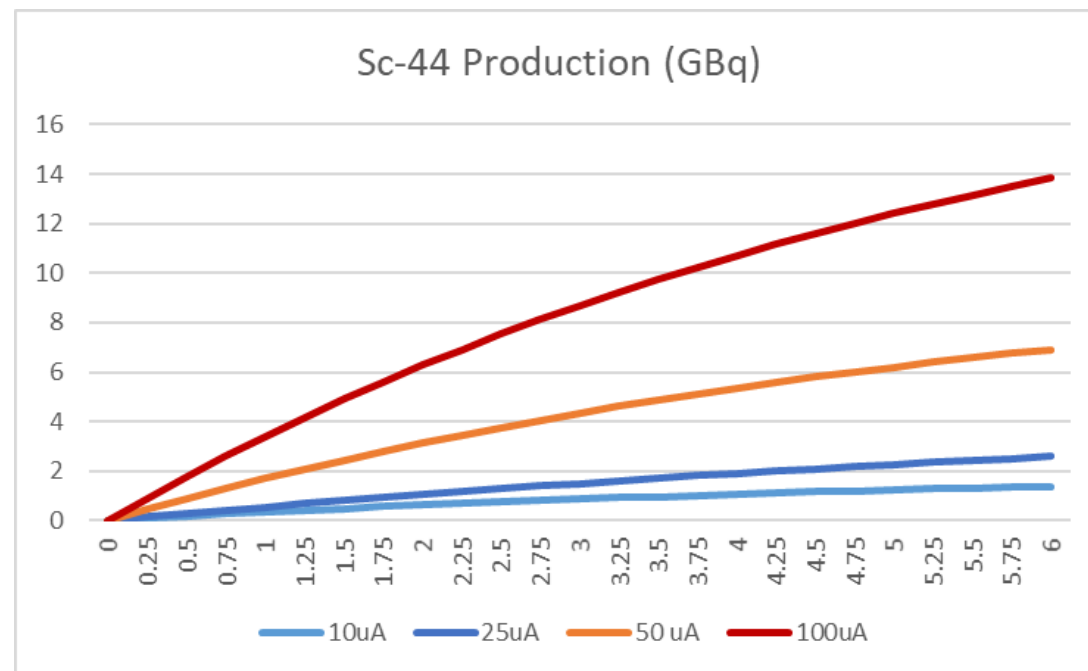
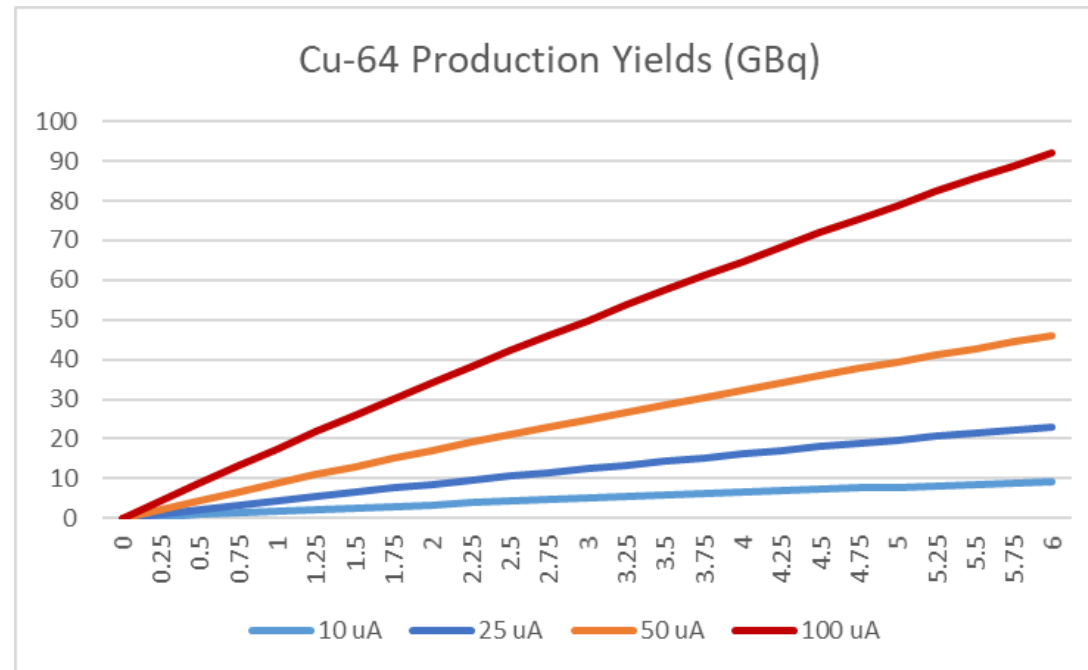
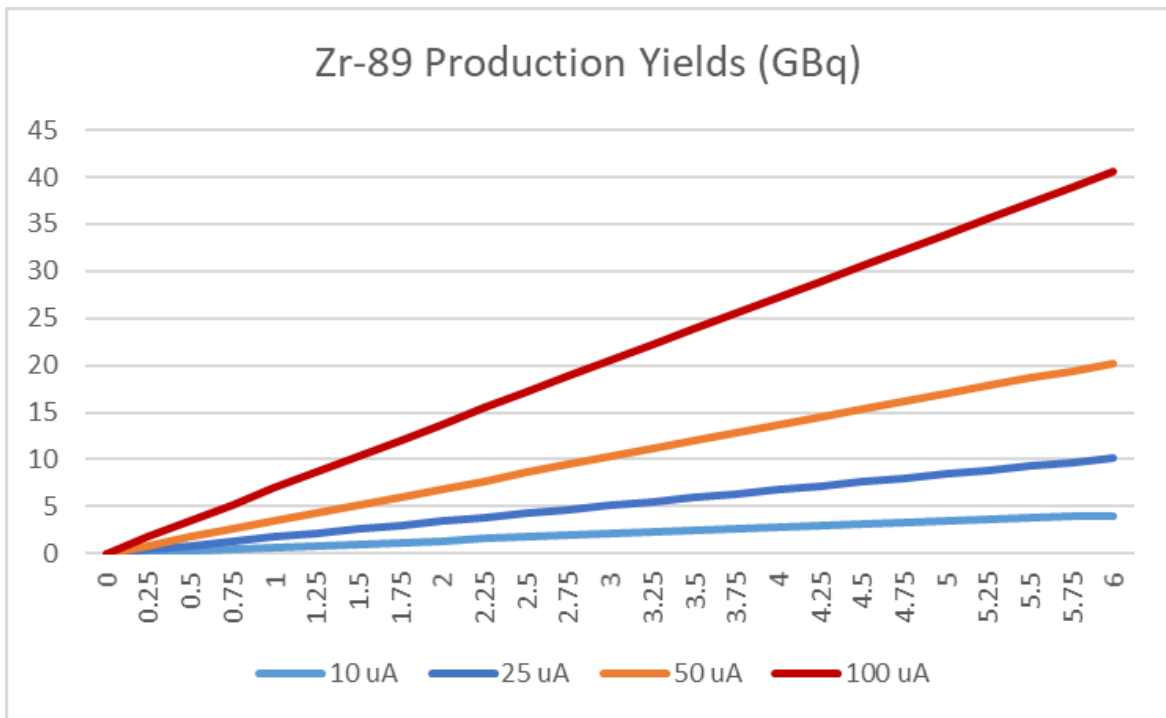
Solid targets for other metallic isotopes



⁶⁸Ga PSMA 11



⁶⁸Ga RM2

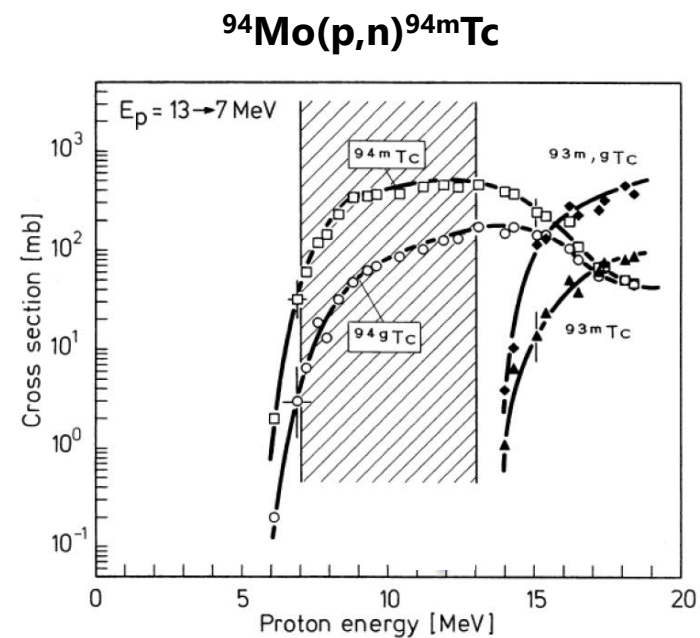
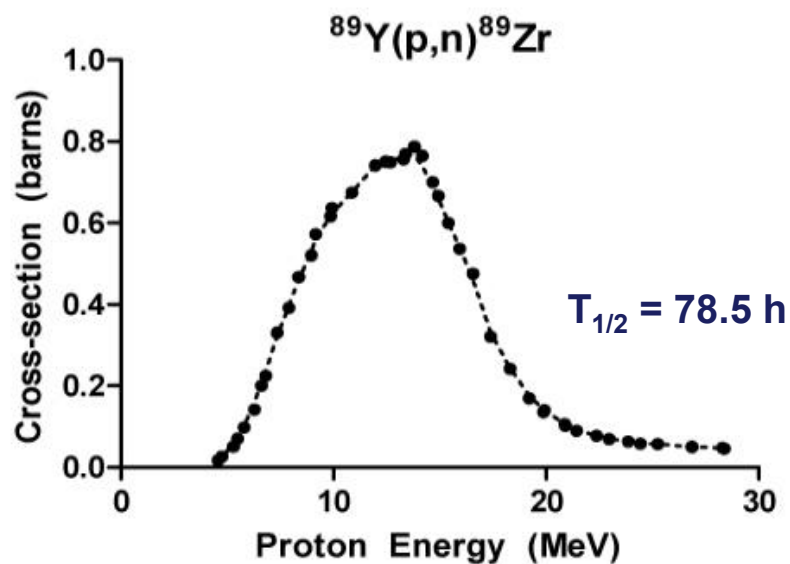
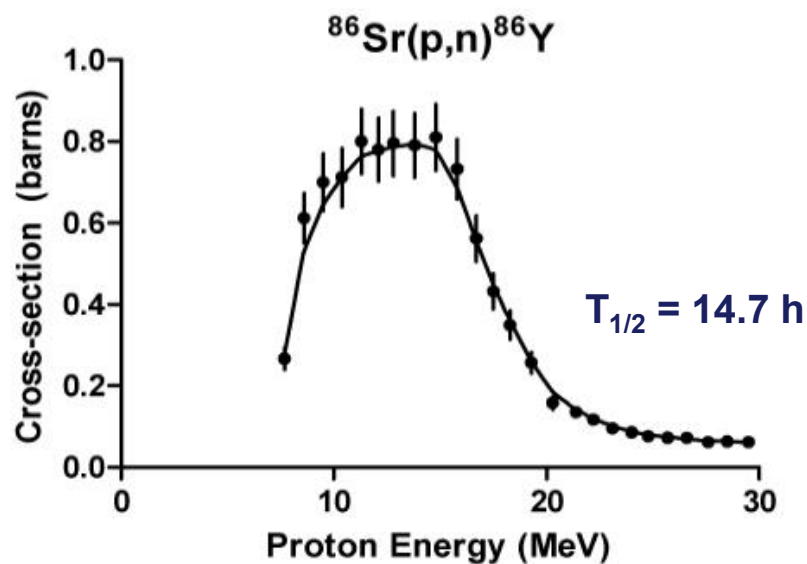
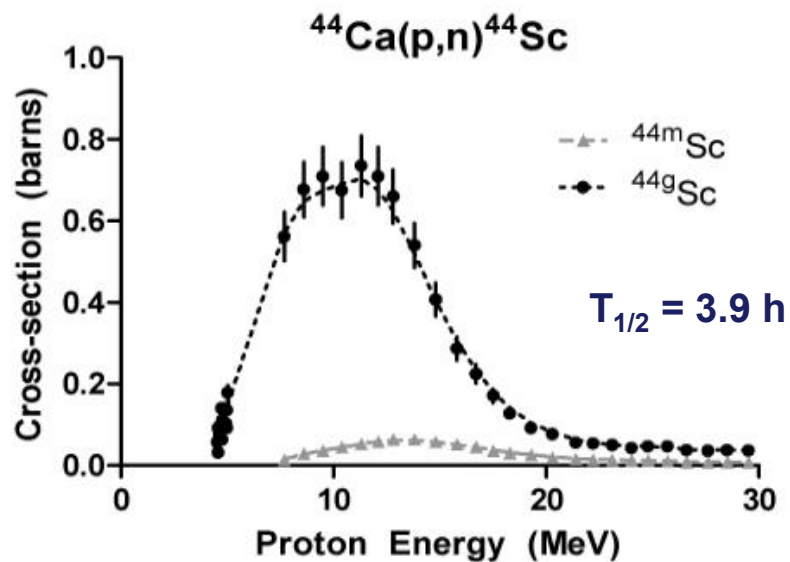
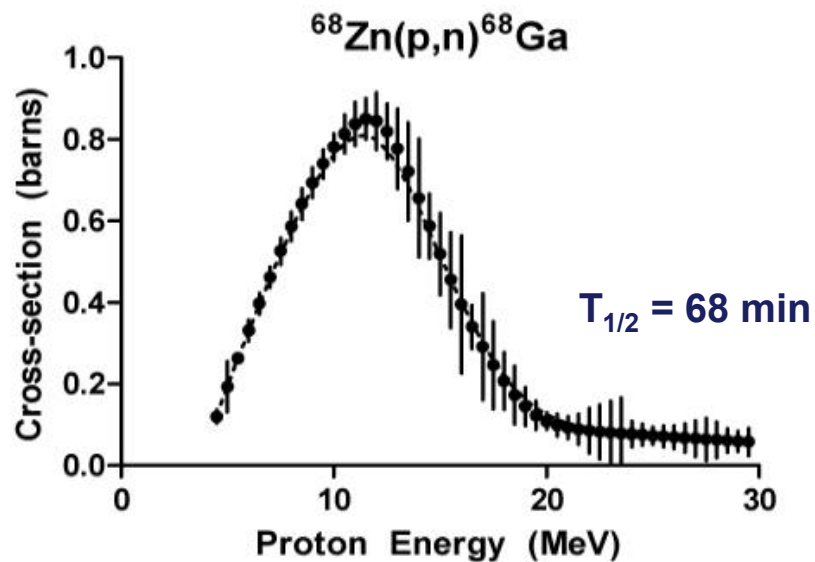


Making metals in a liquid target

- Hypothesis: Established cyclotron centers can obtain research, and possibly clinical quantities of various radiometals by irradiating salt solutions in modified liquid targets
- Leverage existing liquid target infrastructure for the production of other PET isotopes (^{18}F)
- Allows for rapid biomolecule-isotope pairing and optimization

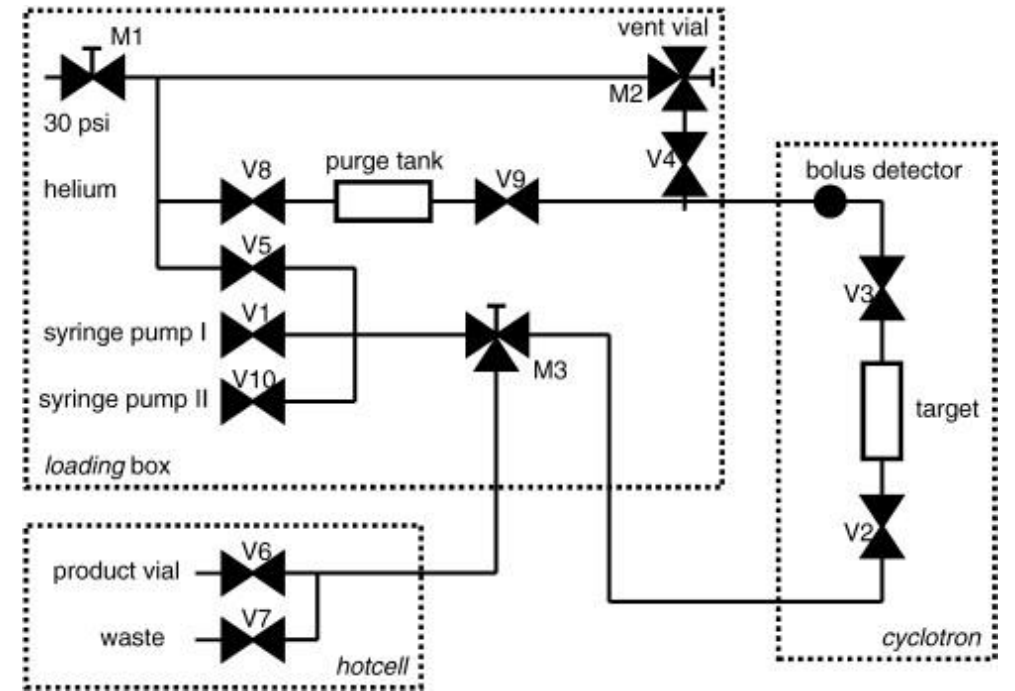
Accepted trade-off:

Lower production yields in exchange for isotope versatility

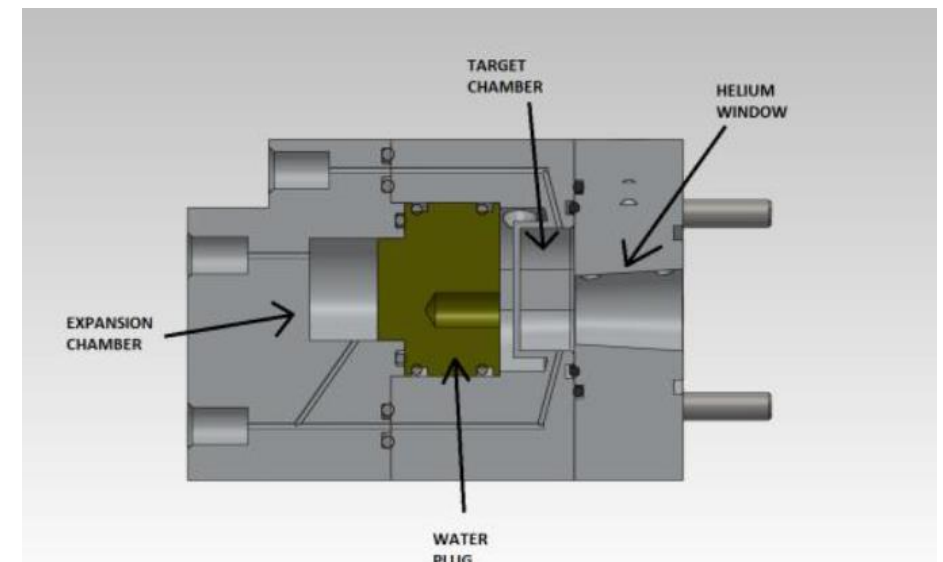


High level considerations

- Manual vs. automated loading
- Cl vs NO₃ metal salts
 - Chemical compatibility
 - Activation byproducts
- Nitric acid (HNO₃)
 - Counteract water radiolysis, gas evolution
- Cylindrical vs. Syphon target
 - Allow for pressure oscillations during irradiation



25



Composition of tested solutions.

Metal	Components			Density (g/mL)	Metal conc. (g/cm ³)	Molarity (mol/L)
Zinc	Zn(NO ₃) ₂ · 6H ₂ O (g)	H ₂ O (g)	conc. HNO ₃ (mL)	1.56 ± 0.005	0.2550 ± 0.0008	3.90 ± 0.01
	75.0	22.7	2.3			
Strontium	Sr(NO ₃) ₂ (g)	H ₂ O (g)	conc. HNO ₃ (mL)	1.35 ± 0.005	0.1960 ± 0.0007	2.24 ± 0.01
	14.0	22.7	2.3			
Yttrium	Y(NO ₃) ₃ · 6H ₂ O (g)	H ₂ O (g)	conc. HNO ₃ (mL)	1.49 ± 0.005	0.2040 ± 0.0007	2.30 ± 0.01
	37.5	22.7	2.3			

Densities (molarities) were determined by measuring volume and mass of each sample. Metal concentrations were calculated from the density values.

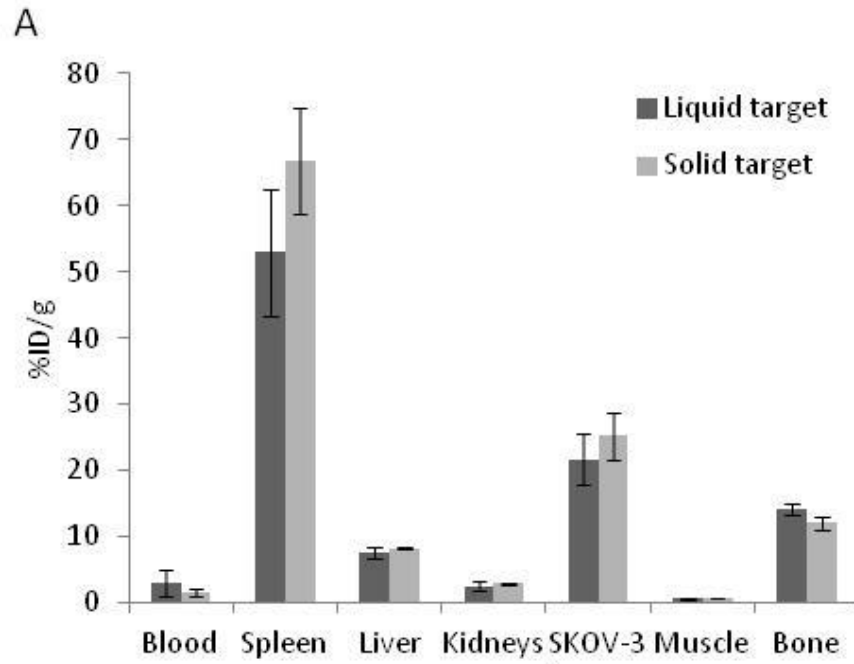
Irradiation conditions with experimental conditions and corresponding yields compared to theoretical yields.

Isotope	Metal conc. (g/cm ³)	Beam current (μA)	Irradiation length (min)	Yield (MBq/μA)	Theo. yield (MBq/μA)	Highest achieved yield in a single run (MBq)	Saturation yield (MBq/μA)	Theo. saturation yield (MBq/μA)
⁶⁸ Ga	0.255 ± 0.0008	6.96 ± 0.06	60 ± 0.2	64 ± 3	95.1	480 ± 30	141 ± 6	207.3
⁸⁶ Y	0.196 ± 0.0007	4.6 ± 0.3	60 ± 0.2	1.44 ± 0.06	2.4	7.4 ± 0.5	31 ± 1	52.5
⁸⁹ Zr	0.204 ± 0.0007	7.3 ± 0.6	60 ± 0.2	3.17 ± 0.08	4.8	32 ± 2	360 ± 9	540.9

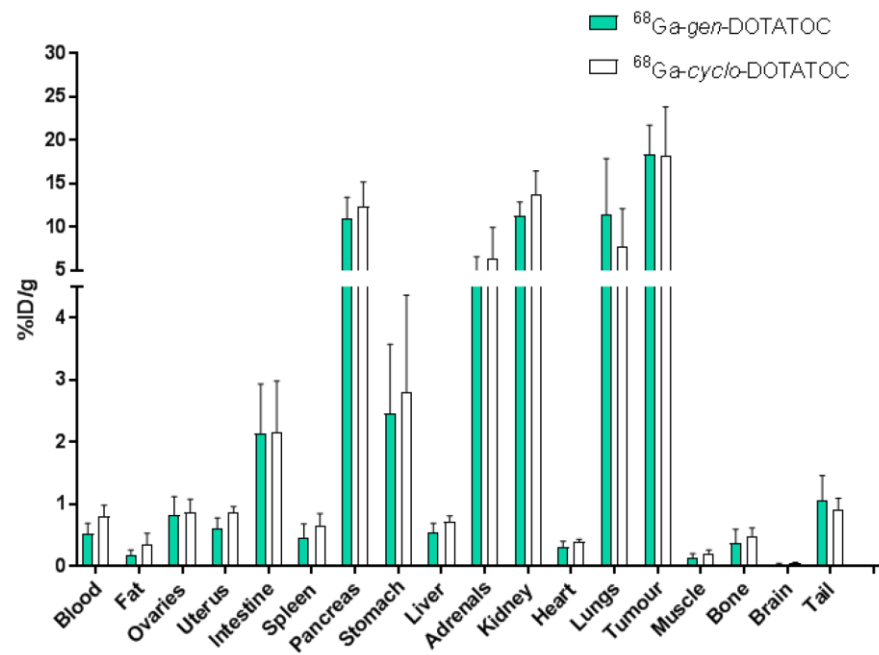
Overview of separation methods.

Isotope	Irradiated metal salt	Separation 1	Separation 2	Final eluate				
				Percentage of total activity received from target (%)	Volume (mL)	Solvent	Specific activity (TBq/ μ mol)	Trace metal content determined by ICP-MS (ppm, n = 3)
^{68}Ga	$\text{Zn}(\text{NO}_3)_2$	AG 50 W-X8	DGA	92 ± 8 (n = 3)	1.0	H_2O	5.2 ± 0.3	Ga (0.0064 ± 0.0001), Fe (7.4 ± 1.2), Cu (0.0043 ± 0.0016), Ni (0.0015 ± 0.0006), Zn (39 ± 17)
^{89}Zr	$\text{Y}(\text{NO}_3)_3$	Hydroxamate resin	–	82 ± 5 (n = 4)	0.75	1 M Oxalic Acid	0.015 ± 0.001	Zr (0.26 ± 0.02), Y (3.12 ± 0.01), Fe (0.072 ± 0.021), Zn (0.44 ± 0.24), Cu (0.053 ± 0.027)
^{86}Y	$\text{Sr}(\text{NO}_3)_2$	DGA	–	99 ± 4 (n = 3)	1.0	H_2O	0.00041 ± 0.00018	Y (1.6 ± 0.7), Sr (6.4 ± 2.3), Fe (0.59 ± 0.78), Cu (0.0021 ± 0.0004), Zn (0.37 ± 0.30)

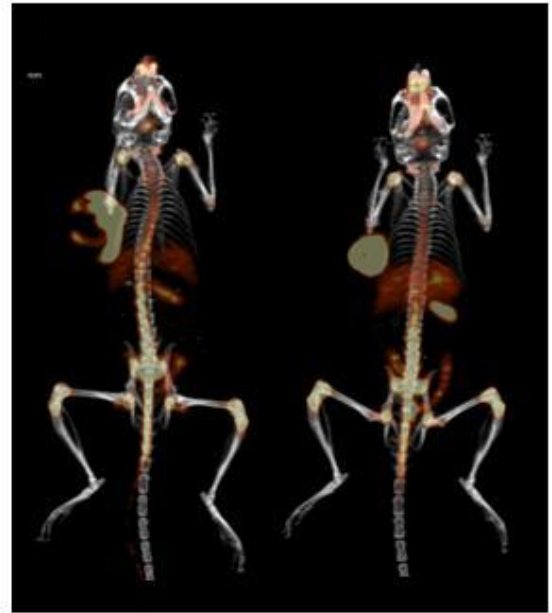
^{89}Zr



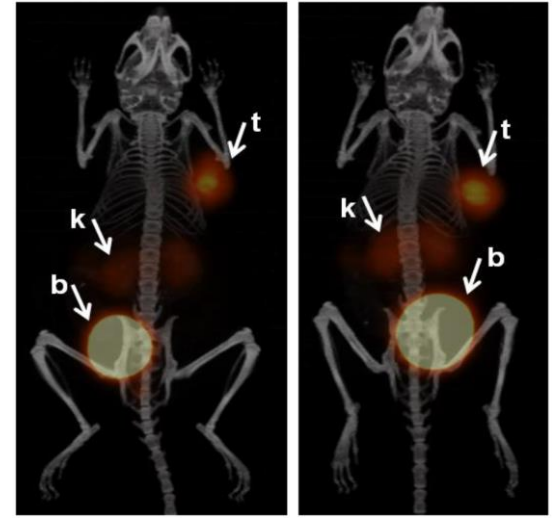
^{68}Ga



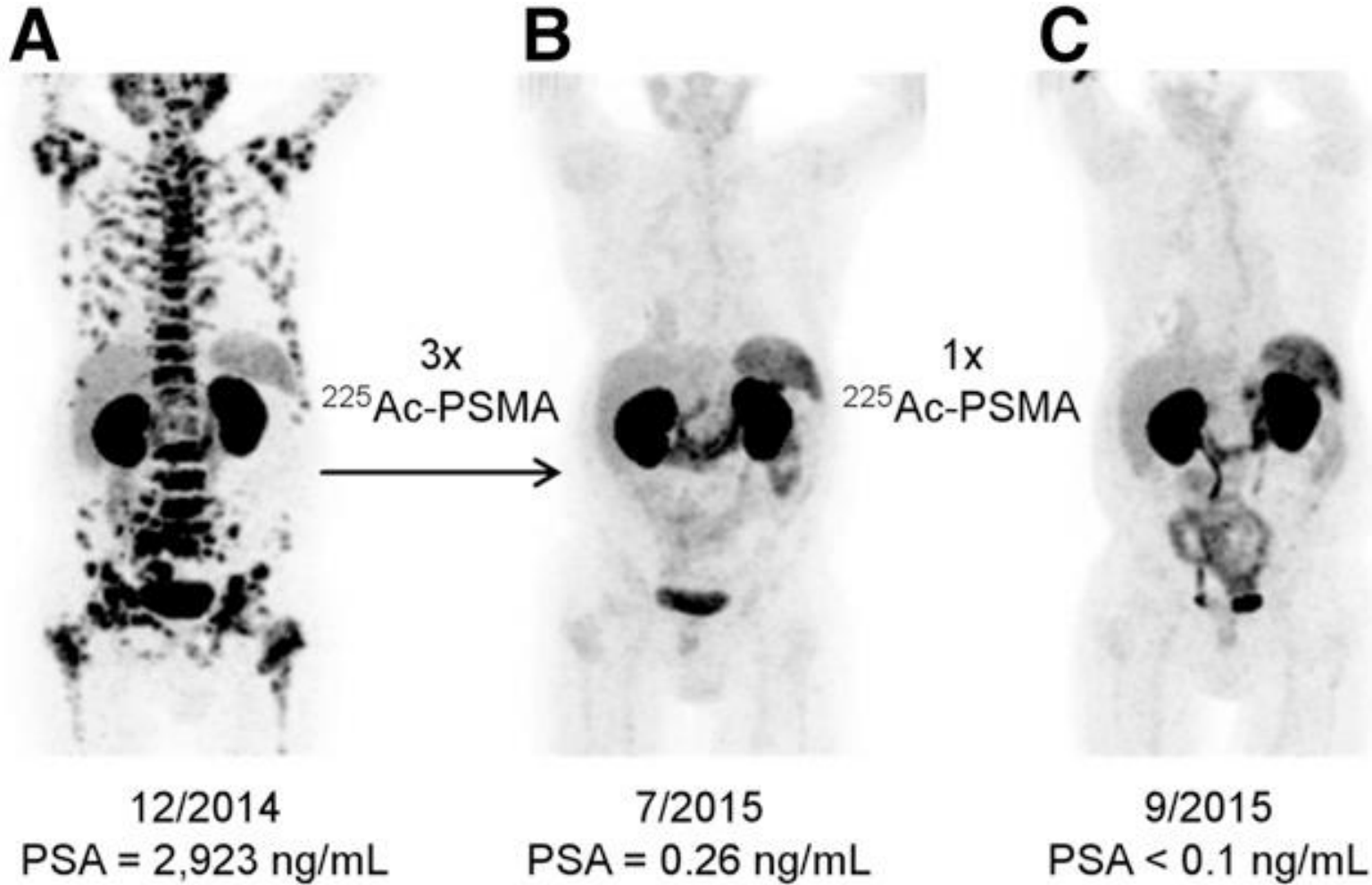
B Solid target Liq. target



Generator Liq. target



Looking ahead: Therapeutic and Theranostic isotopes



Looking Ahead: Implementing an Isotope Toolkit for Therapy

Research interests in alpha- and auger emitters

^{213}Bi

^{90}Nb

^{225}Ac

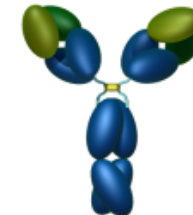
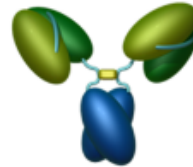
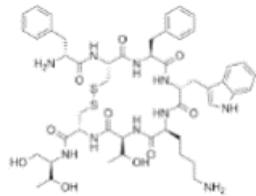
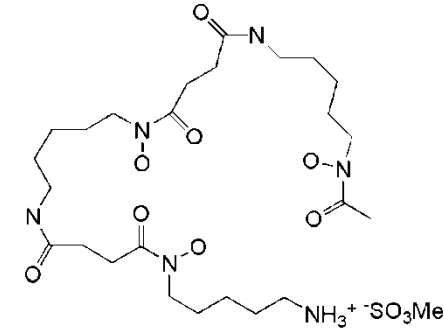
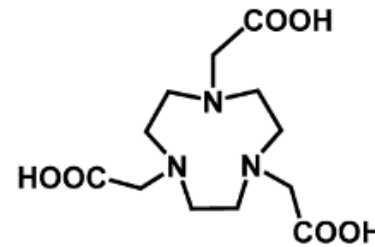
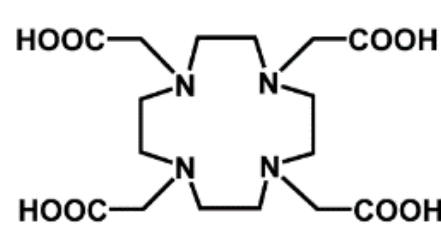
^{119}Sb

$t_{1/2}$ 0.76 h

$t_{1/2}$ 14.6 h

$t_{1/2}$ 238.1 h

$t_{1/2}$ 38.2 h



0.1 -50 KDa

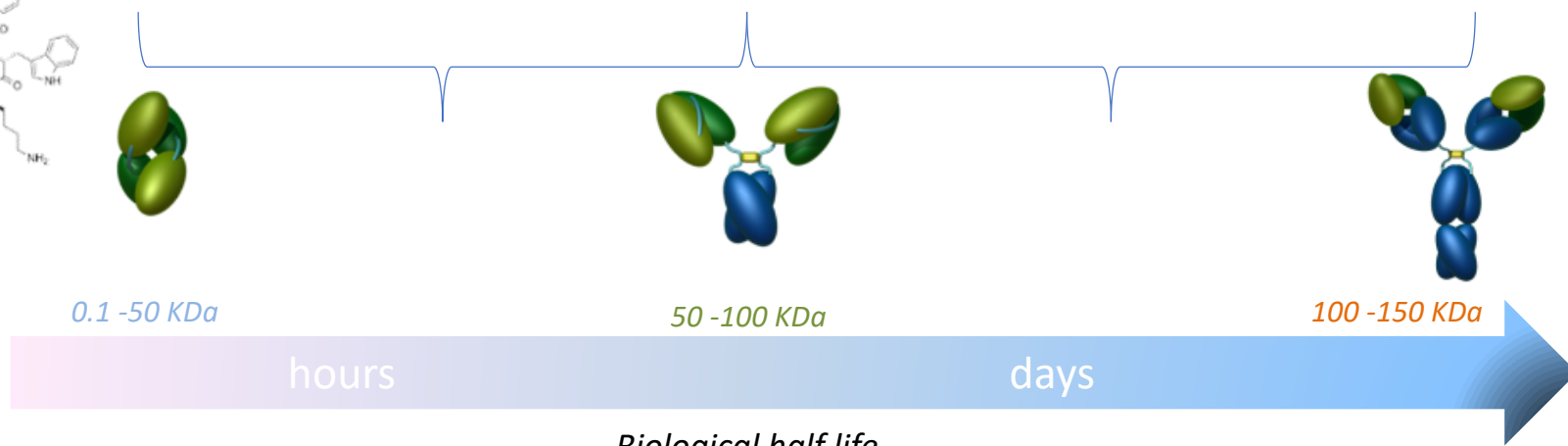
50 -100 KDa

100 -150 KDa

hours

days

Biological half life

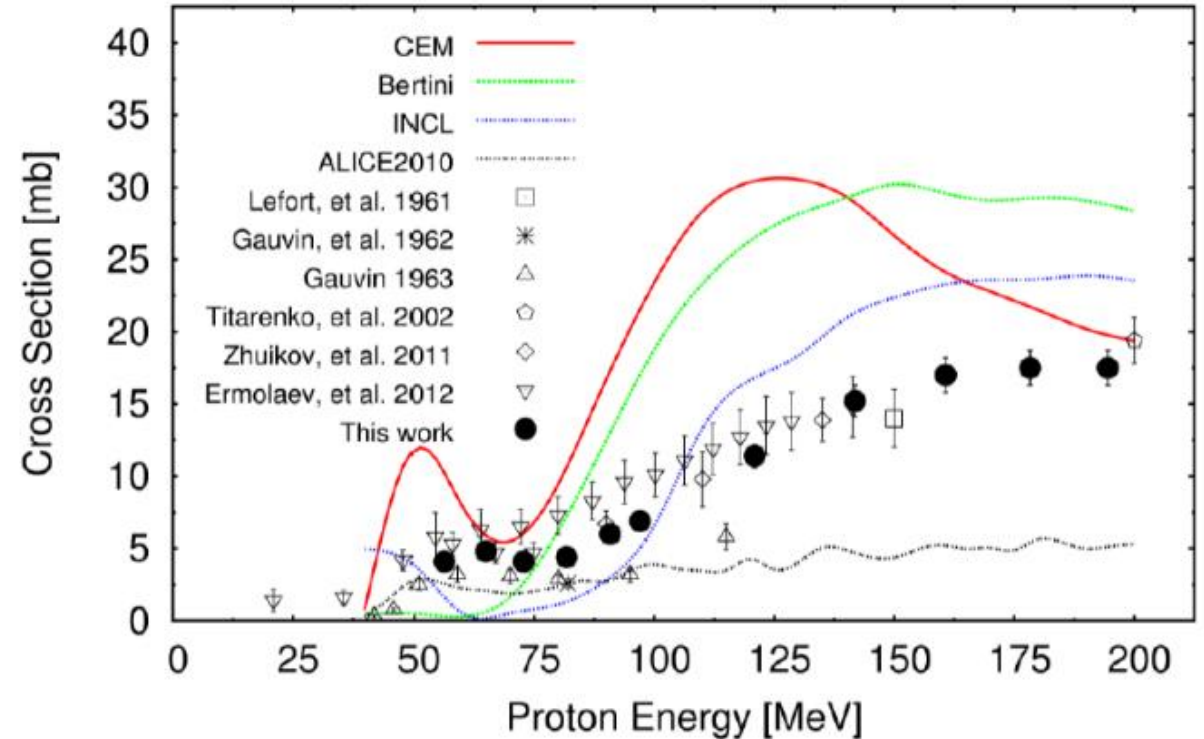


Primary ^{225}Ac sources:

- $^{229}\text{Th}/^{225}\text{Ac}$ generator ($t_{1/2} \sim 7880$ y) sourced via legacy stockpile, ORNL, ITU
- DOE Tri-Lab efforts: $^{232}\text{Th}(p,x)$ spallation
- Alternatives sought: ^{226}Ra irradiation

Global production is $\sim 1\text{-}2$ Ci per year (<5000 patients)

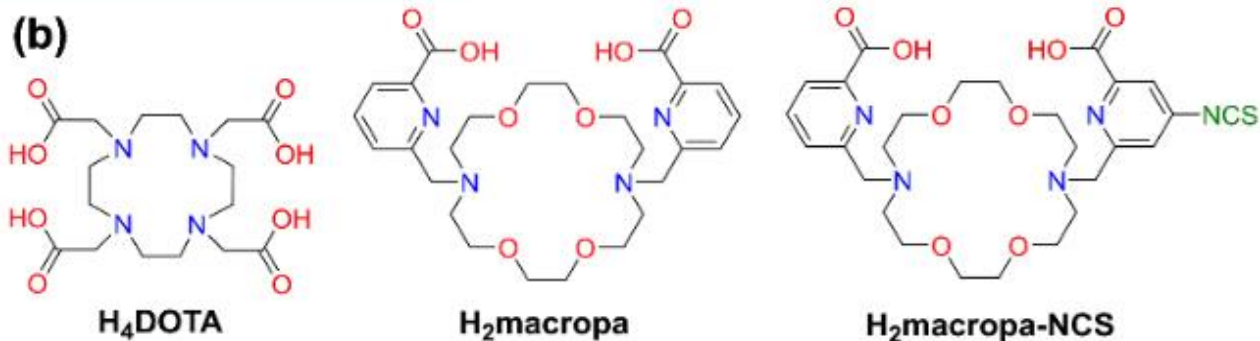
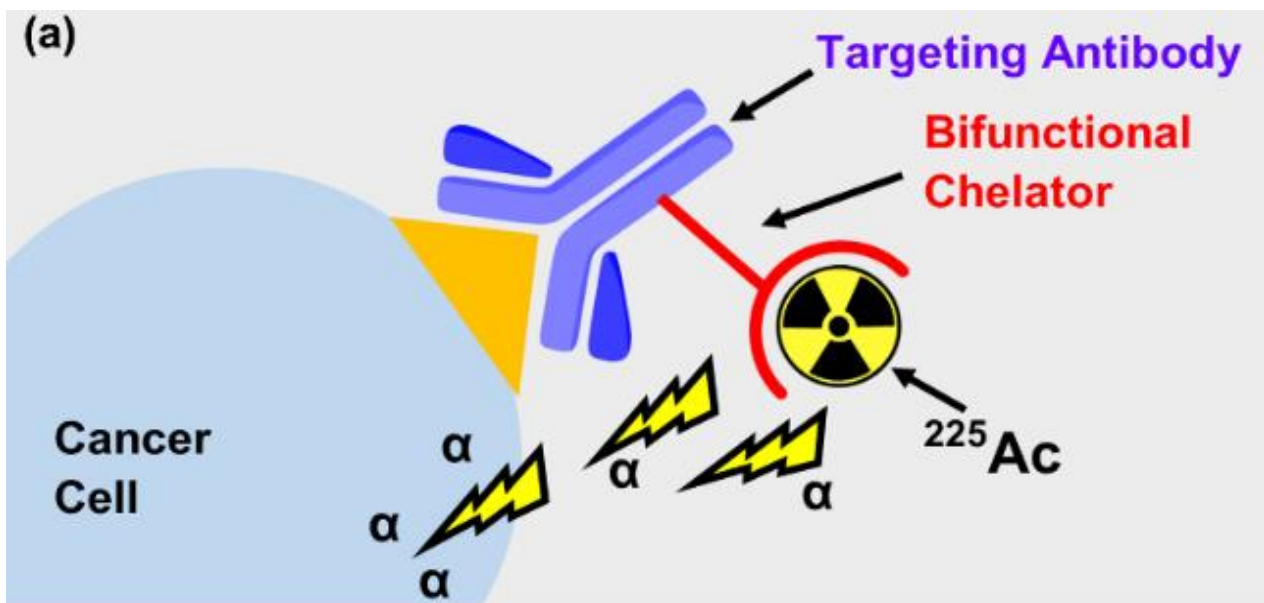
- Promising early clinical trial results
- Supply vs demand is out of balance, but market needs to be nurtured, and supply needs to increase and be reliable
- Efforts underway at TRIUMF to establish feasibility of producing bulk quantities of ^{225}Ac



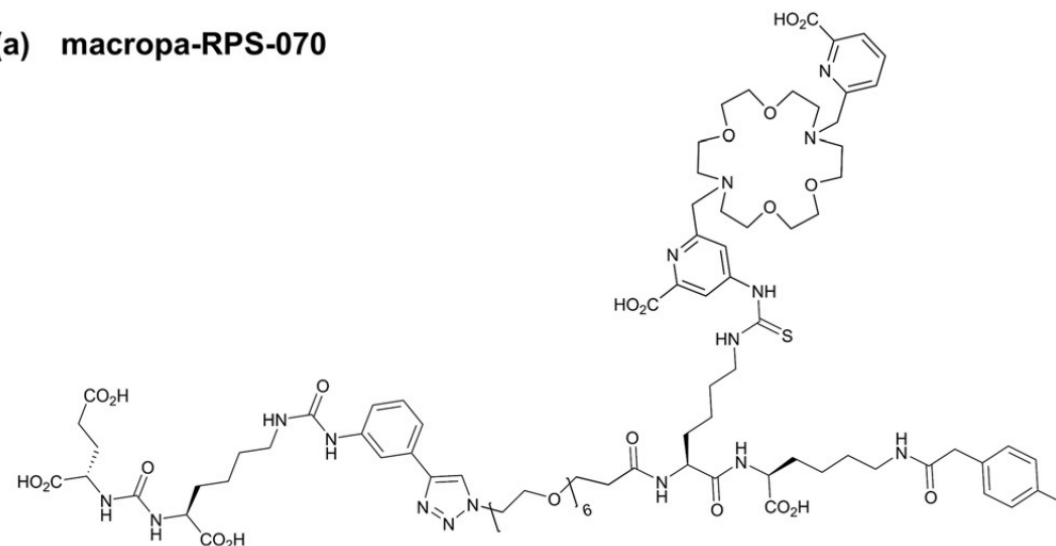
J.W. Weidner et al. Appl. Radiat. Isotop. 2012, 70, 2602

Ac-225 isolated using TRIUMF ISOL facility

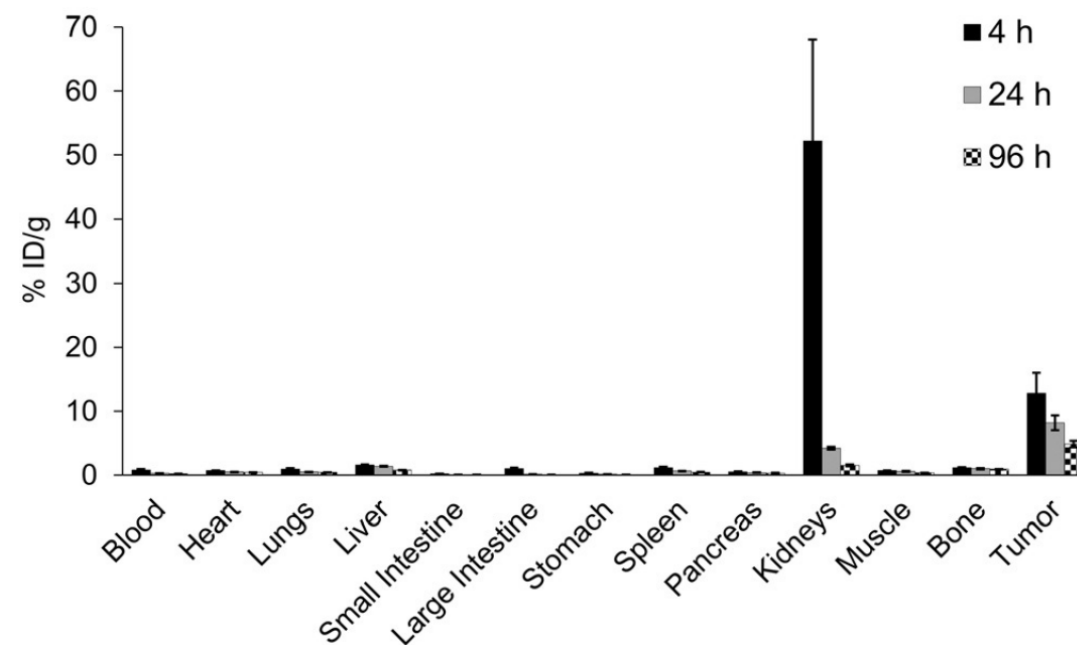
- Enabled feasibility purification, coordination studies



(a) macropa-RPS-070

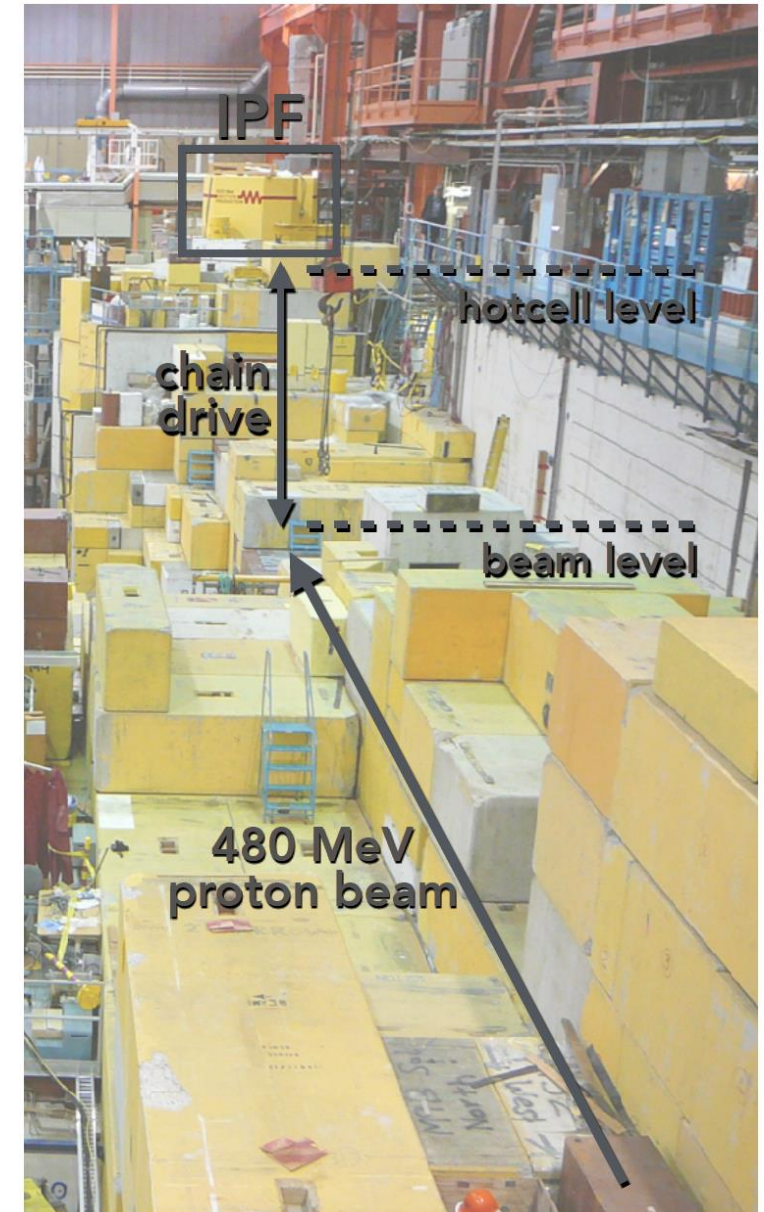
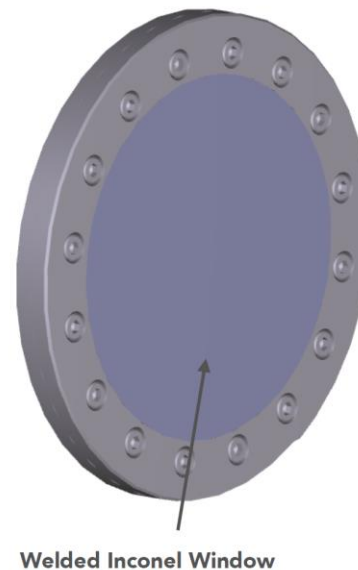
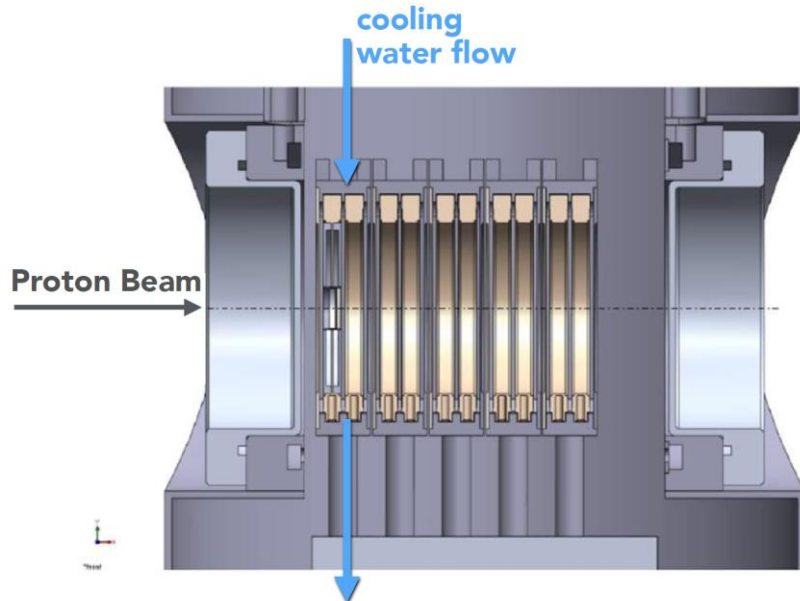


(b) ^{225}Ac -macropa-RPS-070

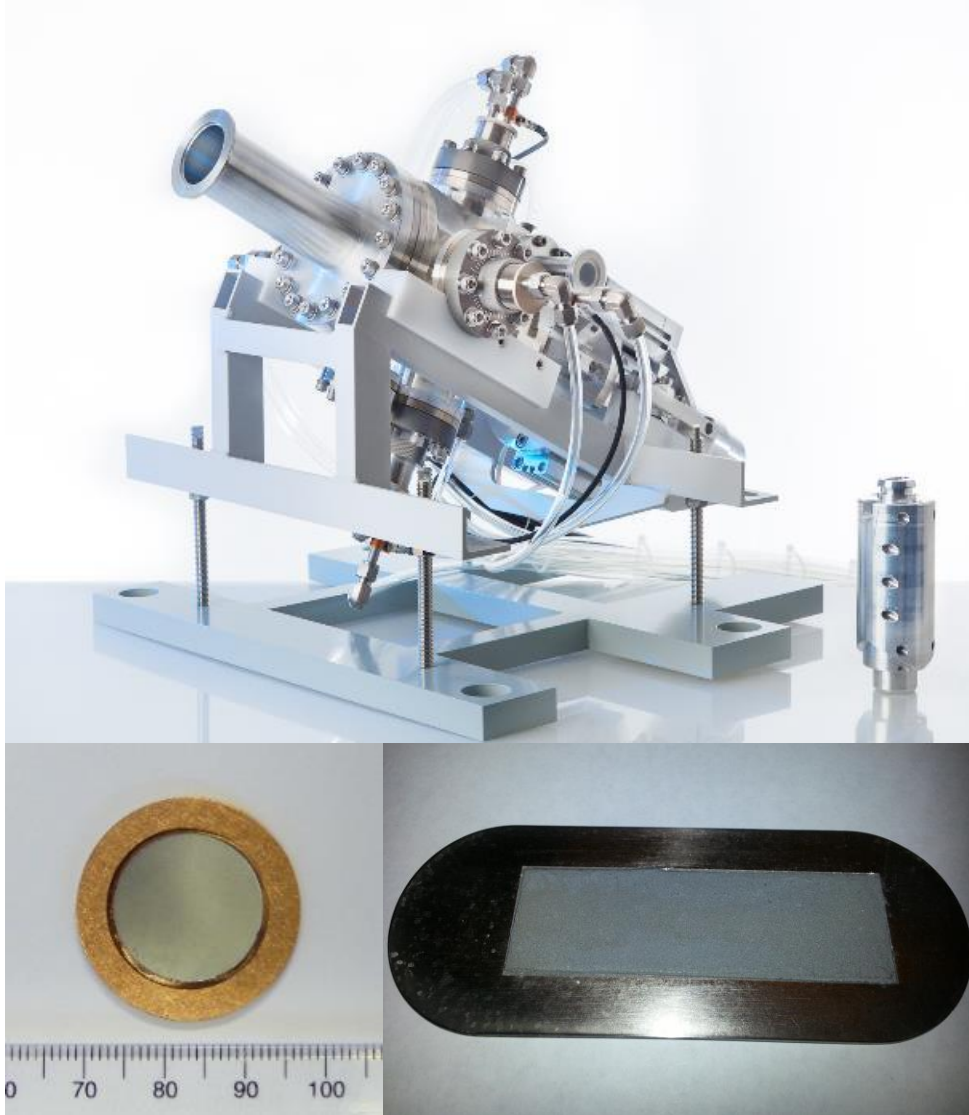


^{225}Ac at TRIUMF

- Th-232 irradiation on BL1A
- Safety review, irradiation completed
 - 480 MeV, 85 μA for 31 hrs
 - Anticipated yield: ~12 mCi Ac-225
 - Chemistry development underway
- Next irradiation: May-June 2018 (10 mCi)
- Scale-up to 100 mCi by Fall 2018
- Implement symbiotic target >2021



Summary



- Global shift to higher-energy cyclotrons
 - yesterday: low E (<16 MeV), low current (<100 μA)
 - today: higher E (16 – 24 MeV), higher current (>100 to 1000 μA)
 - Higher specific activity
- New approaches (i.e. salt target)
- Emerging solid target technologies enabling high power (E + μA) irradiation
- Improved handling and processing

- But...some isotopes can not be efficiently made by accelerator (^{60}Co , ^{192}Ir , ^{125}I ...)

Acknowledgements

TRIUMF Team

M Adam,
K Buckley,
M Dodd,
L Graham,
V Hanemaayer,
C Hoehr,
J Huser,
J Klug,
S McDiarmid,
Q Miao,
D Prevost,
V Radchenko,
C Ramogida,
TJ Ruth,
M Stachura,
S. Varah,
H Yang,
S Zeisler

TRIUMF Team (cont'd)

B Badesso
H Chen
S Ferguson
A Fong
J Hanlon
K Hayashi
A Lam
C Lee
K Li
A Limoges
P Martini
K McDuffie
N McLean
T Morley
E Oehlke
F Pau
A Roberston
P Tsao
N Unick
K Young
N Zacchia

TRIUMF and BCCA machine shops

BC Cancer Agency

F Bénard,
H Corbett
G Dias,
W English,
K Frantzen
KS Lin
G Langlois
J Song
J Schlosser
M Vuckovic,

ARTMS

K Wilson – CEO
M Cross – COO
J Kumlin
B Hook

Collaborators

F Prato (Lawson)
M Kovacs (Lawson)
S Foster (Lawson)
J Corsault (Lawson)
N Cockburn (Lawson)
J Valliant (CPDC)
M Cross (CPDC)
T Besanger (CPDC)
F Gleeson (CPDC)
J McEwan (CPDC)
P Ruddock (CPDC)
A Goodbody (CPDC)
J McCann (CPDC)
R Harper (CPDC)
C Economou (CPDC)
M Martinez (UBC),
C Orvig (UBC),
E Price (UBC, now U Sask),
A Celler (UBC),
J Tanguay (UBC),
X Hou (UBC)
J Wilson (Cornell)
J Babich (Cornell)



Thank you
Merci

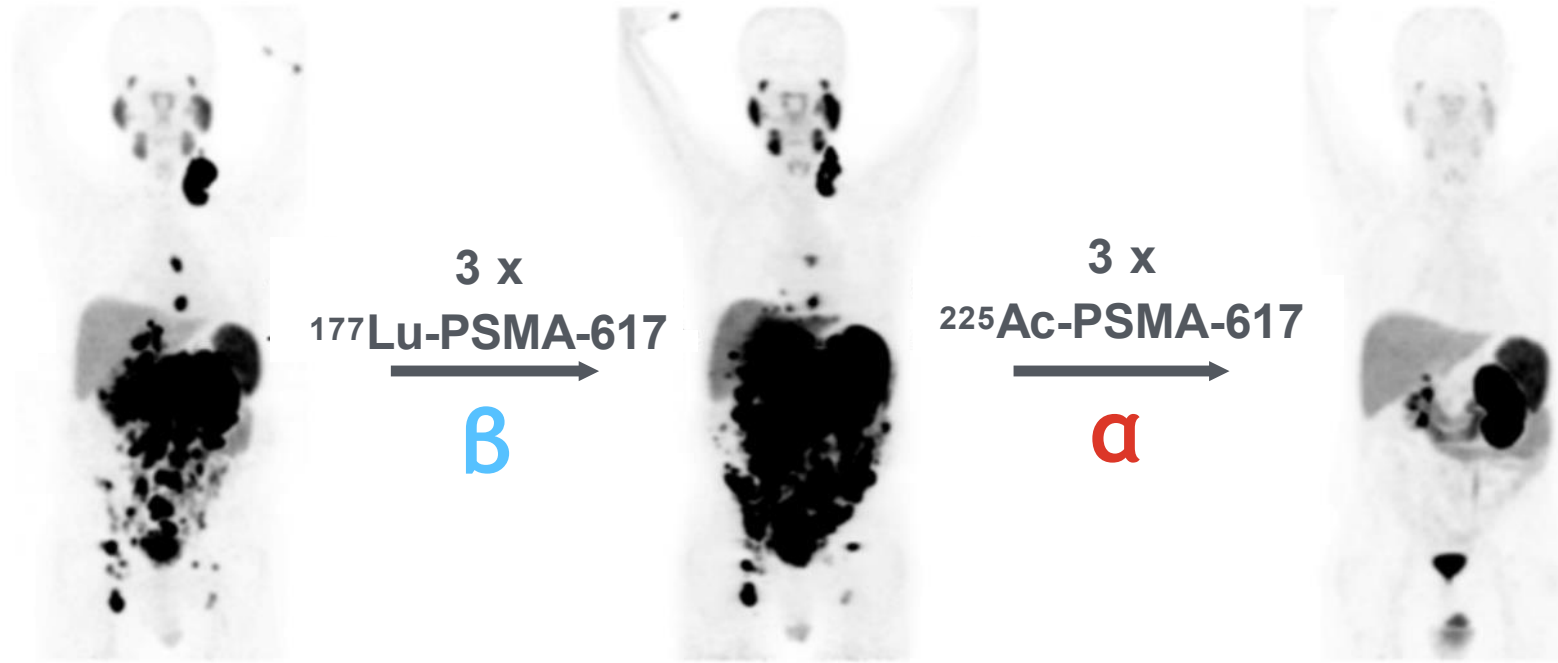
www.triumf.ca

Follow us @TRIUMFLab



Discovery,
accelerated





^{225}Ac Purification Chemistry

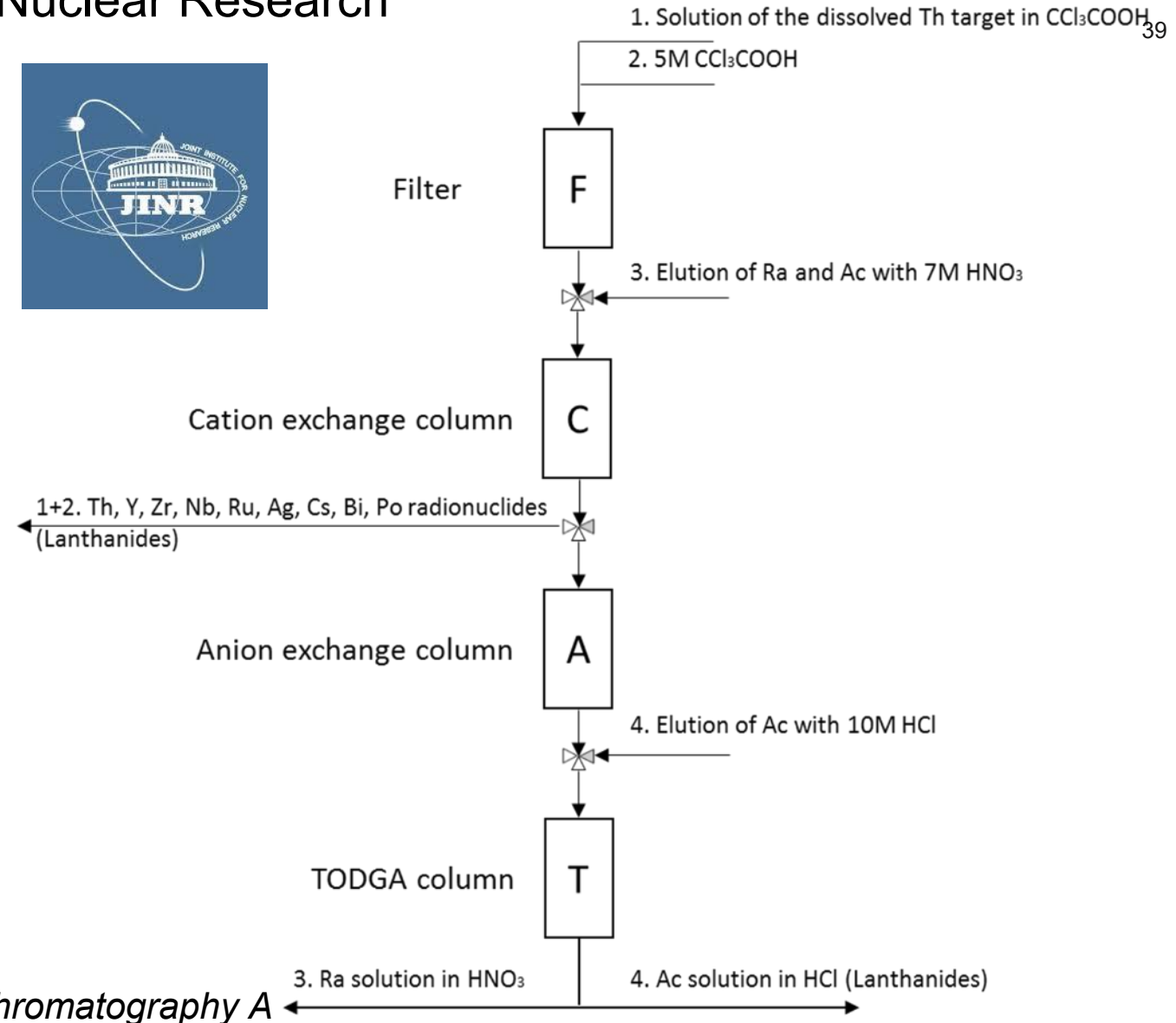
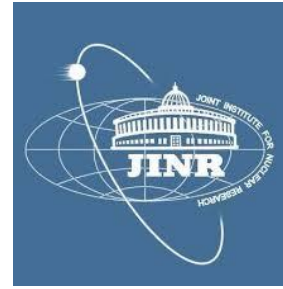
Collaboration effort with the Joint Institute for Nuclear Research

Proof-of-principle chemical separation with irradiated thorium:

- Most of the fission products follow thorium and were not retained on the cation column
- Ac and Ra retain on the column during loading and washes with trichloroacetic acid
- Further, Ac and Ra (over 95%) eluted with 7 M HNO_3 and directly loaded on anion exchange column
- Anion exchange column in 7 M HNO_3 retains traces of thorium and Ac and Ra were passed through without absorption
- Ac and Ra were transferred to DGA for separation from each other and lanthanides using HCl

✓ Provide faster separation

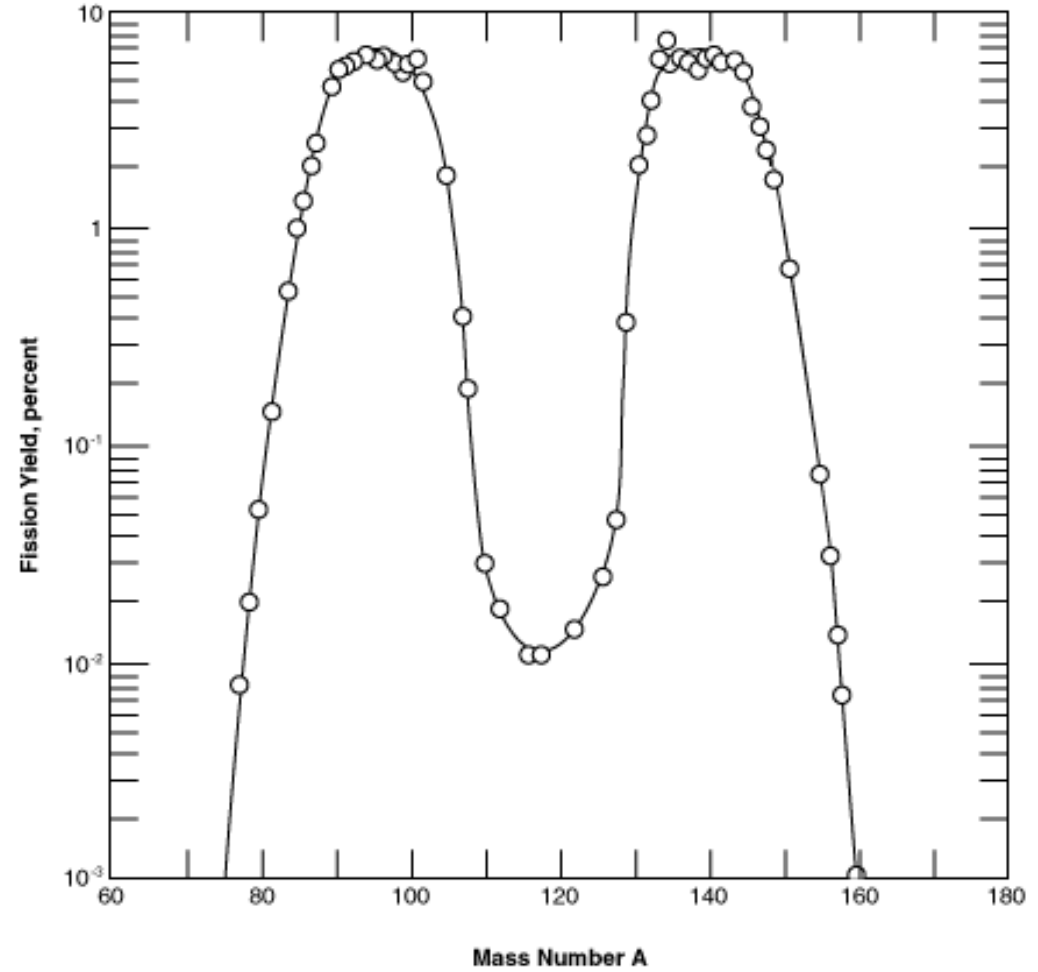
✓ Suitable for larger thorium masses



A. Baimukhanova et al. in preparation for submission to J. Chromatography A



Thermal Neutron Fission of U-235



Accelerators at origin of several emerging alternatives

- Production of ^{99}Mo via phototransmutation of ^{100}Mo : $^{100}\text{Mo}(\gamma, n)^{99}\text{Mo}$

Current players:



- Production of ^{99}Mo via subcritical fission of ^{235}U : $^{235}\text{U}(n, F)^{99}\text{Mo}$

Current players:



- Direct production of $^{99\text{m}}\text{Tc}$ via proton irradiation of ^{100}Mo : $^{100}\text{Mo}(p, 2n)^{99\text{m}}\text{Tc}$

Current players:



**Belgravia
Tech, Inc.**