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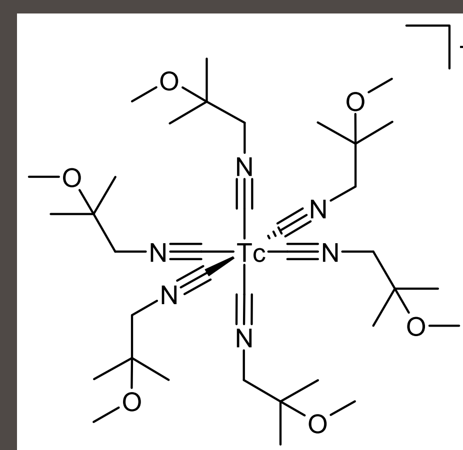

Accelerating the Future of Medical Isotope Production

ARIS 2014, Tokyo, Japan

Paul Schaffer | Head, Nuclear Medicine | TRIUMF

Overview

Part 1: Direct production of Tc-99m

Part 2: Radiotherapeutic Isotopes via ISOL

Takeaway Message:

- Networks of accelerators (cyclotrons) are a viable option for large-scale medical isotope production and distribution
  - Funding for basic physics research leads to tangible societal benefit

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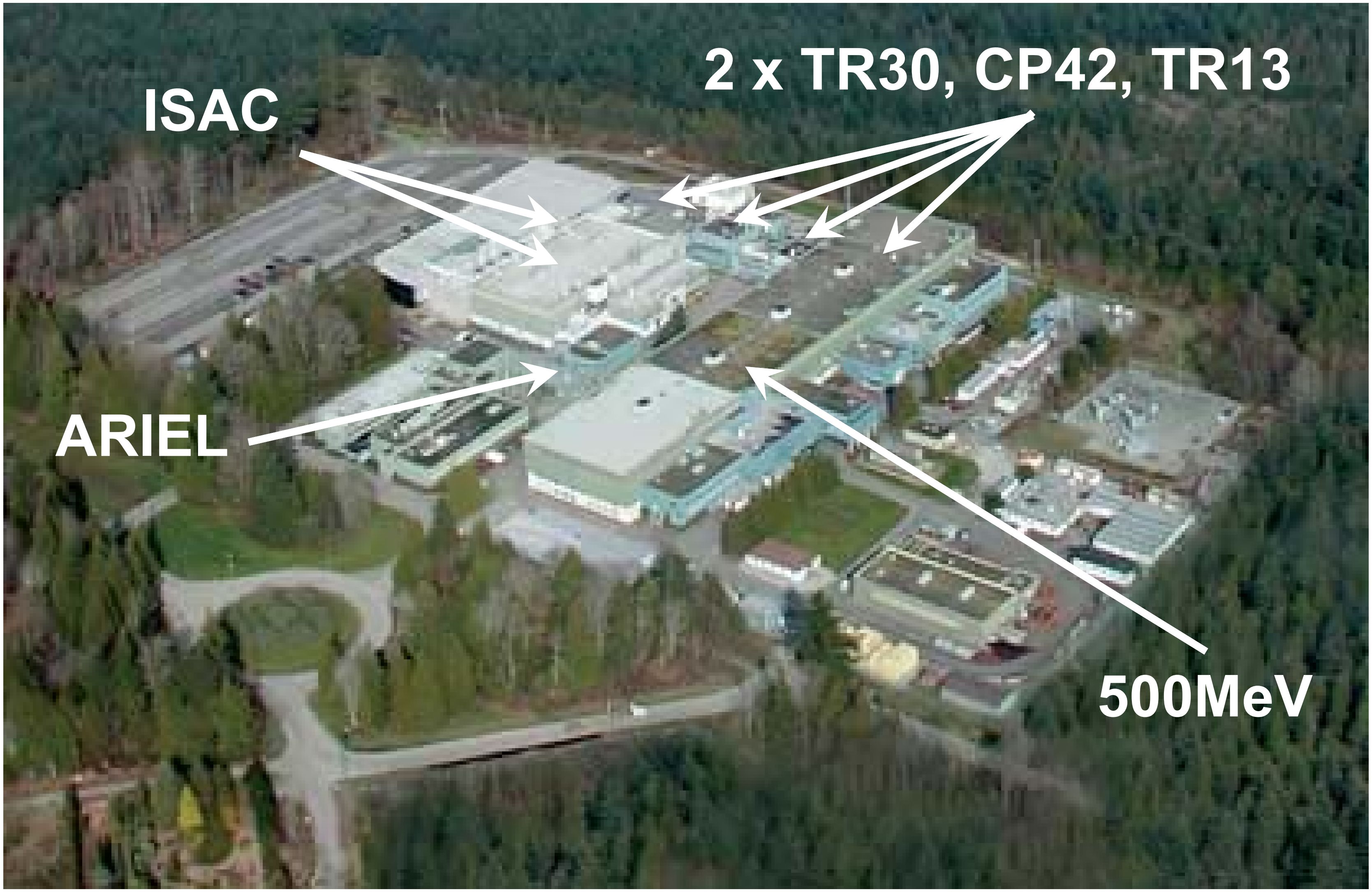

^{11}C, ^{18}F,
^{44}Sc,
^{52}Mn
^{55}Co,
^{68}Ga,
^{86}Y,
^{89}Zr

Also:
^{82}Rb
^{103}Pd
^{123}I
^{201}Tl
etc.

Owned and operated as an independent joint venture between 19 Canadian universities

Part 1: Direct Production of ^{99m}Tc - Background

- Demand (^{99}Mo/^{99m}Tc, global): 20 - 40 million doses/yr
- Prevalence: 85% of all Nuc. Med. scans use ^{99m}Tc
- Frequency: 76,000 scans/day (>1 scan/second)
- Production (of ^{99}Mo via $^{235}U(n,F)$):
  - Canada (~40%), Netherlands (~40%), France (~5%), Belgium (~5%), S. Africa (~5%), Australia (~5%)
  - Recent work in S. Africa and Australia is creating new dynamics
- Issues:
  - Reactor shutdown(s): widespread shortages, costs escalating/fluctuating
  - Unknown future ^{99}Mo production capacity
    - Aging global reactor infrastructure,
    - Expensive new construction,
    - Full-cost-recovery mandates (eliminate gov't subsidies),
    - Enriched uranium - non-proliferation efforts,
    - Regulatory and nuclear safety challenges
- Hypothesis: Future production will be from variety of sources (neutron, proton, electron) and market driven

Alternatives for ^{99m}Tc production

- Alternatives are well known

Neutron 'solution(s)':
LEU $^{235}U(n,F)^{99}Mo$
$^{98}Mo(n,\gamma)^{99}Mo$
Photon 'solution(s)':
$^{238}U(\gamma,F)^{99}Mo$
$^{100}Mo(\gamma,n)^{99}Mo$
Proton 'solution':
$^{100}Mo(p,2n)^{99m}Tc$

All at various stages of feasibility/concept development

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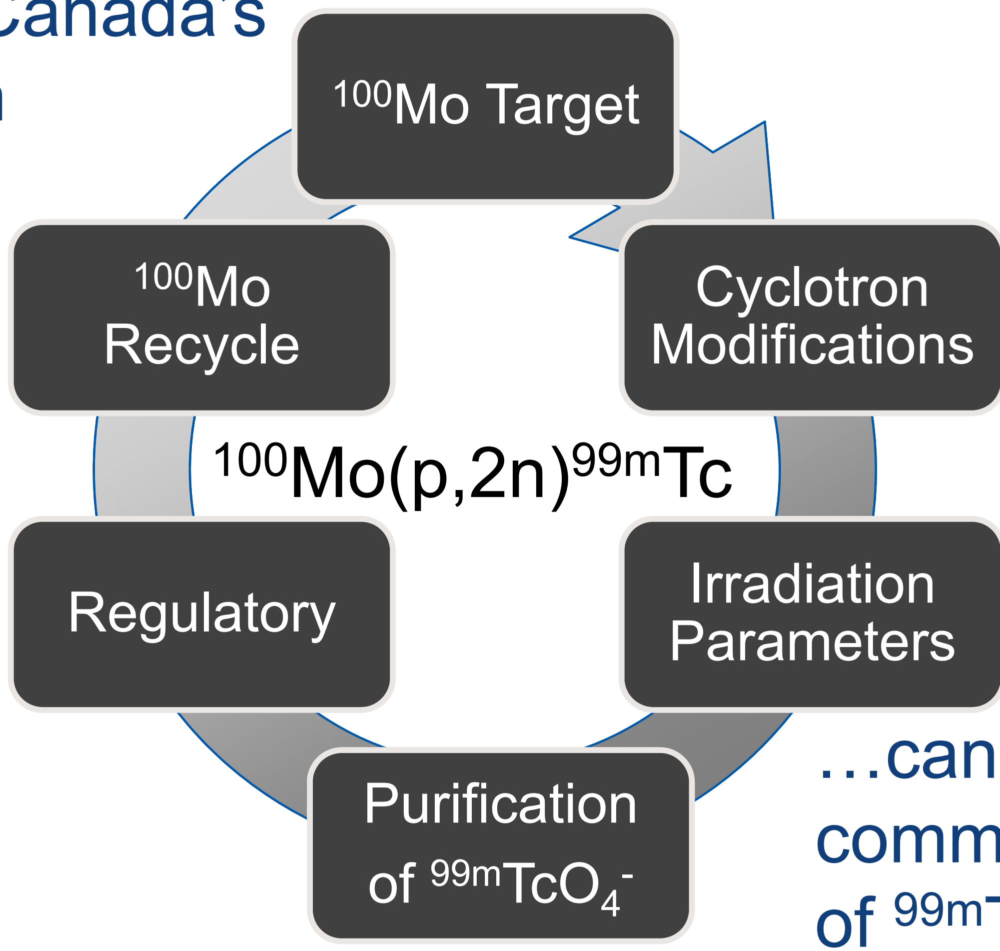
$^{100}Mo(p,2n)^{99m}Tc$ at the commercial scale

To demonstrate Canada's existing cyclotron infrastructure...



...can produce commercial quantities of ^{99m}Tc

Goals: 1) Formulate policy on $^{99}Mo/^{99m}Tc$ isotope production
2) Demonstrate Feasibility/Concept
3) Translate to Commercial Sector

Direct Production of ^{99m}Tc in 1971

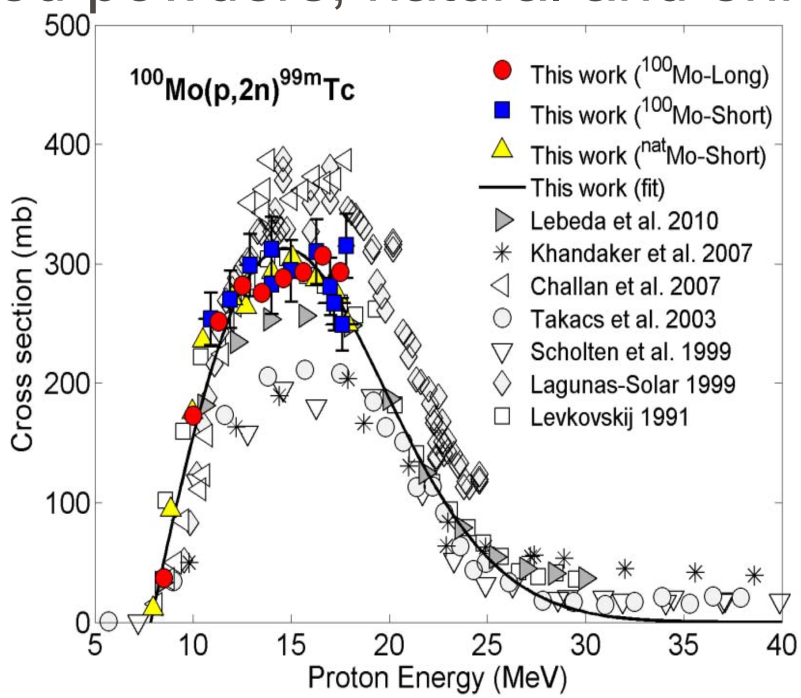
Background (Beaver and Hupf, U Miami):

- **^{99m}Tc via cyclotron:**
  - ^{nat}Mo foils 13 x 0.935” x 0.003”, 0.0061μA·hr, 22 MeV
  - ^{100}Mo powder at 21.4, 20.2, and 15.2 MeV,
  - integrated beam: 0.00046, 0.0296, 0.00068 μA·hr, respectively.
- **Conclusions:**
  - ^{100}Mo (97.42%) at 22 MeV and 455 μA will produce **15 Ci/hr of ^{99m}Tc and 500 mCi/hr of ^{99}Mo**
  - Assuming an operating cost of $100/hr, cost of ^{99m}Tc production = $0.015/mCi !!!

J.E. Beaver and H.B. Hupf, J. Nucl. Med. 1971, 12, 739-741

1971-2009 Development Focus: Uncertainty in $^{100}Mo(p,2n)$

- No motivation to pursue given avail. of $^{235}U(n,F)^{99}Mo$
- Progress limited to data refinement in subsequent years
  - Lagunas-Solar, Challan, Takács, Lebeda, Gagnon…
  - Foils, pressed powders; natural and enriched Mo



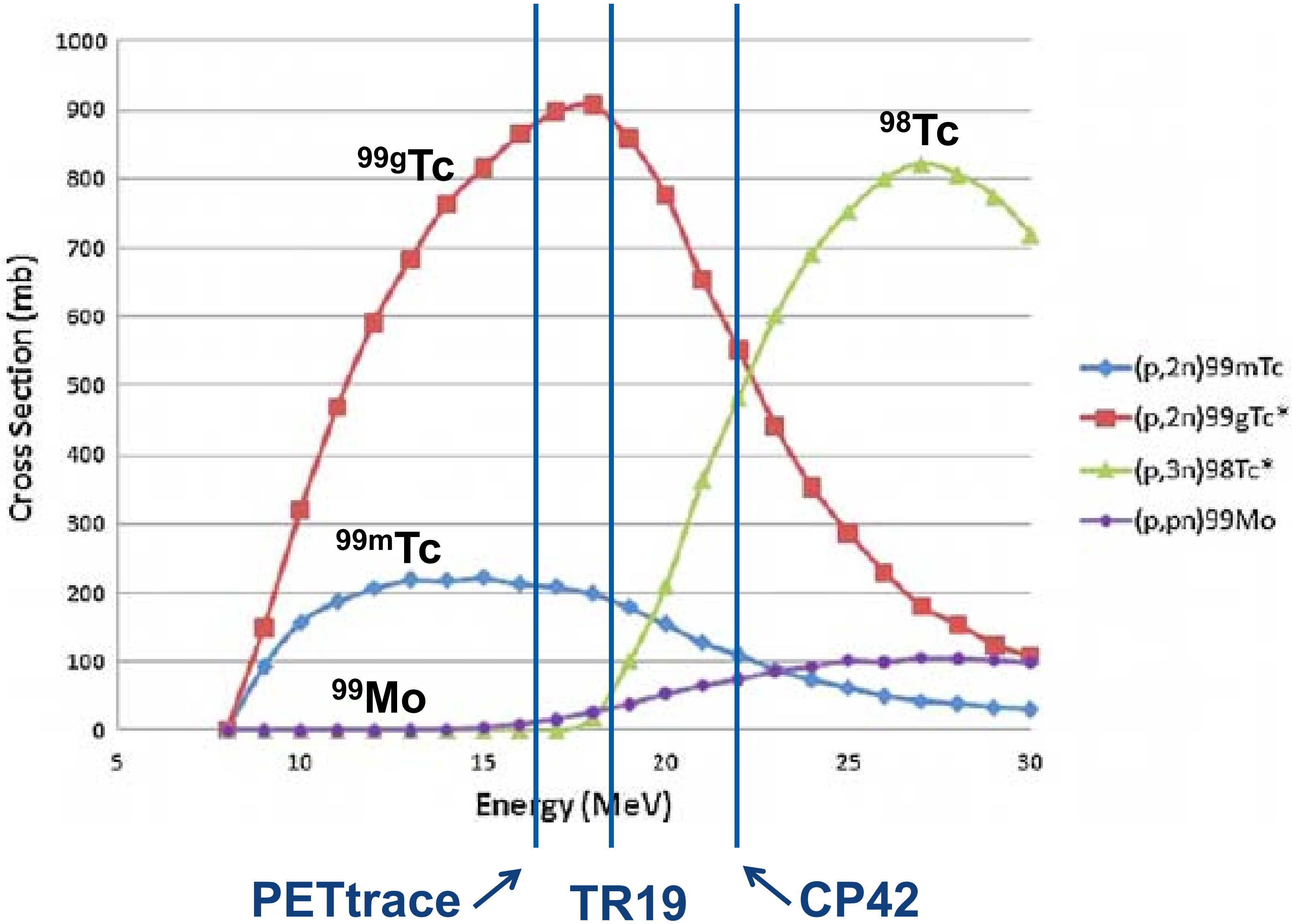
K. Gagnon et al., Nuc. Med. Biol. 2011, 38, 907-916

- Consider also contributions from (p,x) on ^{100}Mo and ^{9x}Mo, etc.

A. Celler, X. Hou, F. Bénard, T. Ruth, Phys. Med. Biol. 2011, 56, 5469

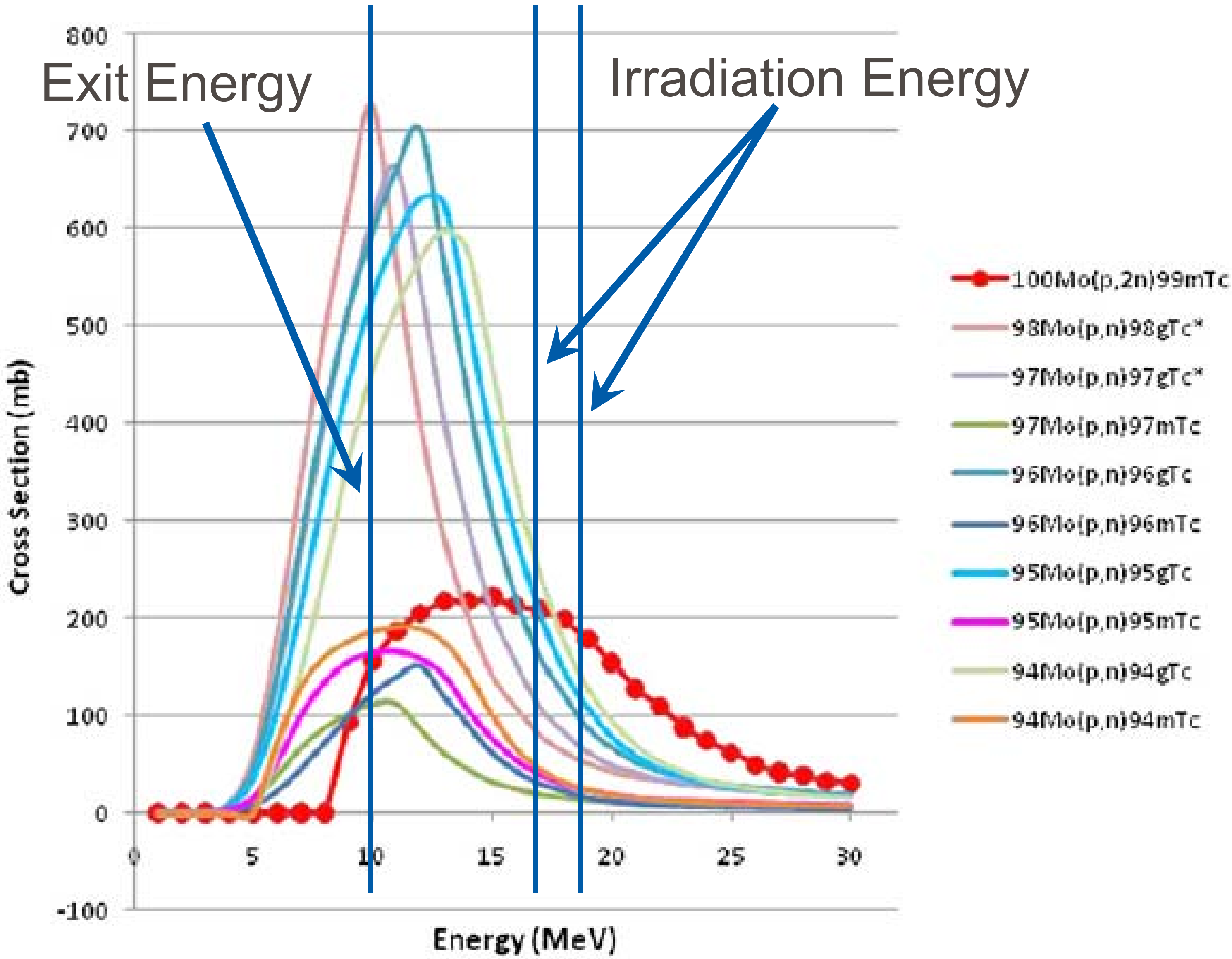
The Calculated Approach: Predicting Products/Yields

$^{100}Mo(p,x)$ reactions of highest probability



A. Celler, X. Hou, F. Bénard, T. Ruth, Phys. Med. Biol. 2011, 56, 5469

Side Reactions: $^{94-97}Mo(p,n)$



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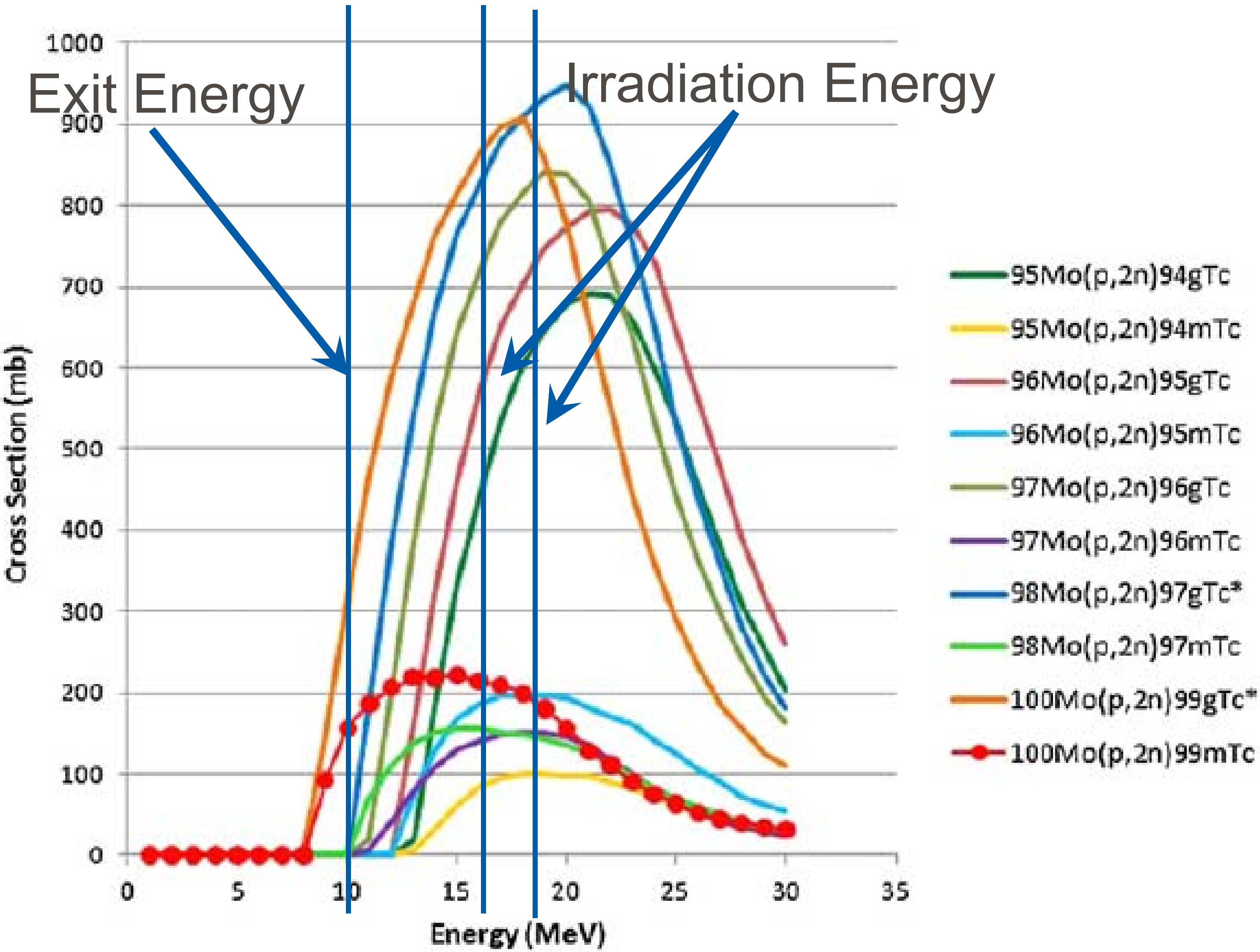


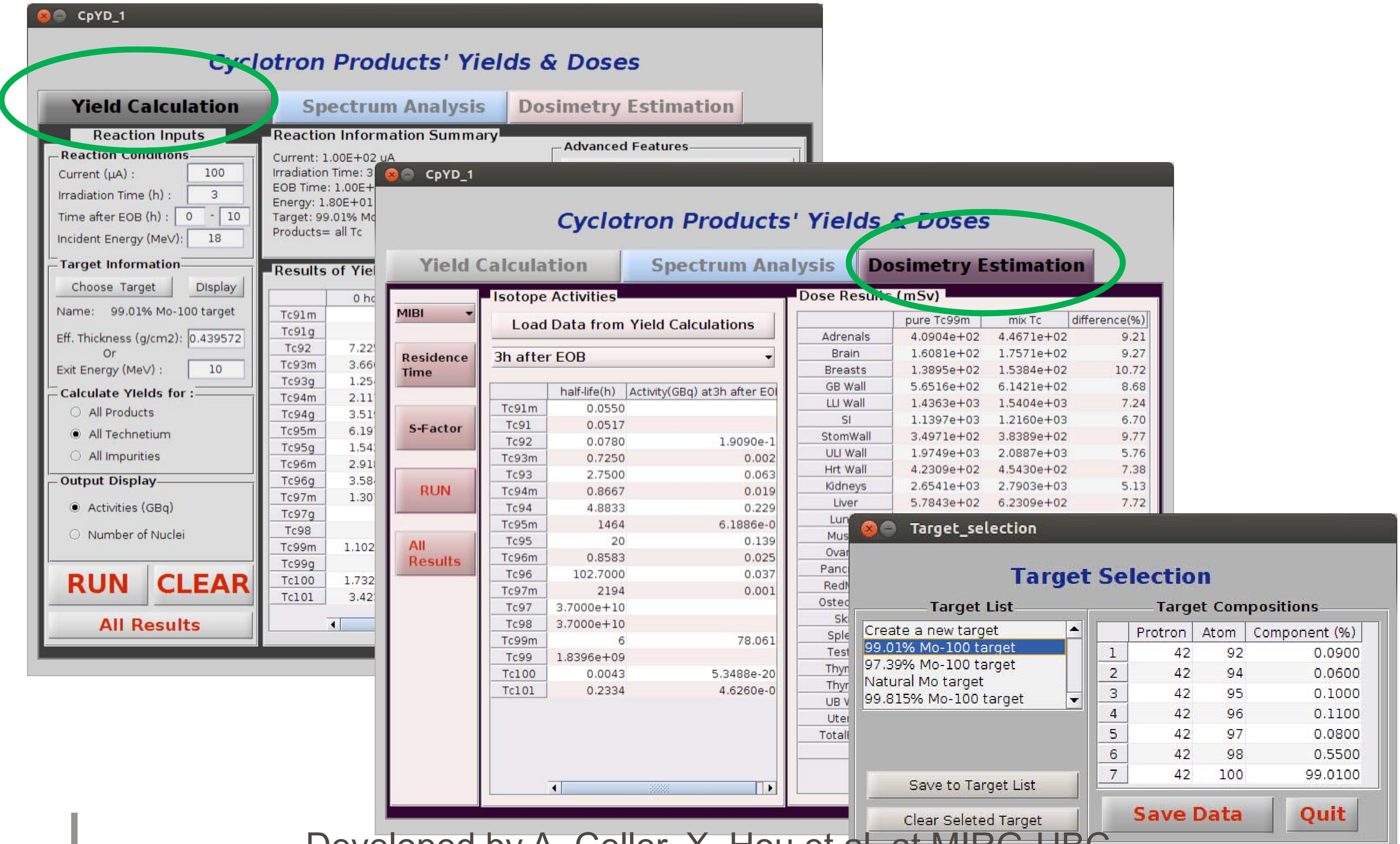
A. Celler, X. Hou, F. Bénard, T. Ruth, Phys. Med. Biol. 2011, 56, 5469

Target Enrichment: $^{94-97}Mo$ vs ^{100}Mo

Isotope	Enriched				Natural
	A	B	C	D	
^{92}Mo	0.005	0.006	0.09	0.003	14.85
^{94}Mo	0.005	0.0051	0.06	0.003	9.25
^{95}Mo	0.005	0.0076	0.1	0.003	15.92
^{96}Mo	0.005	0.0012	0.11	0.003	16.68
^{97}Mo	0.01	0.0016	0.08	0.003	9.55
^{98}Mo	2.58	0.41	0.55	0.17	24.13
^{100}Mo	**97.39**	**99.54**	**99.01**	**99.815**	**9.63**

Higher ^{100}Mo enrichment $\neq$ higher purity product

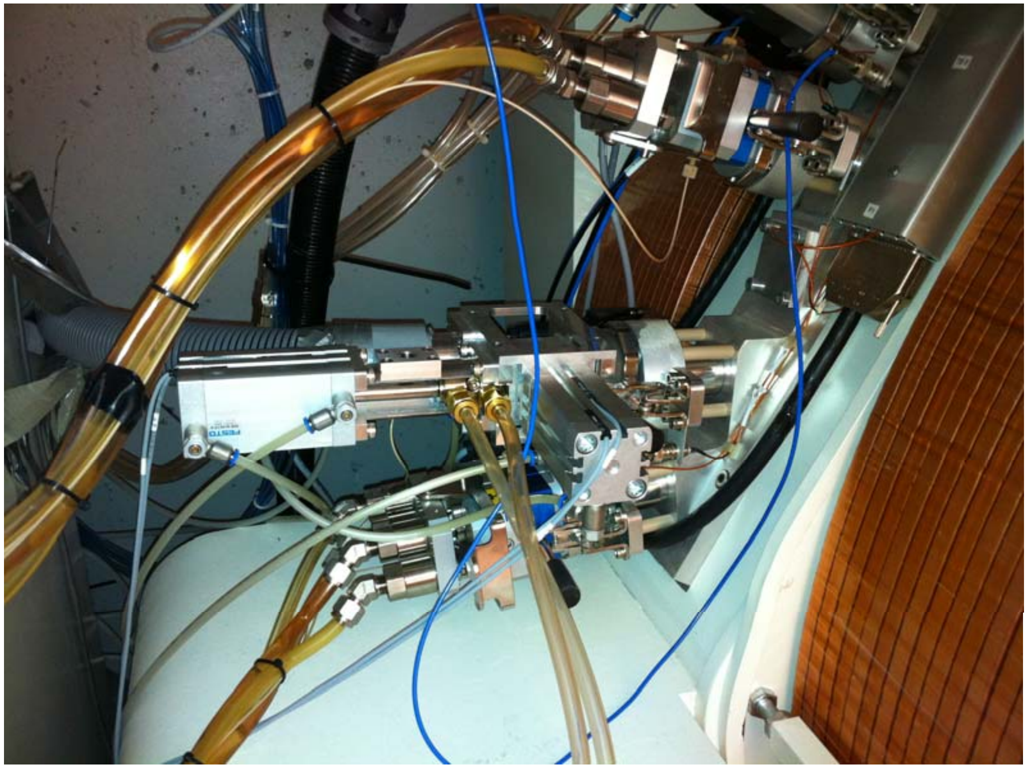
Graphical User Interface (GUI) for Yield and Dose Projections



Developed by A. Celler, X. Hou et al. at MIRG-UBC

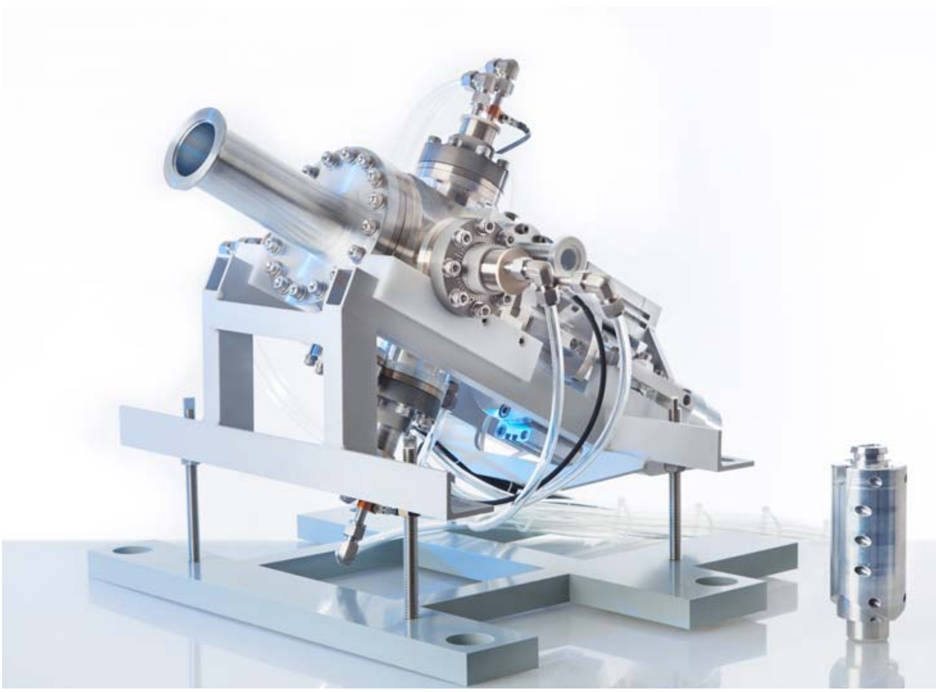
^{99m}Tc Production via Solid Target Irradiation (GE PETtrace)

- PETtrace target assembly
  - 130 μA, 16 MeV on target for 360 min
  - Saturation yields: 2.8 GBq/μA (75.6 mCi/μA)
  - Demonstrated yields of ~4.7 Ci



TR19 Solid Target System (BCCA)

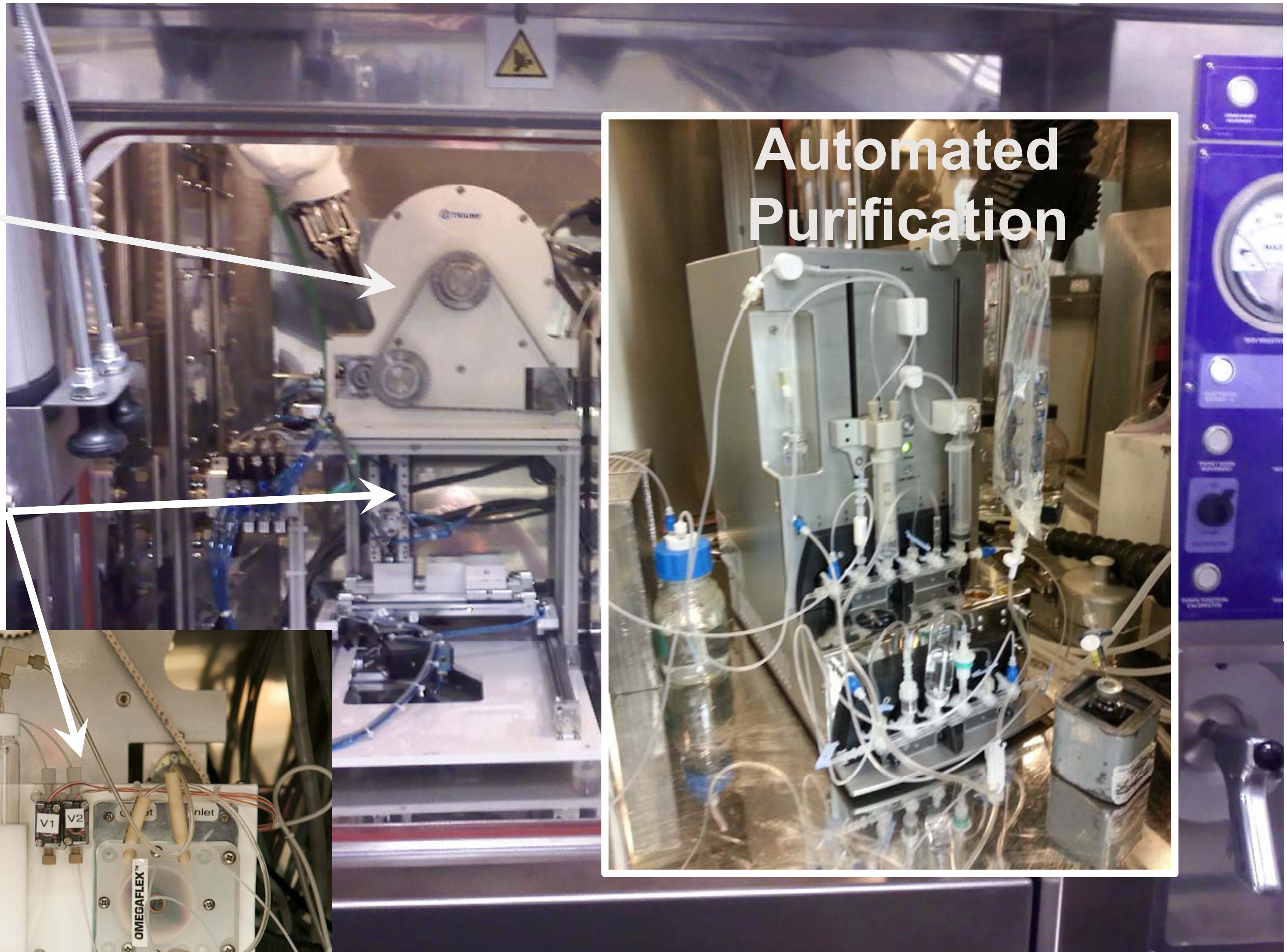
- TR19 target assembly
- Progress:
  - 240μA, 18 MeV on target (360 min)
    - **~9.4 Ci (370 GBq) ^{99m}Tc**
  - Next: 300μA, 18 MeV (360-540 min)
  - Saturation yield: 3.8 GBq/μA (103 mCi/μA)

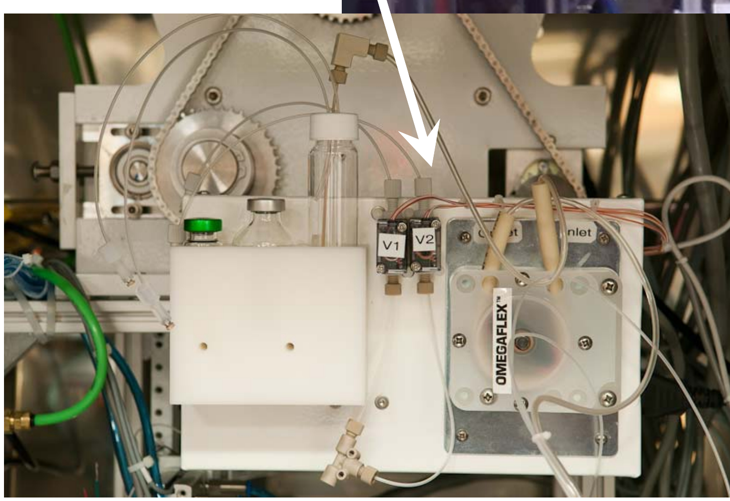


2010-2014: Development and Installation of High-Power Solid Targets, Associated Hardware

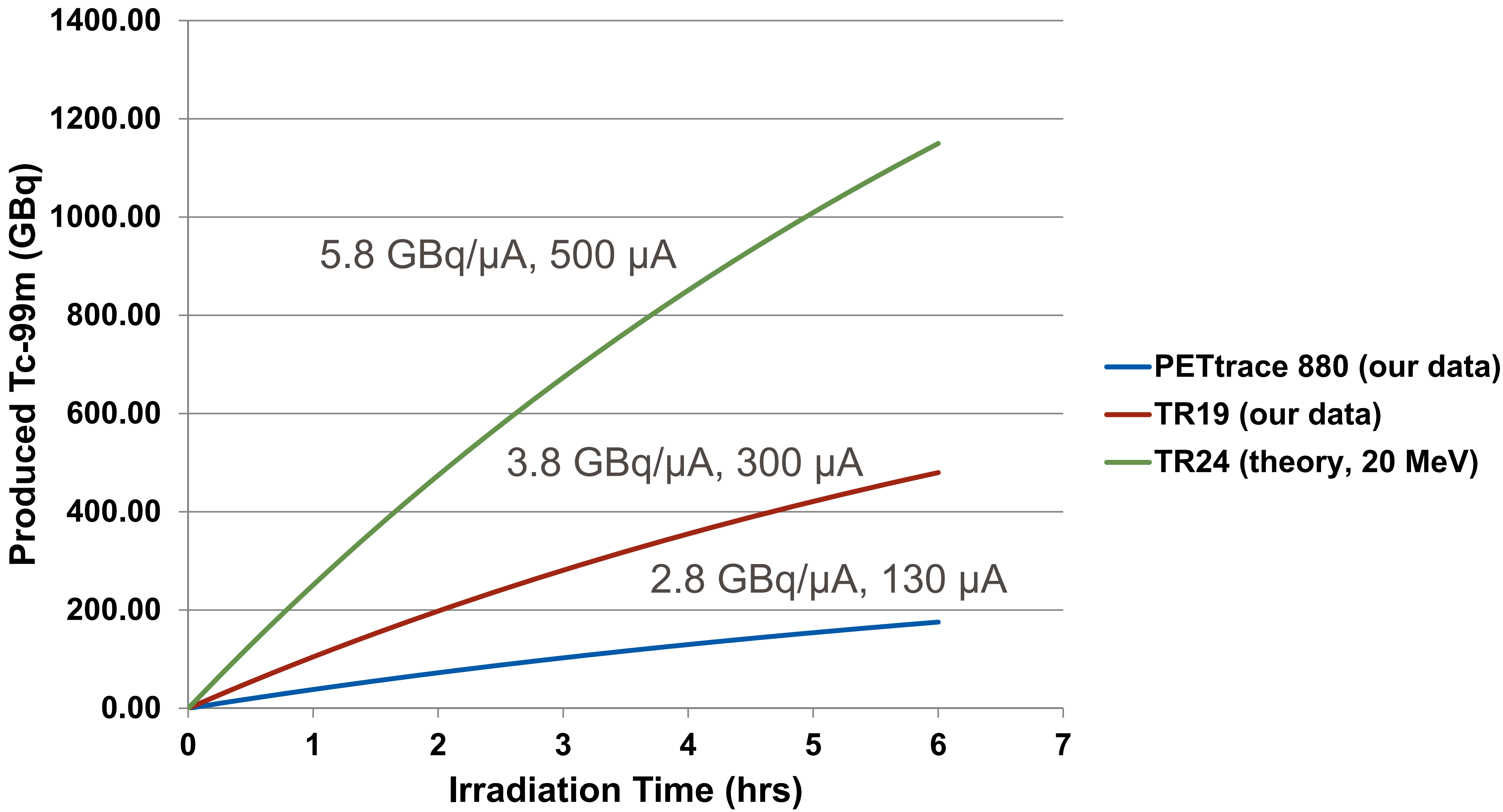
Transfer Drive

Receive and Dissolve





Yield Comparison: Energy, Current Considerations



Technical Summary of Results

- Target manufacture process, risks addressed…so far
- Yields: ~340 GBq (TR19), ~174 GBq (PETtrace)
- Recovery: ~93% as $Na^{99m}TcO_4$
- Radiopharmaceutical Production:
  - 3 types of kits (Sestamibi, HMPAO, MDP) radiolabeled successfully and passed standard QC (n = 3 each)
- Radiochemical Purity:
  - Small amounts of ^{93}Tc, ^{94m}Tc, ^{94}Tc, ^{95}Tc, ^{96}Tc impurities were observed – full quantitation underway
  - Non-Tc by-products (^{95}Nb, ^{99}Mo) collected in waste along with ^{100}Mo; negligible amounts in final product
  - ^{100}Mo recycled with 85% recovery yield (range 80 – 92%)
- Clinical Trial work to begin late 2014

See Bénard et al., J. Nucl. Med. 2014, 55, 1017-1022

Results Interpretation (so far)

- Production capacity: energy, time, current
  - Energy – intrinsic to machine (16-19 MeV, <22MeV)
  - Time – defined by other commitments (3-6 hrs)
  - **Current – intuitive for production boost (80-300+ μA); requires cyclotron power, target capabilities**
- ^{100}Mo isotopic purity is important
  - ^{95,96,97}Mo content is more important
- ^{99m}Tc specific activity needs regulatory consideration
  - Presence and affect on chemistry, dosimetry
  - Requires regulatory input (USP, EP)

Canada vs. Japan – Substantial ^{99m}Tc Production Capacity Currently in Place

Canada

Population: ~35M (2012)

Annual ^{99m}Tc needs: 971 TBq

With losses: **1900 - 3000 TBq**

Cyclotrons: 22+6 (16-24 MeV)

Existing Capacity: 2483 TBq

(2 x 6hr runs/d, 240d/yr)

Japan

Population: ~ 128M (2012)

Annual ^{99m}Tc needs: 3552 TBq

With losses: **7,100 - 11,100 TBq**

Cyclotrons: ~60 (>16 MeV)

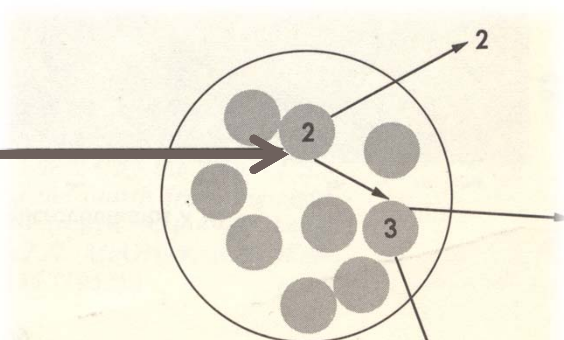
Existing Capacity: ~10,000 TBq

(2 x 6hr runs/d, 240d/yr)

Part 2: Isotope production at ISAC and ARIEL

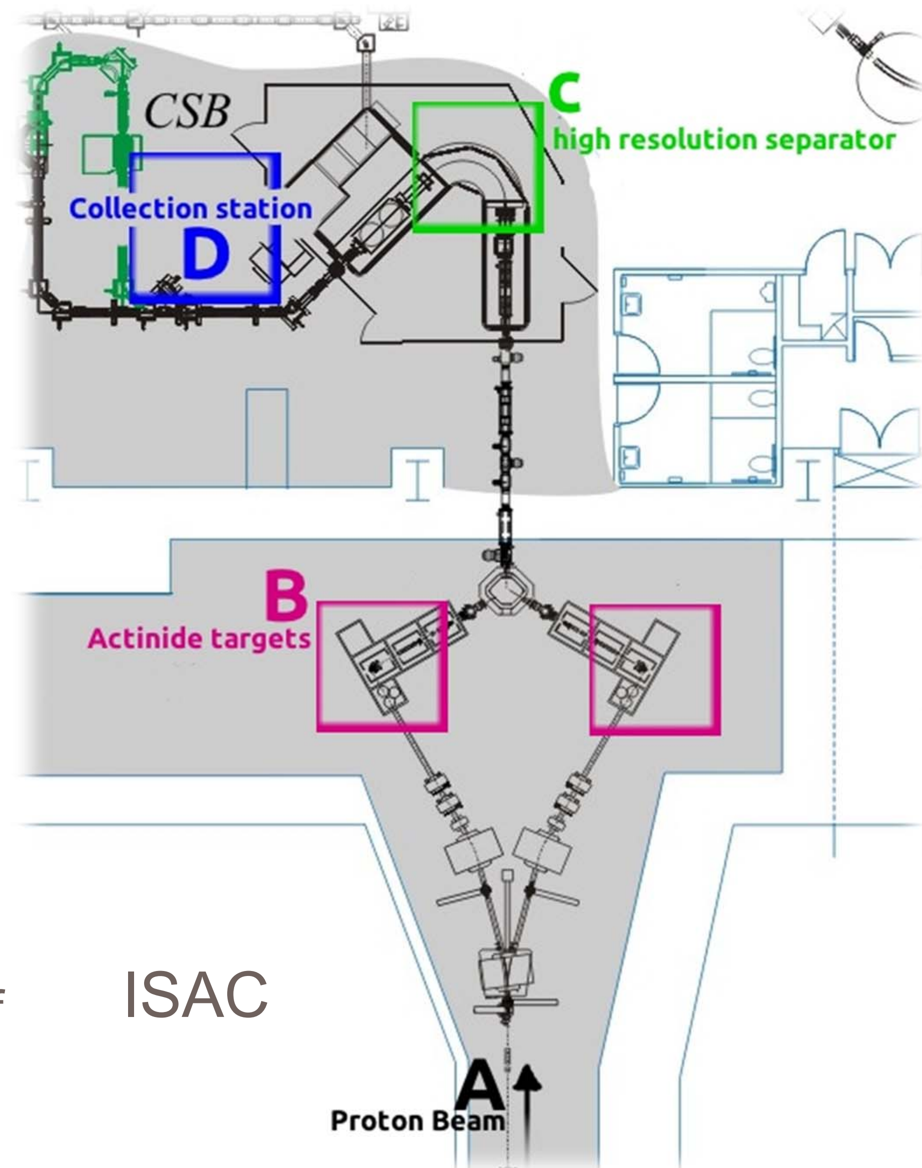
High mass isotope production by spallation of ^{238}U:

480 MeV Protons



Variety of isotopes produced

Uranium target



^{213}Fr implantation for ^{209}At

α-emitters of interest:

^{211}At (^{209}At)

$^{212\text{-}213}Bi$

^{223}Ra

^{225}Ac

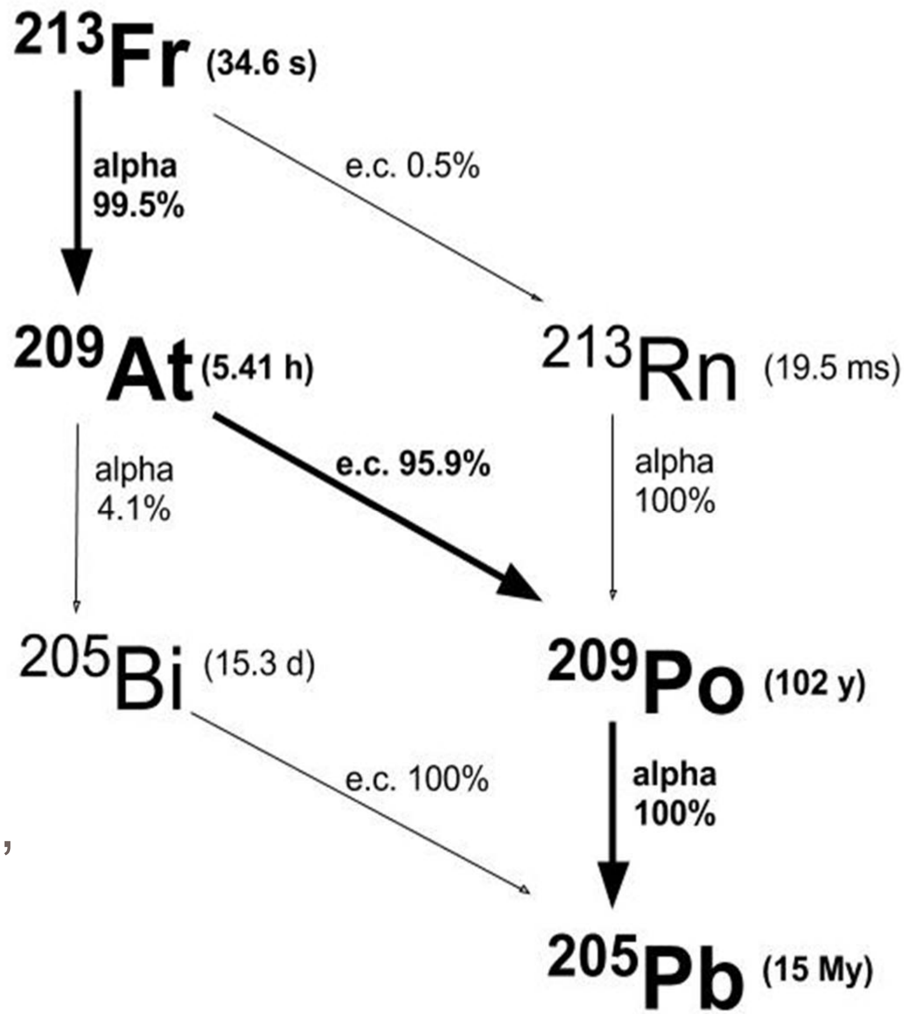
ISAC yield measurements:

$^{213}Fr = 7.7\times10^{8}$ ions/s,

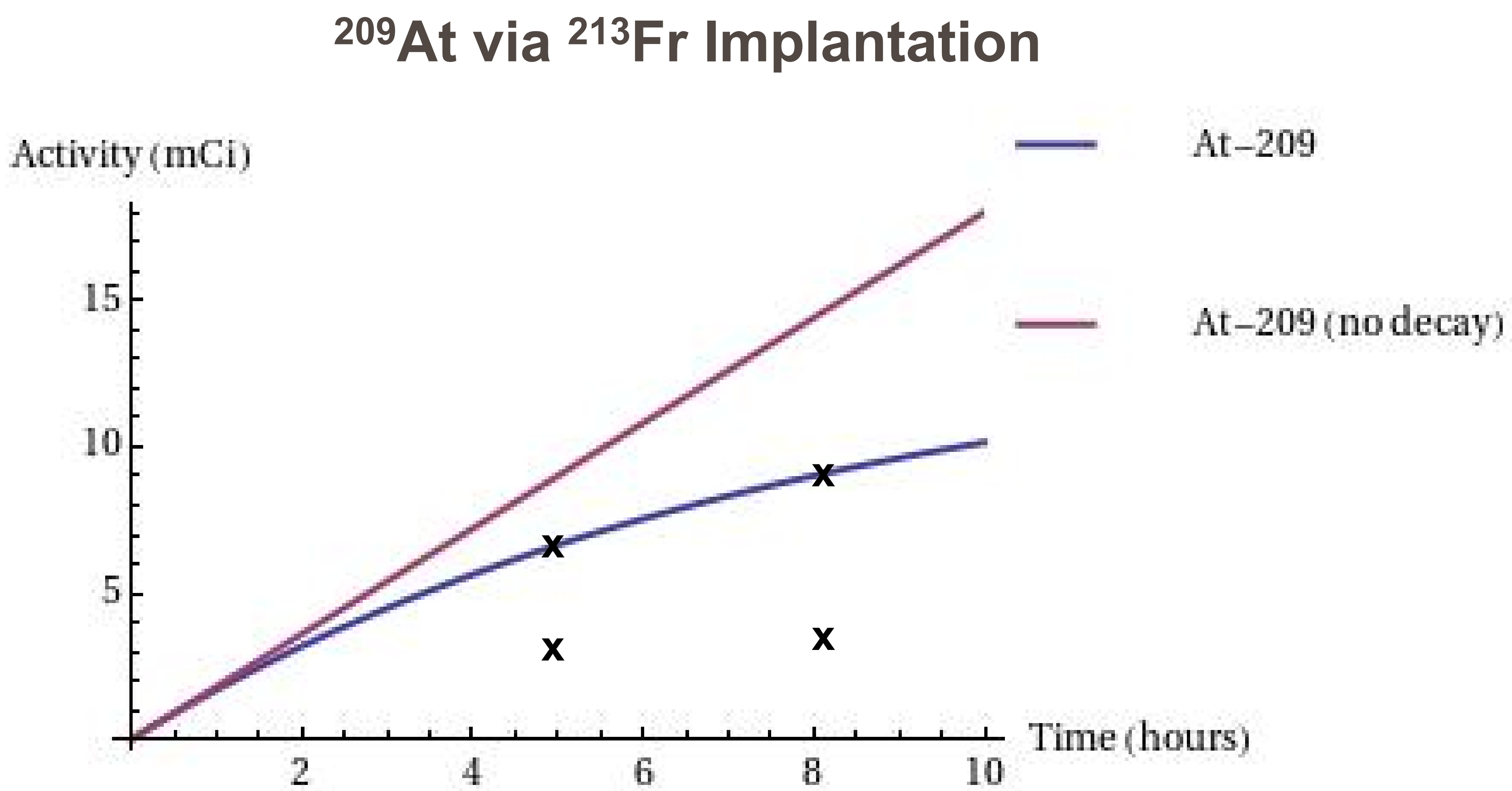
$^{213}Ra = 1.6\times10^{8}$ ions/s

Radium-213 is co-implanted (30%),

- 20% decays to $^{213}Fr \rightarrow {}^{209}At$
- 80% decays to ^{209}Rn ($t_{1/2}$=29m)
- 83% of ^{209}Rn decays to ^{209}At



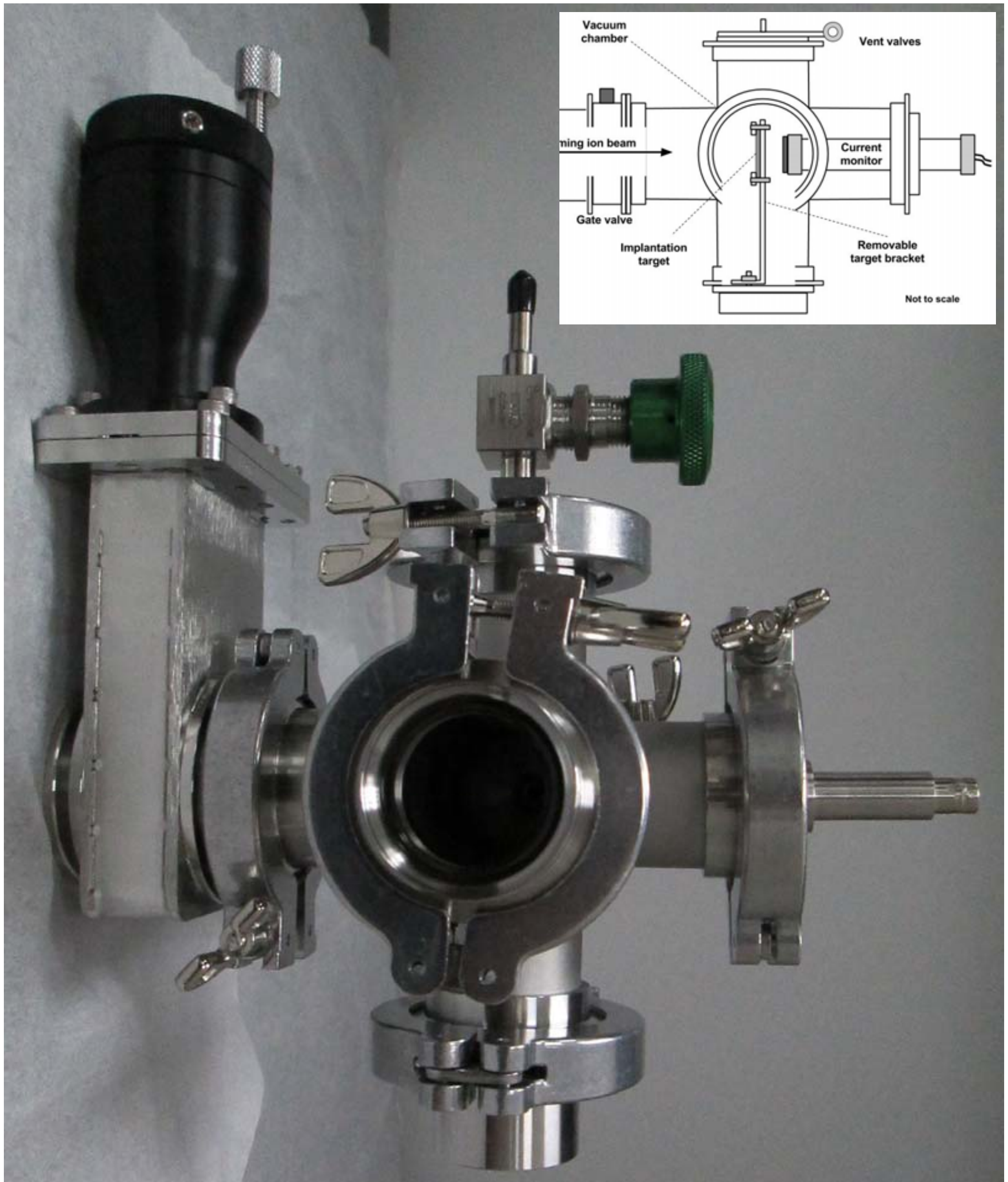
Theoretical ^{209}At build-up during ^{213}Fr implantation



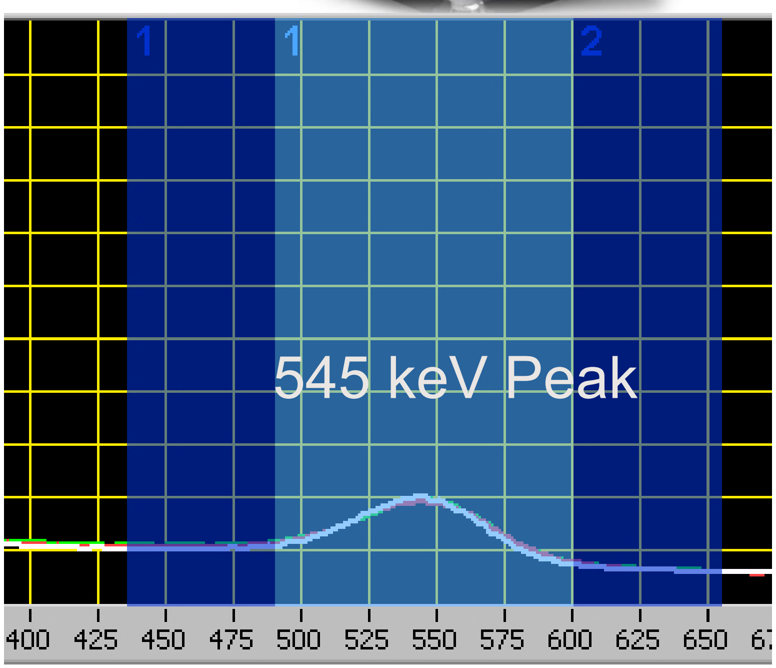
8.2 hr implantation ⟶ 3.2 mCi @EOB
5.0 hr implantation ⟶ 3.0 mCi @EOB

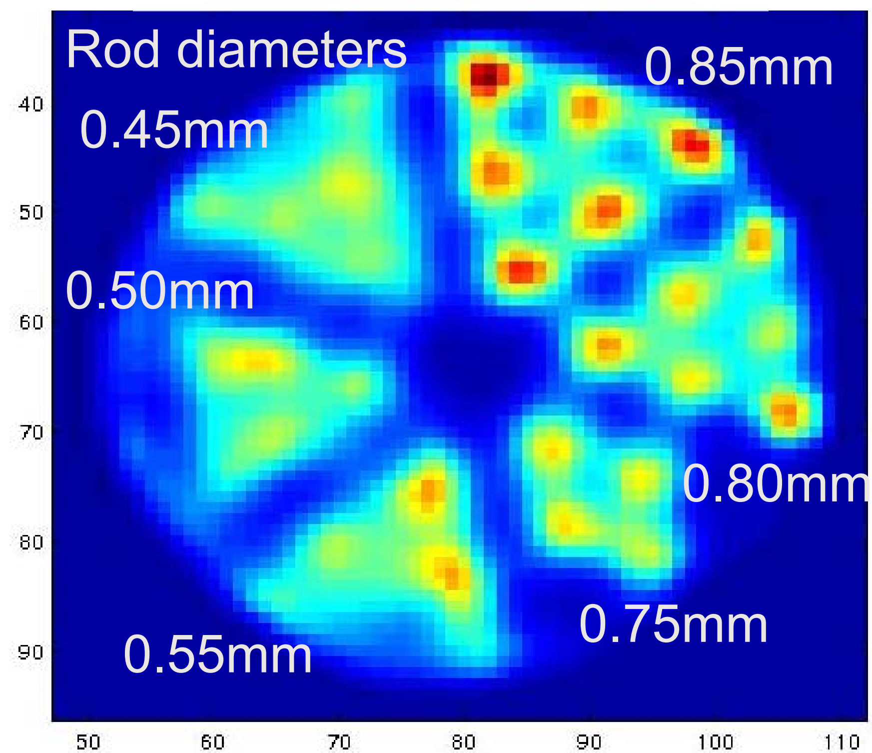
Purity of ^{209}At >99%
No unexpected inventory
No other astatine isotopes

Apparatus for $^{213}Fr/^{209}At$ collection



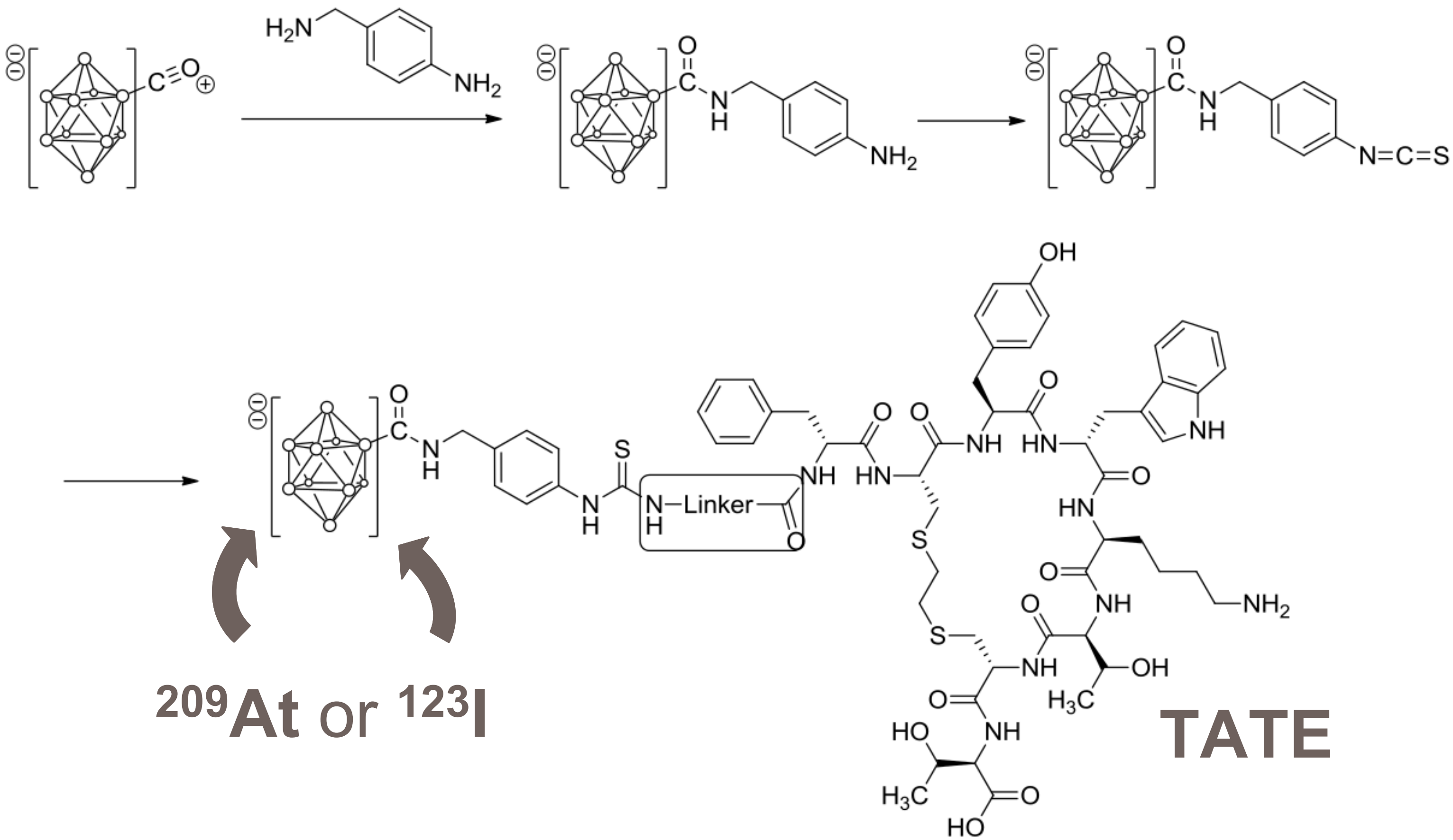
^{209}At-SPECT with hotrod phantom





Radionuclide therapy with astatine-labelled peptides

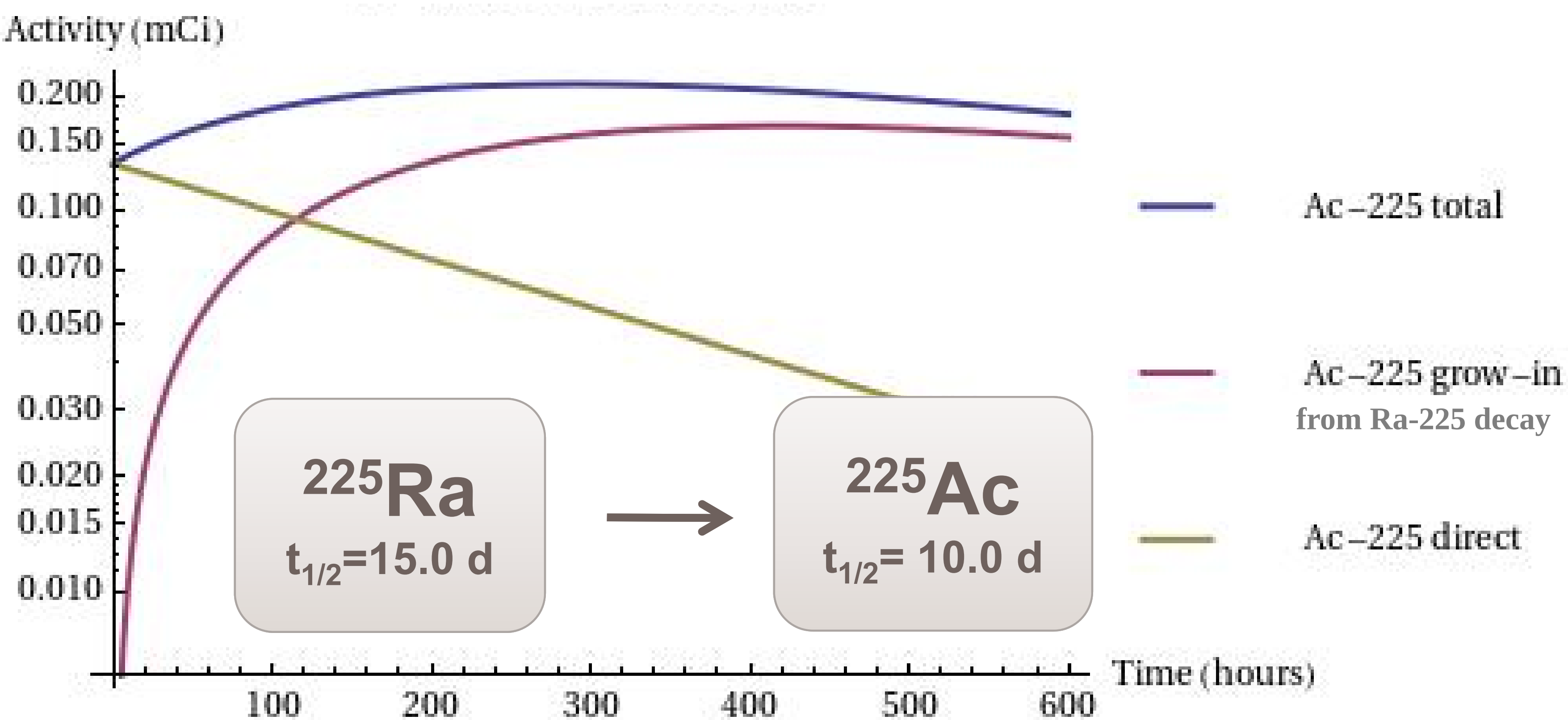
$^{209}At/^{211}At$ labelling studies and small animal imaging for targeting peptides (somatostatin-receptor ligands)



$^{209}At/^{211}At$ labelling development in collaboration with Dr. DS Wilbur, UW
Wilbur *et al, Bioconjugate Chem.* (2007), 18, 1226-1240

Future Direction: ISAC-ISOL

- $^{211}Rn/^{211}At$ generator
- $^{225}Ac/^{213}Bi$ generator



Feasibility/Chemistry in lead up to full target harvest

Future Direction(s): ARIEL

$^{68}Zn(\gamma,p)^{67}Cu$

$^{132}Te(\gamma,p)^{131}I$

$^{154}Sm(\gamma,n)^{153}Sm$

$^{178}Hf(\gamma,p)^{177}Lu$

$^{187}Re(\gamma,n)^{186}Re$

$^{226}Ra(\gamma,n)^{225}Ra \rightarrow {}^{225}Ac$

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Acknowledgements – Tc-99m

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Canada

- **TRIUMF and BCCA machine shops**
- **Finances/Admin**
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Société canadienne du cancer

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Laboratoire national canadien pour la recherche en physique nucléaire et en physique des particules

Thank you!
Merci

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