Production of Medical Isotopes with Electron linacs

NAPAC 2016

Chicago, IL

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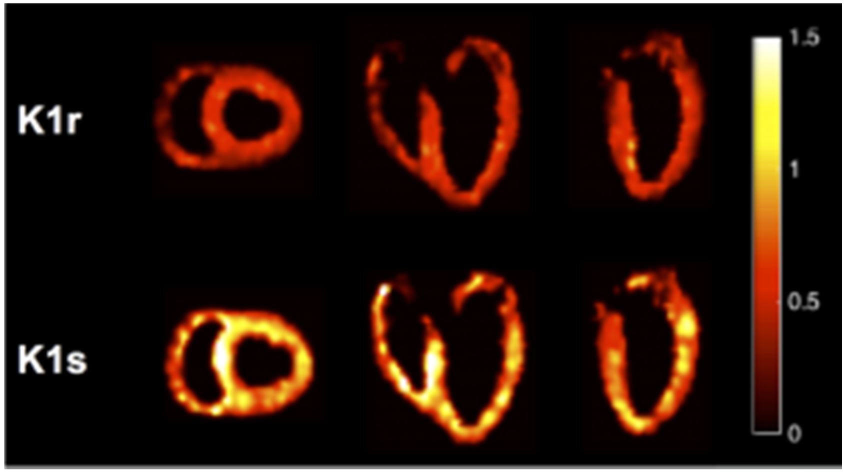
13 October 2016

Radioisotopes for Medical Applications

- Used since the 1930's
  - ^{32}P for treatment of hematological disease

- Expanded to mainstream Diagnostic and Therapeutic
  - Diagnostic – exploiting complete tissue penetration of gamma rays, including positron annihilation (SPECT and PET)
  - Therapeutic – exploiting cellular toxicity of non-penetrating emissions (alpha, beta, Auger-electrons)



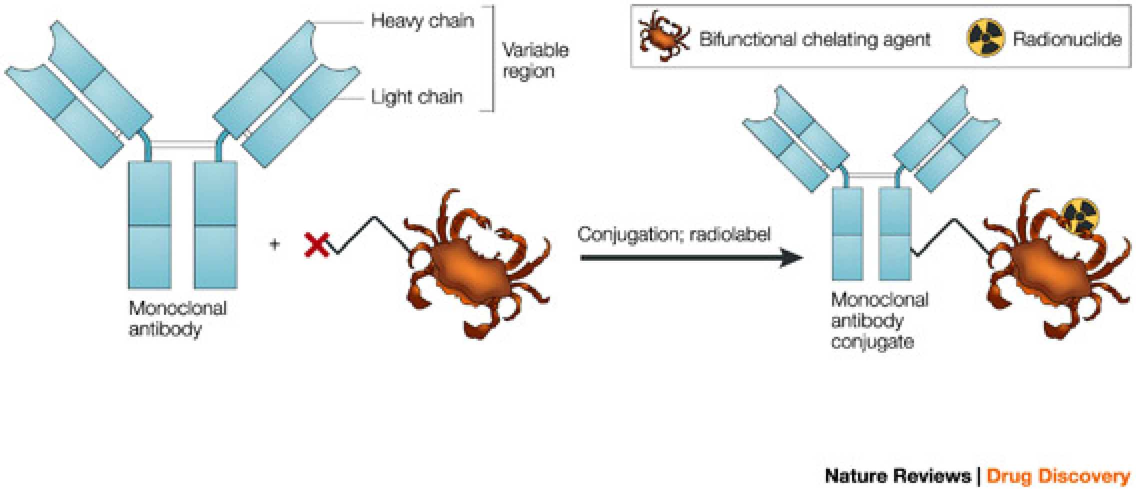
Stress test on pig heart

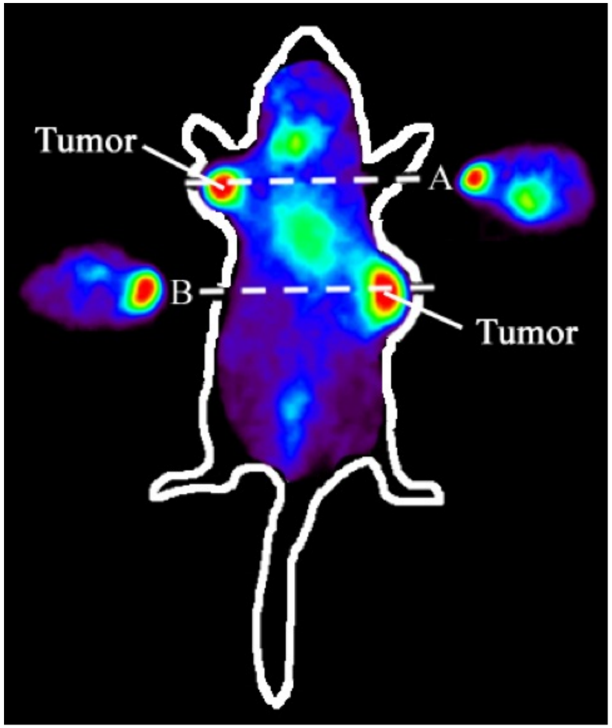
^{99m}Tc for excretion studies

-NI Berlin, et al, Radioisotope Therapy factsheet human experimentation Lawrence Berkely, **1939**
-N Guehl, M Normandin, D Wooten, G Rozen, A Sitek, M Mansour, T Shoup, L Ptaszek, G El Fakhri, N Alpert, J Nucl Med **2015** vol. 56
-M Ljungberg, KS Gleisner, Diagnostic **2015**, 5(3) 296-317
-http://www.ucair.med.utah.edu/FacultyKadrmas/KadrmasGroup.html accessed 2/16/2016

Radioisotopes for Medical Applications

- Targeted Detection and Therapies
  - Biological behaviors and chemical compatibility for incorporation into complex targeting molecules and bioconjugates
  - Bifunctional Chelate Approach

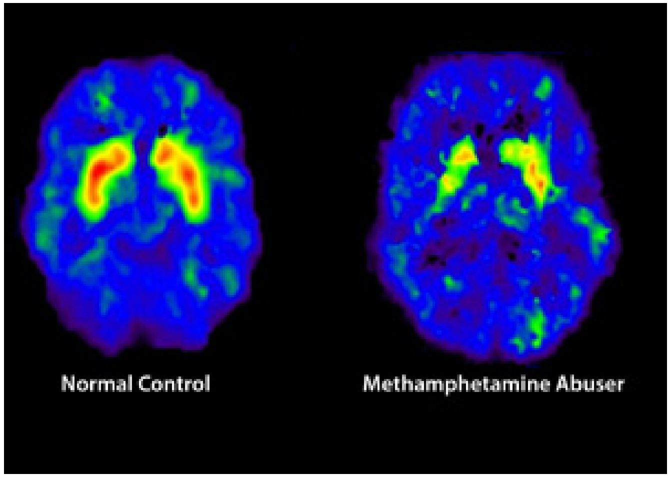


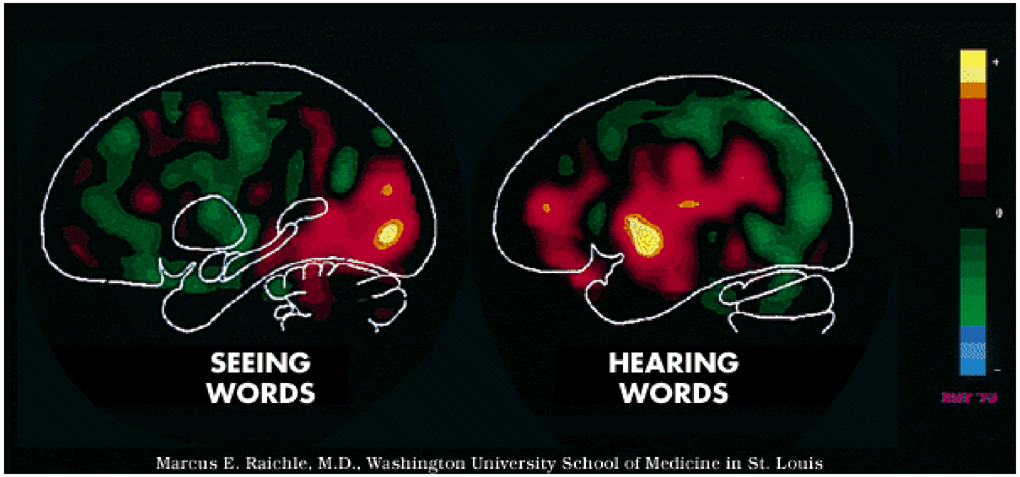


DE Milenic, ED Brady, MW Brechbiel, Nature Reviews Drug Discovery **2004** 3, 488-499
http://www.bms.uu.se/sv/node121 accessed 2/16/2016

Radioisotopes for Medical Applications

- Monitor biological functions
  - Brain activity





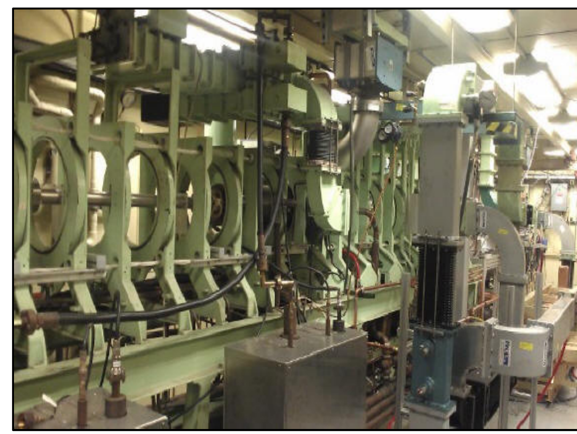
- Bridges multiple disciplines
  - Inorganic and organic chemistry, physicists, radiochemists, biologists, clinicians, pharmacologists, etc.

http://psycheducation.org/brain-tours/pet-scans/ accessed 2/16/2016
http://earthsky.org/human-world/joanna-fowler-explains-the-chemistry-of-drug-addiction accessed 2/16/2016

Low Energy Accelerator Facility (LEAF)

The LEAF serves as a principal investigating conduit for research and development in nuclear applications, such as medical isotope production, radiation damage, material sciences, nuclear chemistry, homeland and national security applications.

3 MeV electron Van de Graaff Accelerator (VDG)



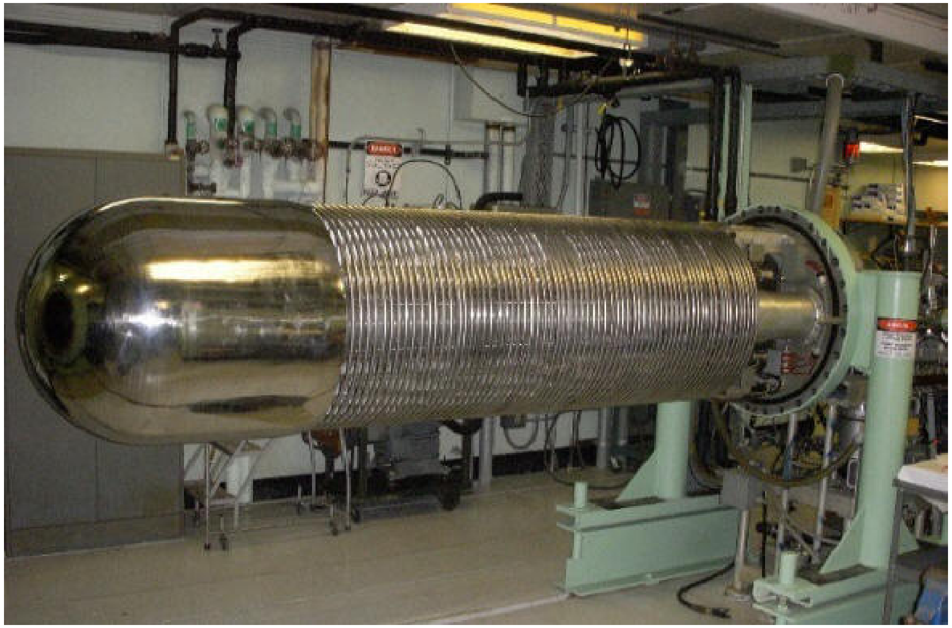
55 MeV L-band Electron Accelerator (LINAC)

Van de Graaf Accelerator (VDG)

- VDF Type: pulsed or D.C.
  - Electron
  - 0.3 – 3.0 MeV

Pulsed electron mode

1. Peak pulse current
   -- continuous variable 10 mA - 2 A
2. Pulse length
   -- fixed pulse width system -5, 10, 25, 55 and 100 nsec
   -- variable pulse width system
   -- 50 ns - 10 us (duty cycle limitation)
3. Pulse repetition rate 1 - 1000 pulses/sec
4. Beam size -0.5 cm diameter
5. pulse stability --±2%



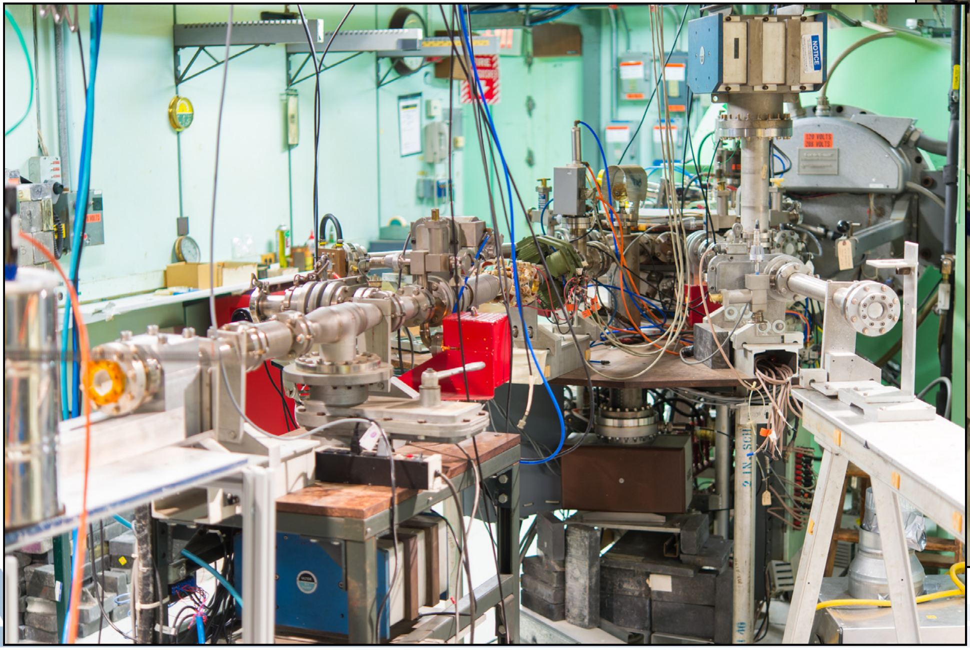
D.C. Electron Mode:

1. Max Current: 80 uA
2. Beam size: ~ 1 cm diameter

- The VDG can be used as an electron beam source or using a converter as a gamma source. Direct electron beam irradiations can be greater than 3,400 Mrad per hour, using the converter doses reach 9,000 Rad/hour 12” from the converter.

VDG

- Radiation Chemistry: testing equipment and material in high radiation fields.
- Specific projects:
  - Automated equipment components
  - Precipitation formation of $UO_{4(s)}$ during irradiation
  - Radiation stability of Mo-ABO complex
  - ABEC column testing
  - HDPE bottles loaded with Mo



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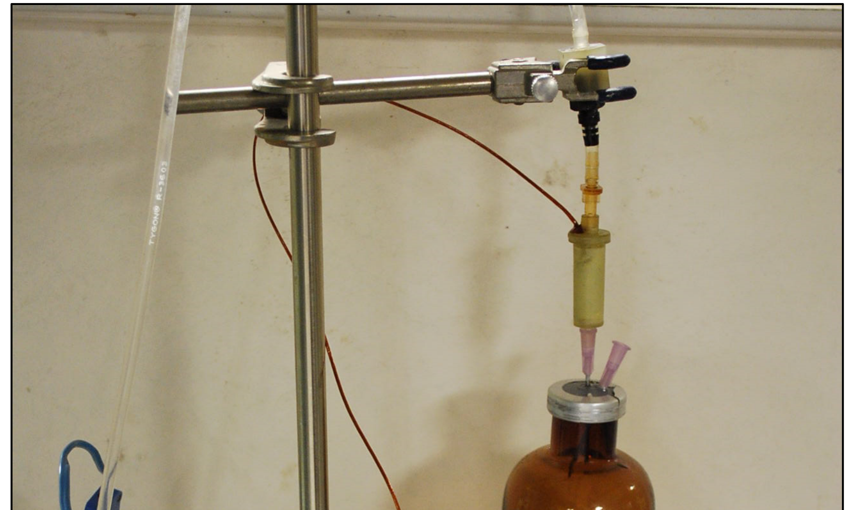
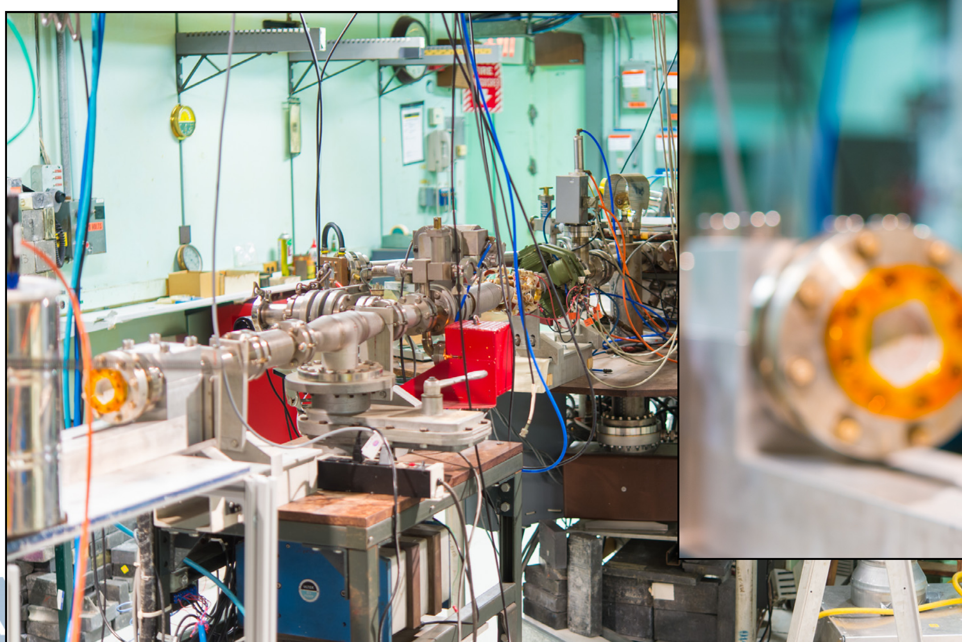
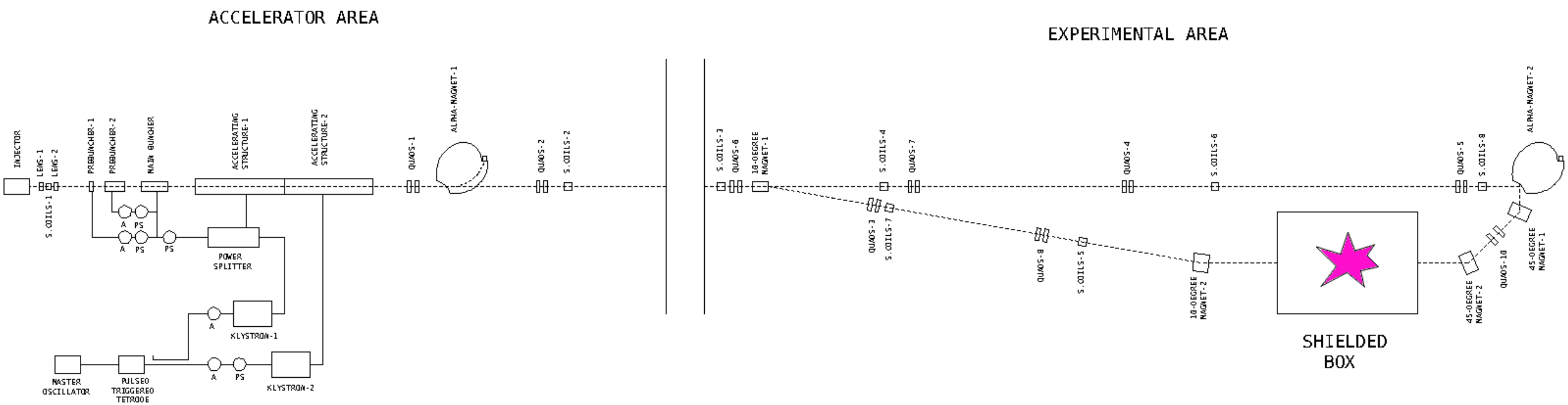


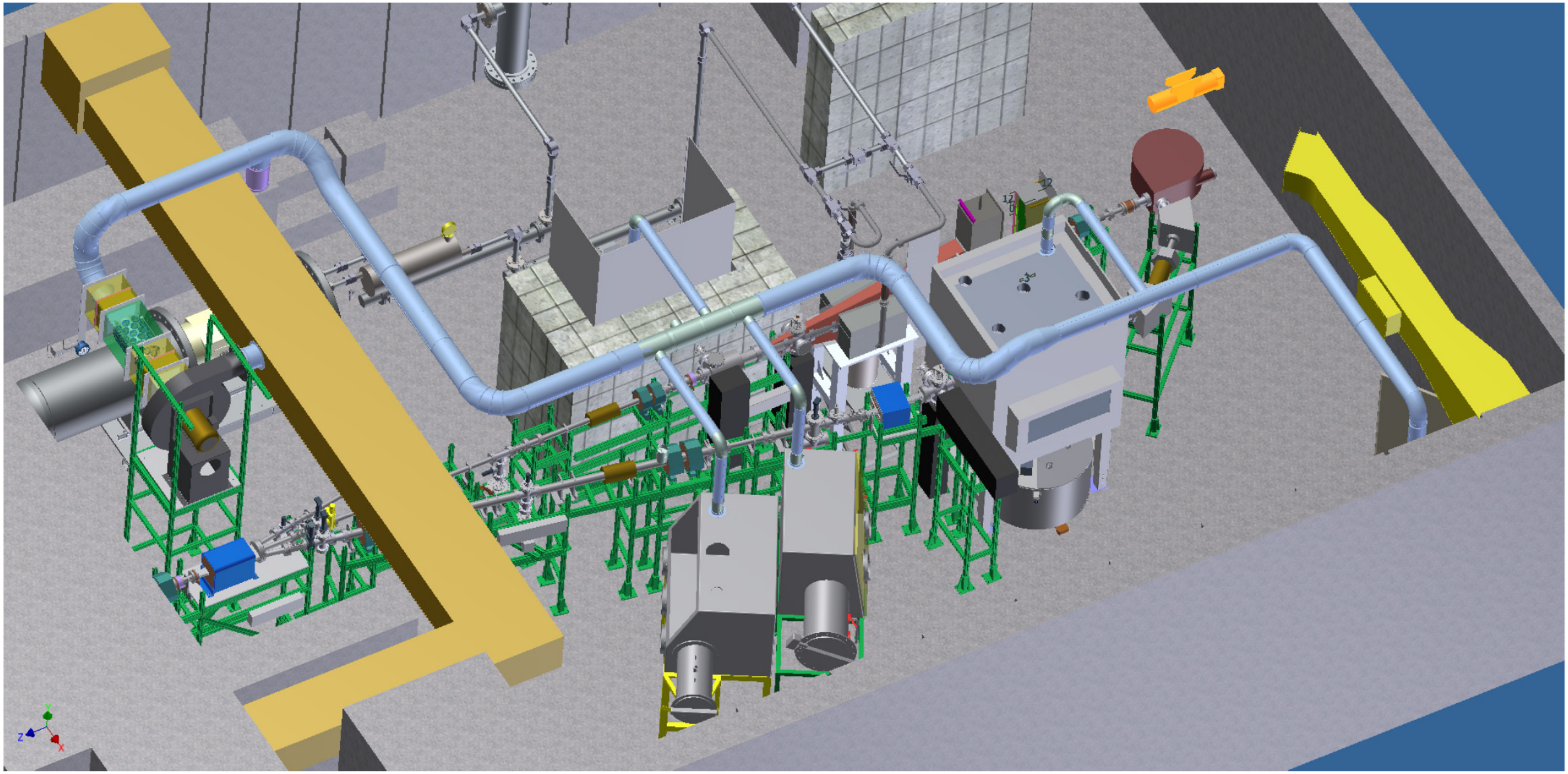


LINAC upgrade

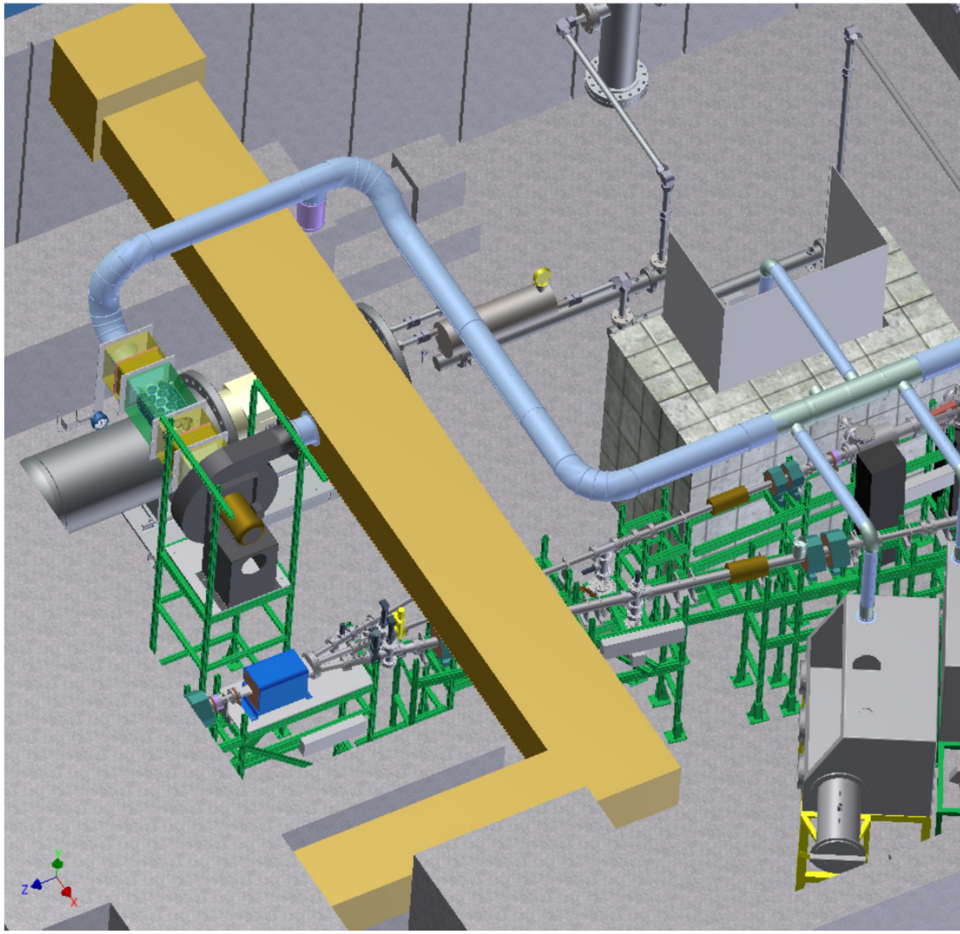
Parameter	Value	Unit
Maximum beam energy	55	MeV
Minimum beam energy	20	MeV
Maximum average beam power	25	kW
RF frequency	1300	MHz
Repetition rate	240	Hz
Length of RF pulse	6.5	ms
Maximum beam pulse width	5	ms
Beam energy spread	3	%

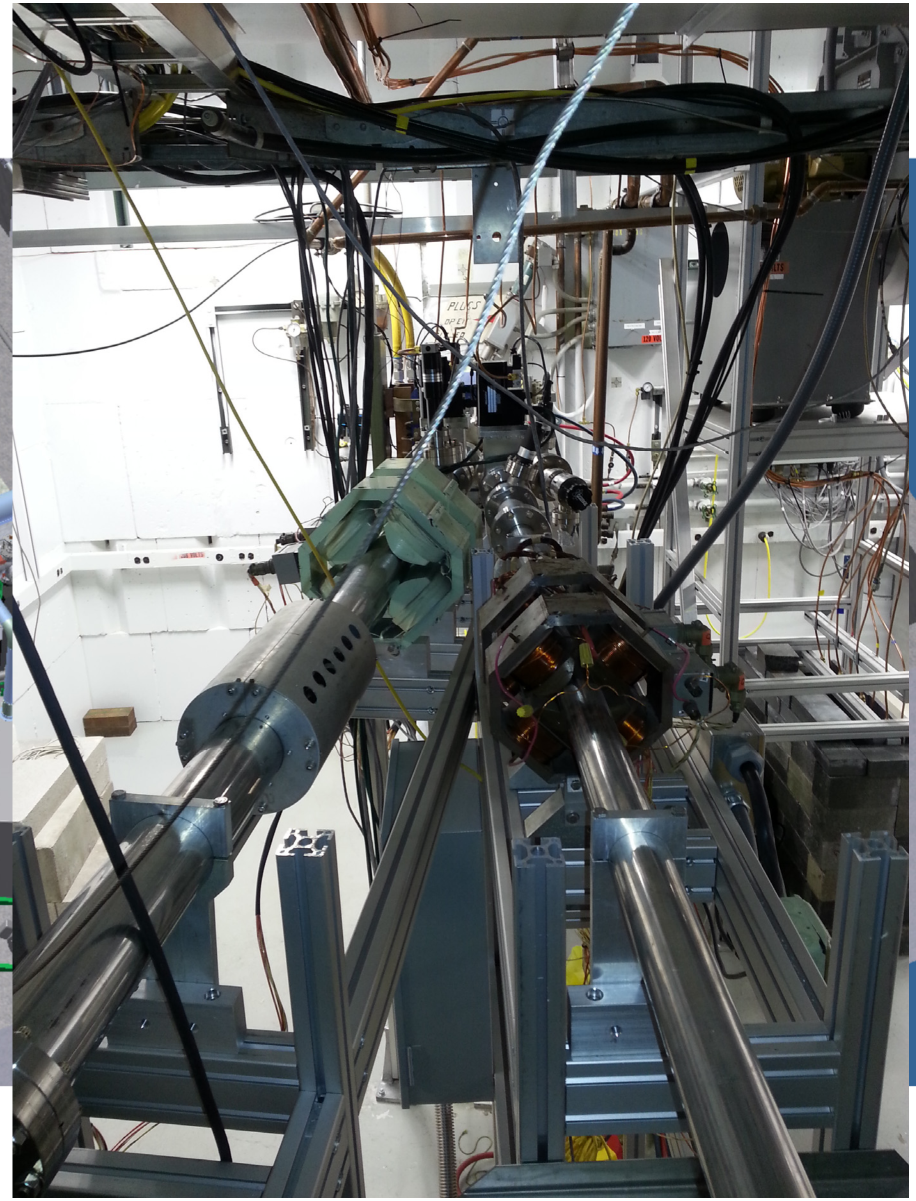


LINAC Beam Floor Layout



LINAC Beam Floor Layout





Current and Emerging R&D

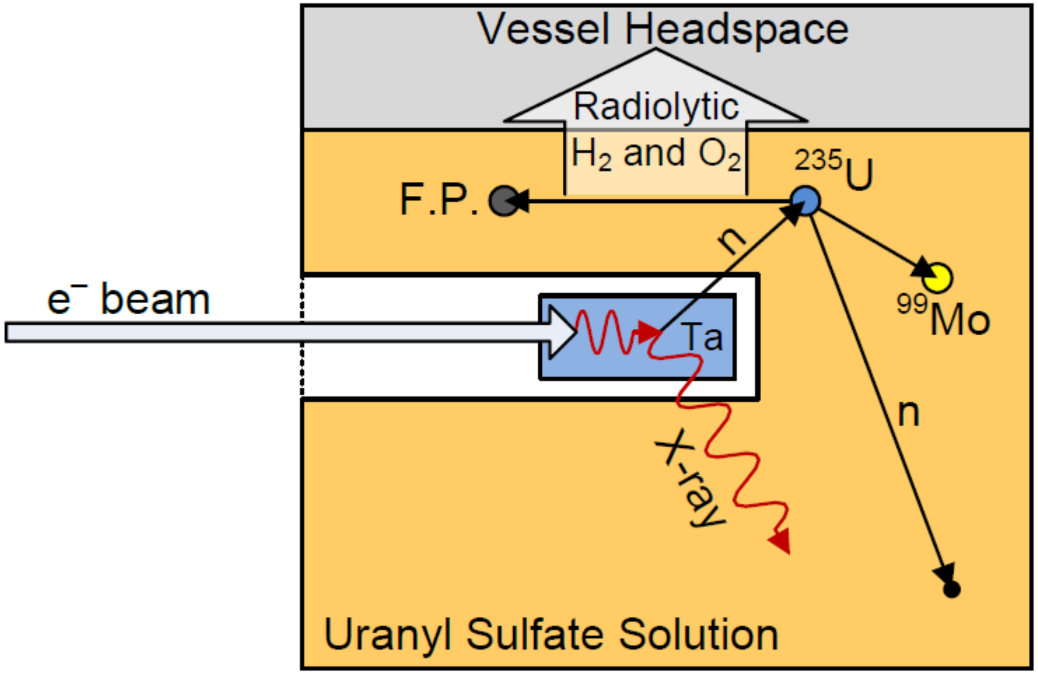
- ^{99}Mo
  - Mother of ^{99m}Tc
    - $t_{1/2}$ = 6 hrs
  - **Diagnostic**
    - γ: 140 keV
    - SPECT
  - Provided as a ^{99}Mo/^{99m}Tc Generator
    - ^{99}Mo $t_{1/2}$ = 66 hrs
  - Most widely used radioisotope for SPECT imaging
  - 80% of 40 million procedures performed annually worldwide

- ^{67}Cu
  - **Theranostic**
    - $t_{1/2}$ = ~2.5 days
    - β-:
      121 keV (56%)
      154 keV (23%)
      189 keV (20%)
    - γ: 184.6 keV (49%)
    - Decays to stable Zn
  - Match pair with ^{64}Cu
    - PET
  - Uses: treatment of non-Hodgkins lymphoma, and other cancers
  - Lack of supply halted clinical trials

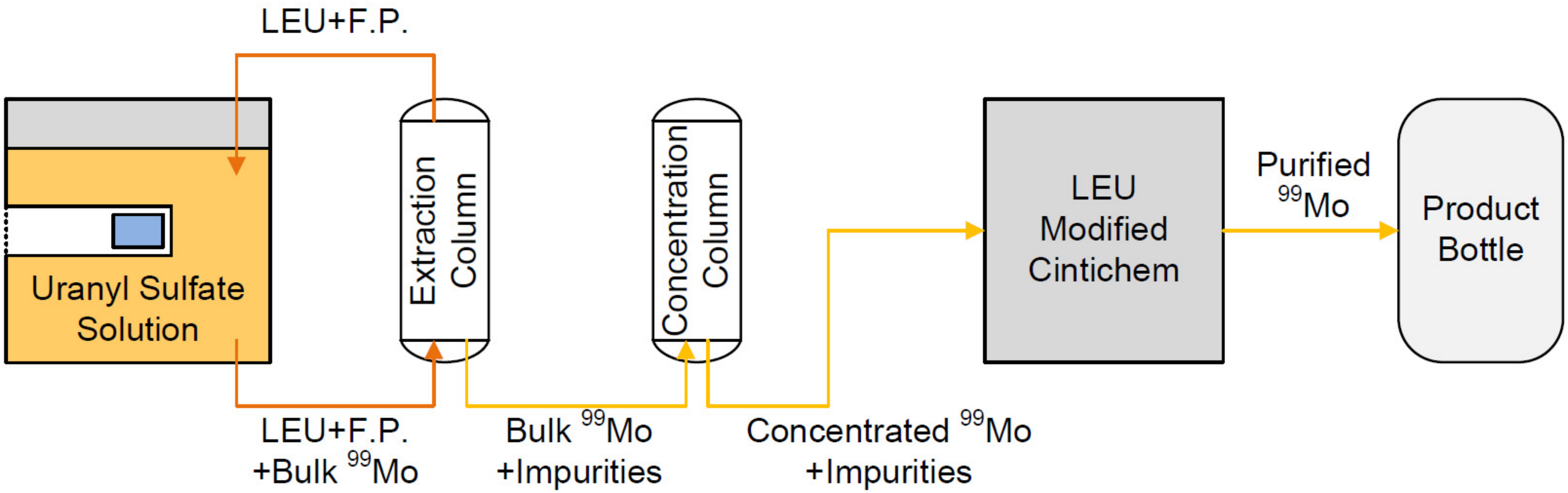
- ^{47}Sc
  - **Theranostic**
    - $t_{1/2}$ = 3.35 days
    - β-:
      142.6 keV (68.4%)
      203.9 keV (31.6%)
      440.9 keV (19%)
      600.3 keV (19%)
    - γ: 159.3 keV (68.3%)
    - Decays to stable Ti
  - Match pair with ^{44}Sc
    - PET
  - Uses: promising candidate for cancer treatment
  - Chemical-cousin to lanthanides who are currently used in pharmaceuticals (MRI-CA)

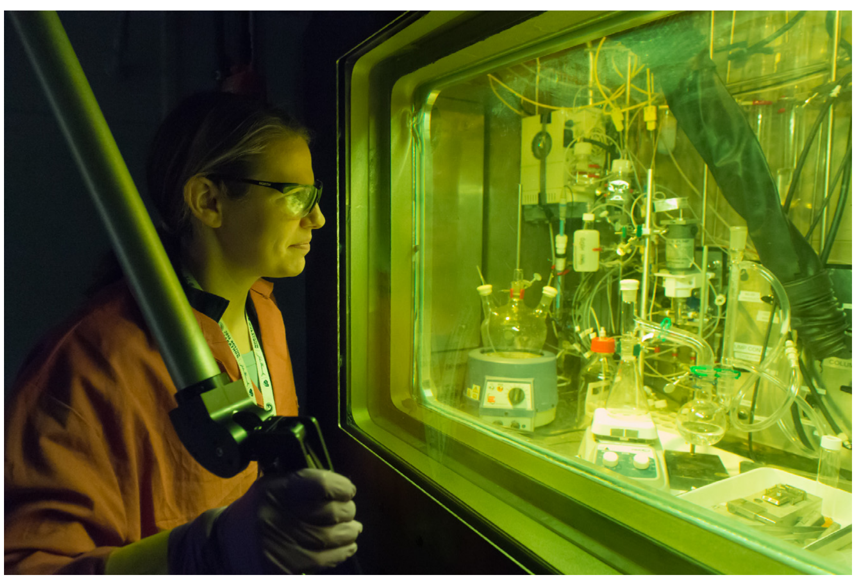
Argonne's Role in Accelerating Domestic Production of Mo-99

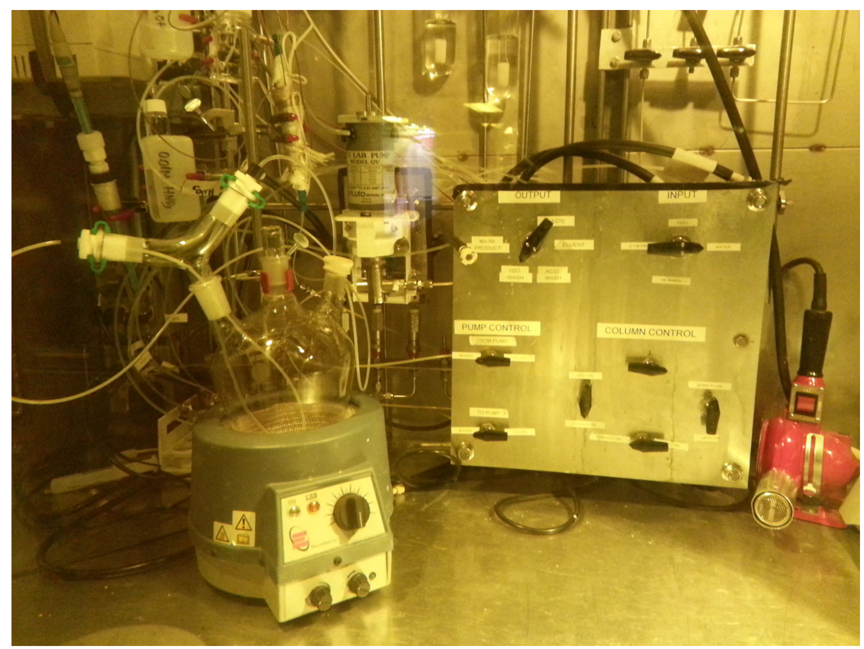
- Major tasks
  - Preparation and irradiation of the uranyl-sulfate target solution
  - Development and design of the Mo-recovery system
  - Use of the LEU-Modified Cintichem process for Mo purification
  - Develop method for periodic cleanup of irradiated target solution
  - Radiation stability of system components
  - Develope understanding of radiolysis effects on
    - Solution chemistry
    - Gas generation
    - Precipitation
  - **Mini-SHINE experiments – sub-pilot-plant**



Flow Diagram





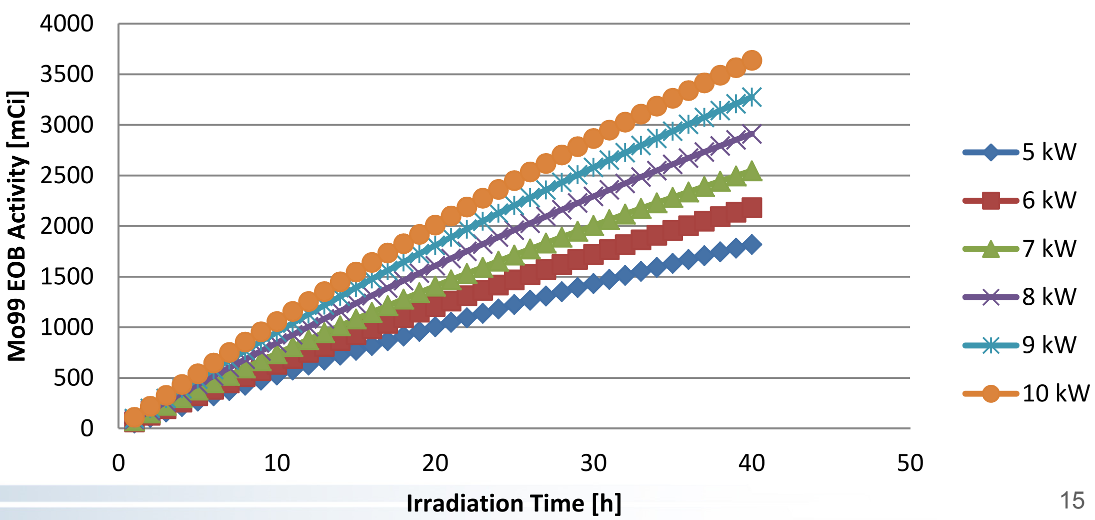


Mo-99 Production from LEU-Uranyl Sulfate

Irradiation	Max Power	Current	Time (hr)	Energy	Mo-99 produced (mCi)	Met Purity Specs	Overall Mo-99 Yield
1	7.3 kW	208 μA	2	35 MeV	70	Yes	95%
2	9 kW	276 μA	8	35 MeV	350	Yes	86%
3	9.4 kW	269 μA	32	35 MeV	810	No	94%
4	9.8 kW	267 μA	20	37 MeV	380	Yes	42%
5	9.8 kW	278 μA	~3.25	35.2 MeV	460	Yes	70%
6	10 kW	285 μA	24	35 MeV	1400	Yes	93%

Ratio (X/^{99}Mo)	Product Specification
^{131}I/^{99}Mo	≤ 5×10^{-5}
^{103}Ru/^{99}Mo	≤ 5×10^{-5}
^{132}Te/^{99}Mo	≤ 5×10^{-5}
^{89}Sr & ^{90}Sr/^{99}Mo	≤ 6×10^{-7}
Σα/^{99}Mo	≤ 1×10^{-9}
Σγ/^{99}Mo	≤ 1×10^{-4}

MCNPX Theoretical Production Curves



Argonne's Role in Accelerating Domestic Production of Mo-99

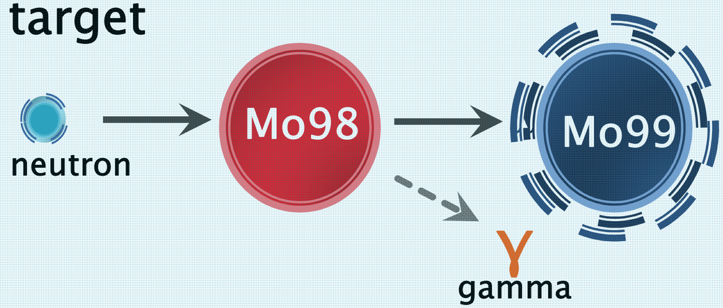
National Nuclear Security Administration

NorthStar MEDICAL RADIOISOTOPES LLC

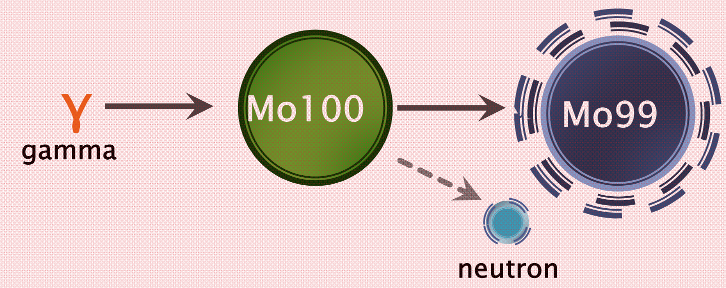
A subsidiary of NorthStar Medical Technologies

- Major tasks
  - Irradiation of sintered Mo targets
  - Chemical processing of irradiated targets
  - Optimization of disk density and dissolution kinetics
  - Optimization of large-scale dissolution (300-600 g)
  - Develop method for recycle of enriched target material
  - Radiation stability studies at VDG
  - Dispensing studies

Reactor production on Mo target



Accelerator production



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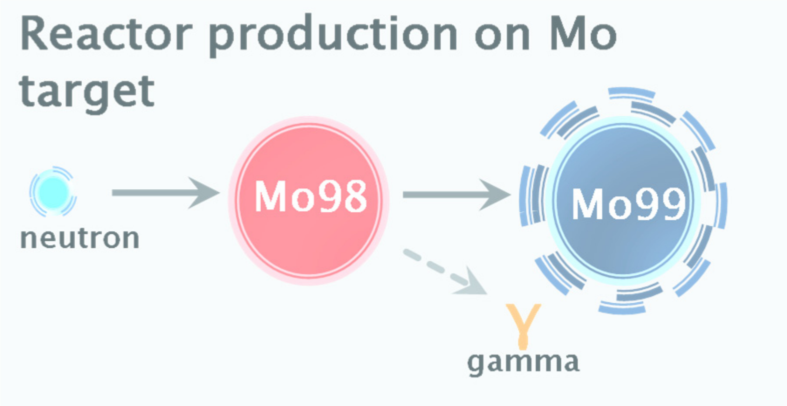
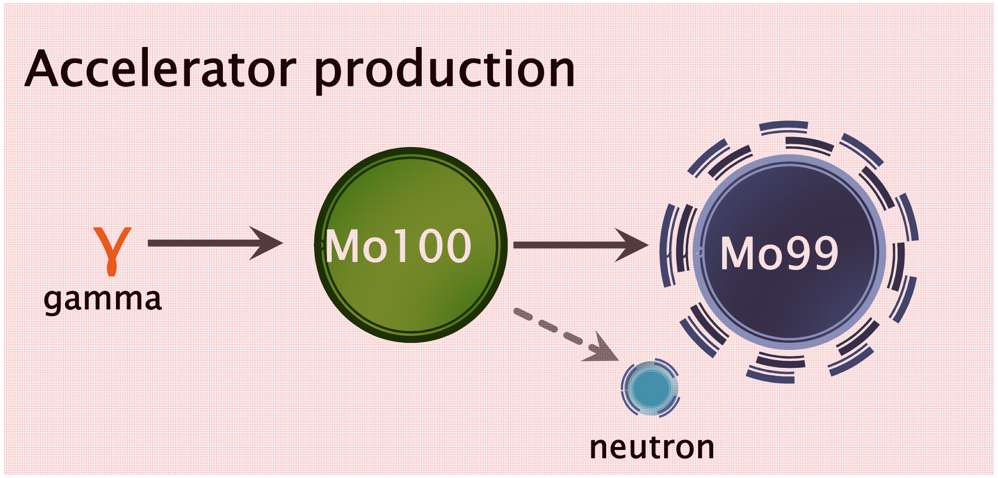
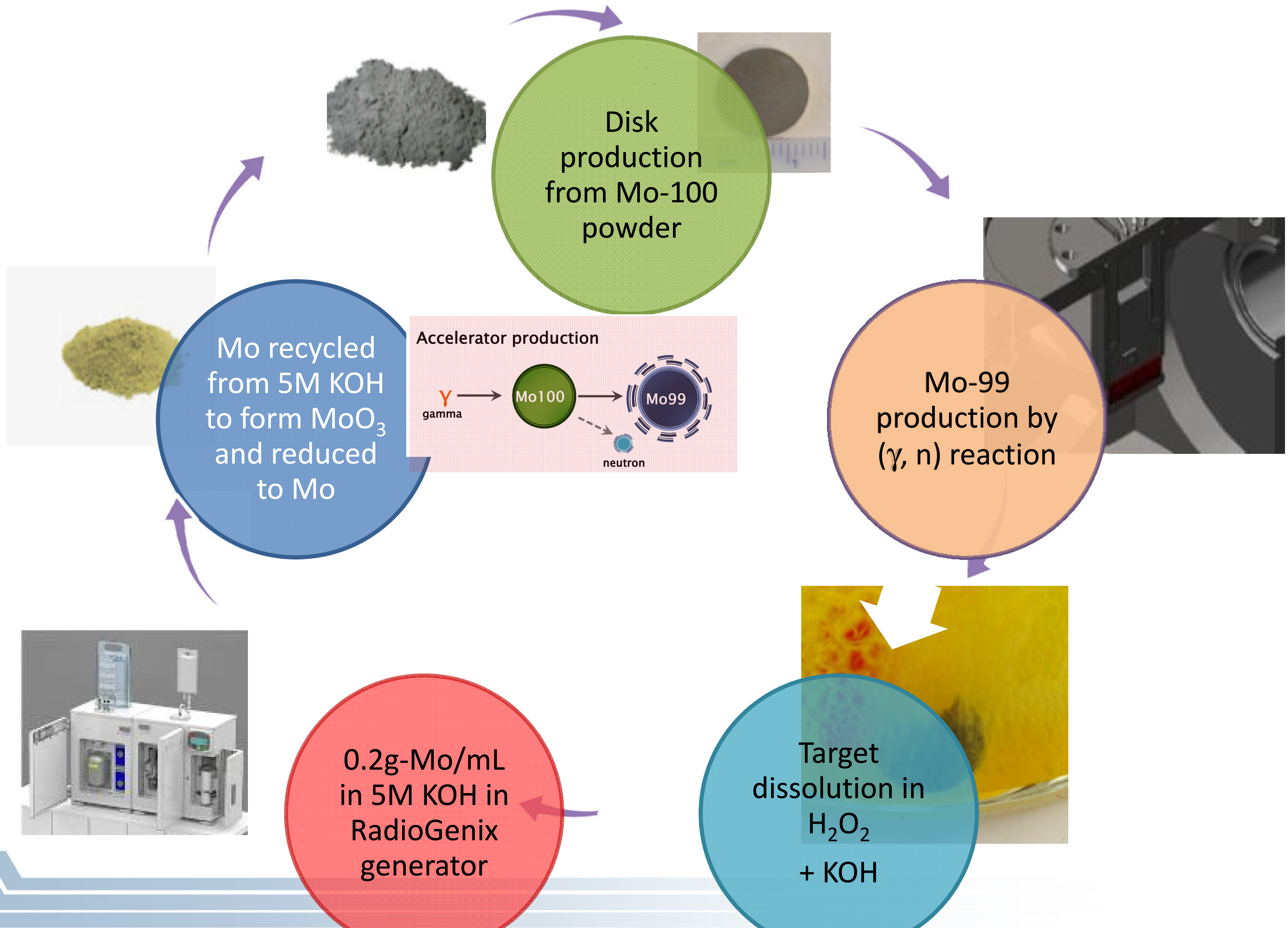


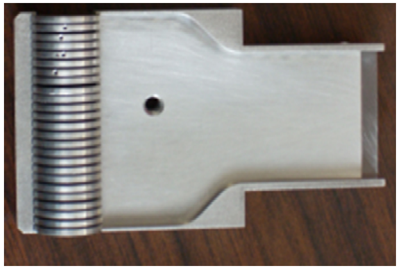


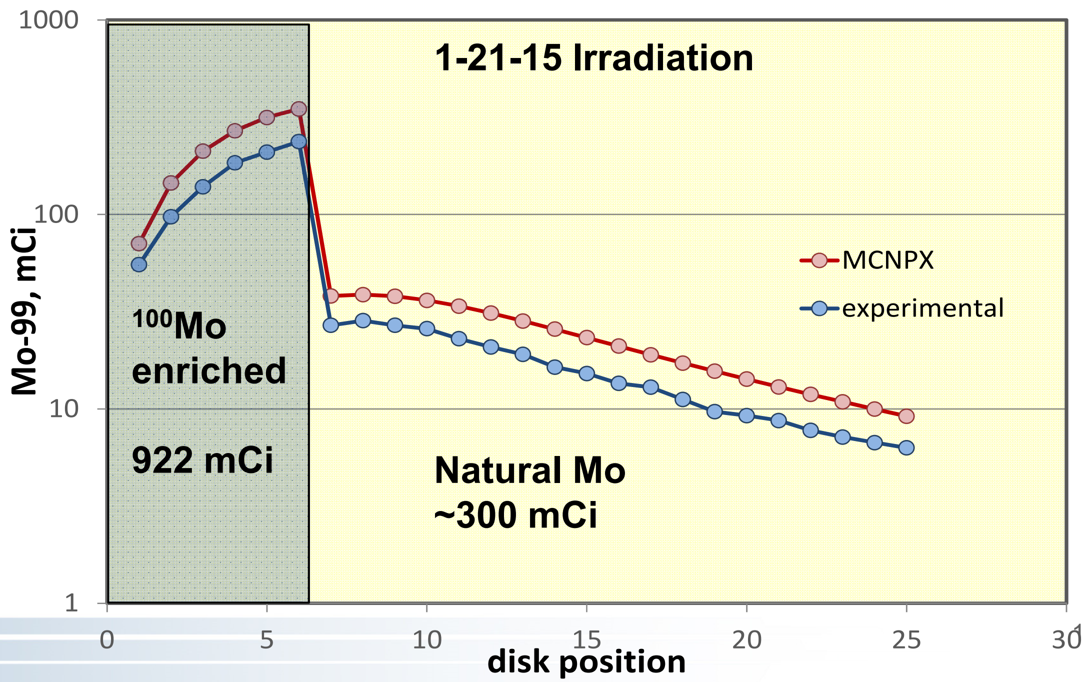
Molybdenum Cycle



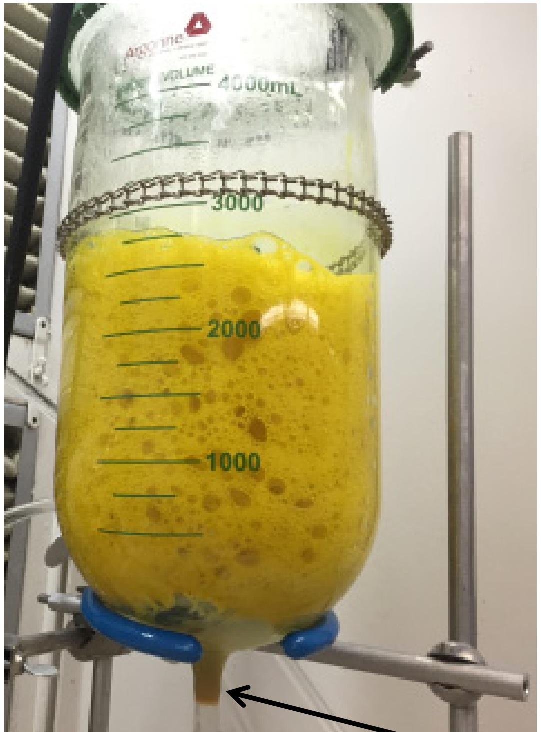
Mo-99 Production via NorthStar Method

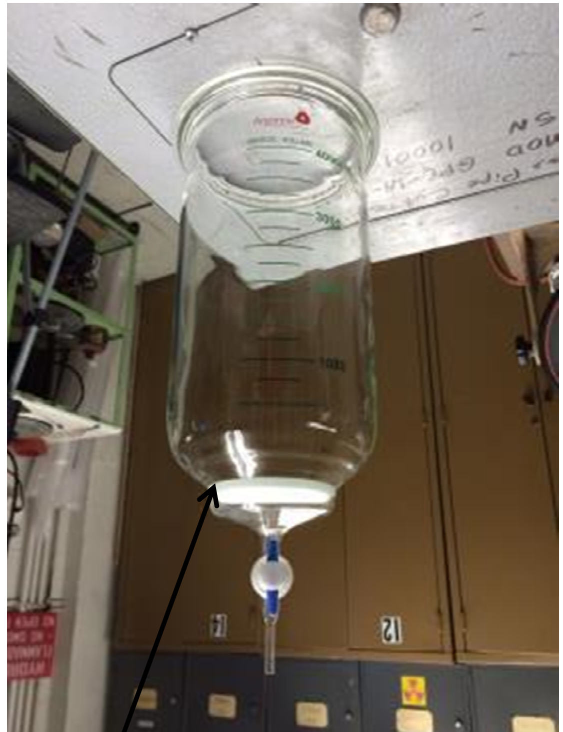
Irradiation date	^{100}Mo-Enrichement (position)	^{99}Mo in 6 disks, Ci	Power	Current	Time, hrs.	Energy
1-21-15	99% (1-6)	0.92	4 kW	95 µA	19	42 MeV
3-19-15	97.4% (3-8)	2.9	7.56 kW	180 µA	21	42 MeV
3-26-15	95.1% (3-8)	2.2	7.56 kW	180 µA	19	42 MeV
5-7-15	99% (3-8)	4.2	9 kW	288 µA	24	35 MeV
9-17-15	99% (3-8)	12.4	9 kW	288 µA	6 days	35 MeV





Large-Scale Dissolution Processing





frit

addition of port

drain

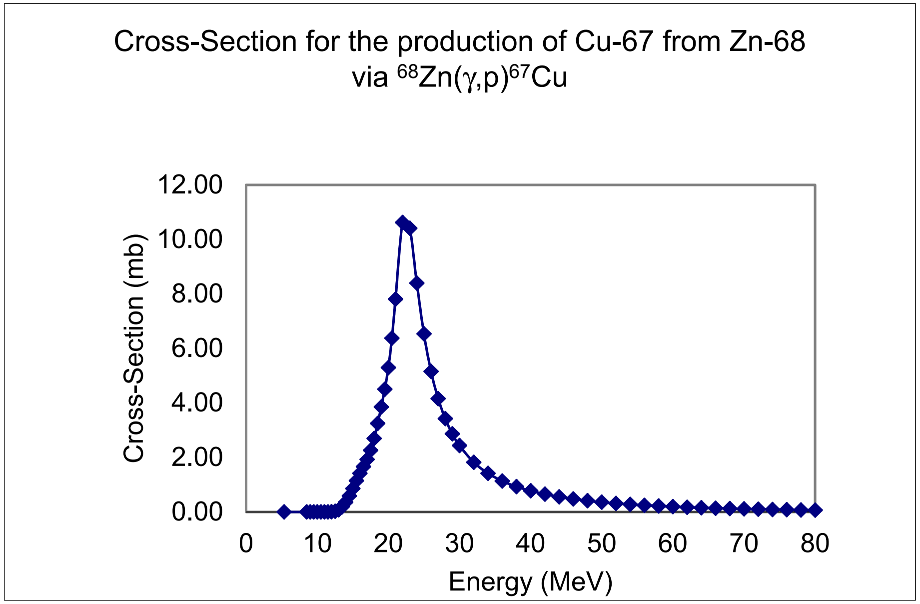
Side access port

Dissolution in H_2O_2 >>> evaporation/ H_2O_2 destruction >>> Fe co-precipitation of Zr & Nb >>> KOH added to make RadioGenix™ Solution

Copper-67

- Bremsstrahlung: $^{68}Zn(\gamma,p)^{67}Cu$
  - "Clean" production with enriched target
    - ^{68}Zn – 19% abundant
  - Separation method: sublimation
    - Has been demonstrated with large targets
    - No dissolution of main zinc mass
    - Still requires dissolution and ion exchange step

- Requires a mid to high energy linac
- ^{67}Cu reaction has a threshold at ~15 MeV and a peak at ~26 MeV
- Enriched targets will virtually eliminate co-produced isotopes
  - Simplifies separation chemistry
  - Exception is ^{67}Zn, which is stable



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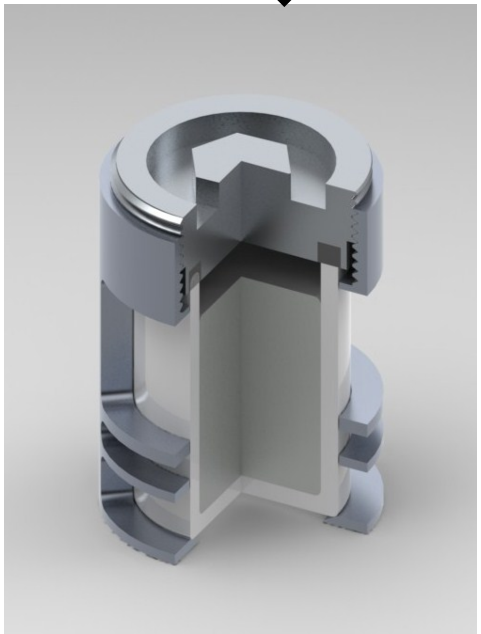
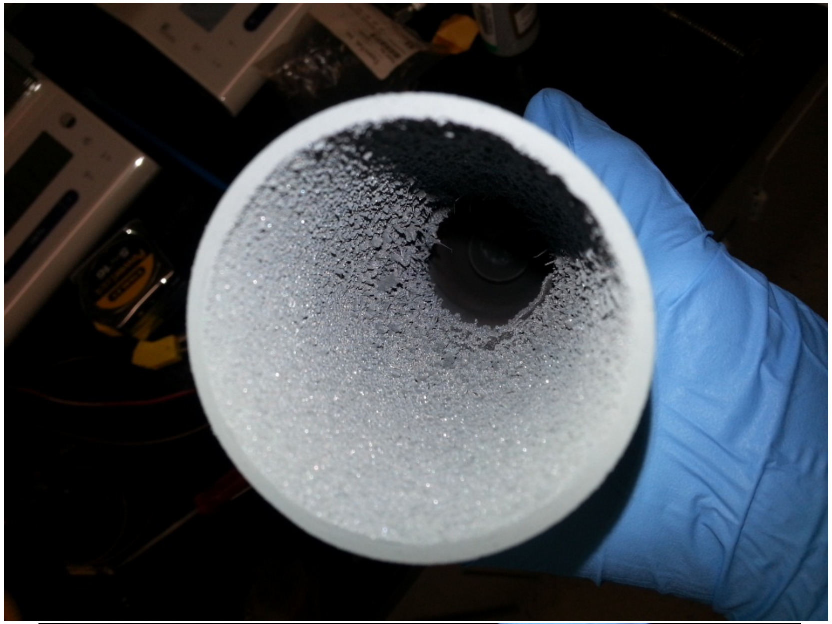
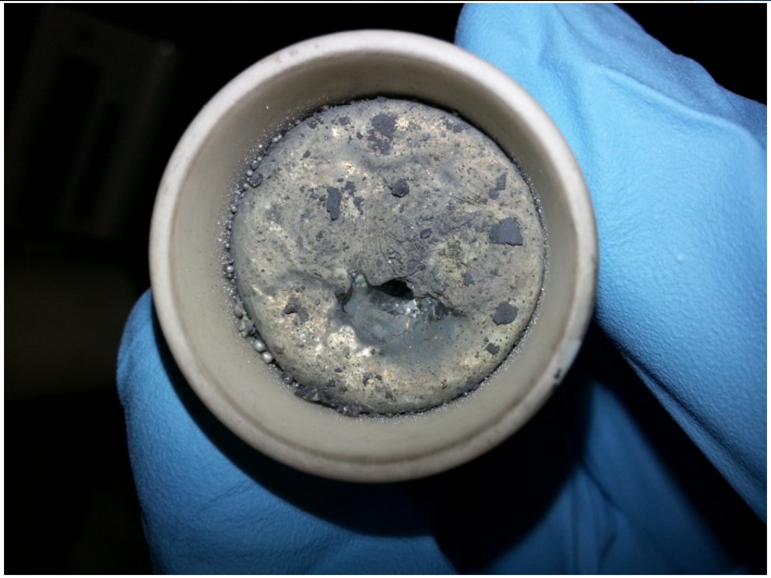


Casting Targets

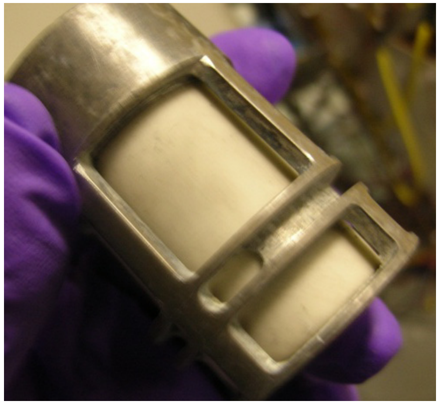


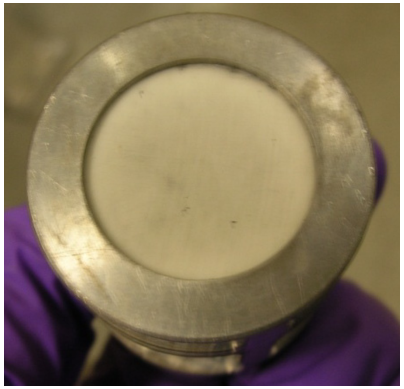


Zinc Irradiations

- Varying multiple parameters
  - Converter material (W or Ta)
  - Beam power
  - Beam current
  - Irradiation "Burn" time

- Slowly increasing the activity produced



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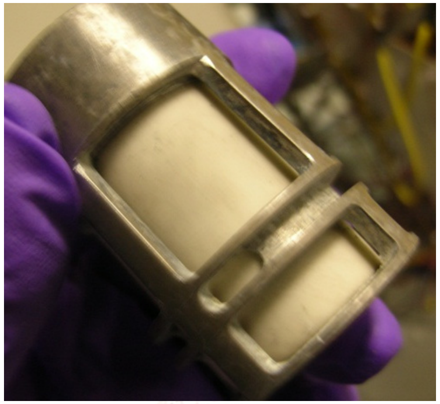
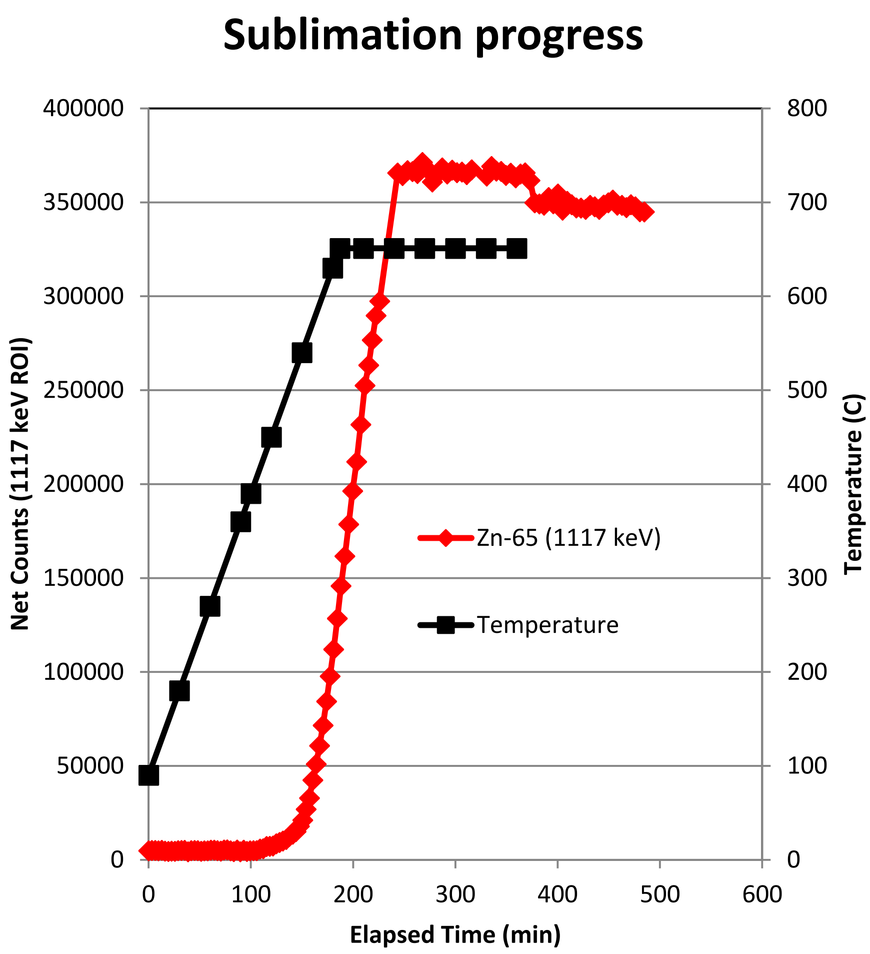


Chemical Processing

- Sublimation
  - Tin metal was used as a holdback agent
  - SubliA NaI(Tl) detector was used to monitor the sublimation
  - Sublimation reached saturation at ~250 minutes
  - 99.6% separation of zinc from copper via sublimation
- Dissolution of Cu/Sn alloy
  - HCl/HNO_3 solution
- Ion Exchange
  - Bio-Rad AG1x8 (200) column
  - Gravity flow
- Formulation specific to end user

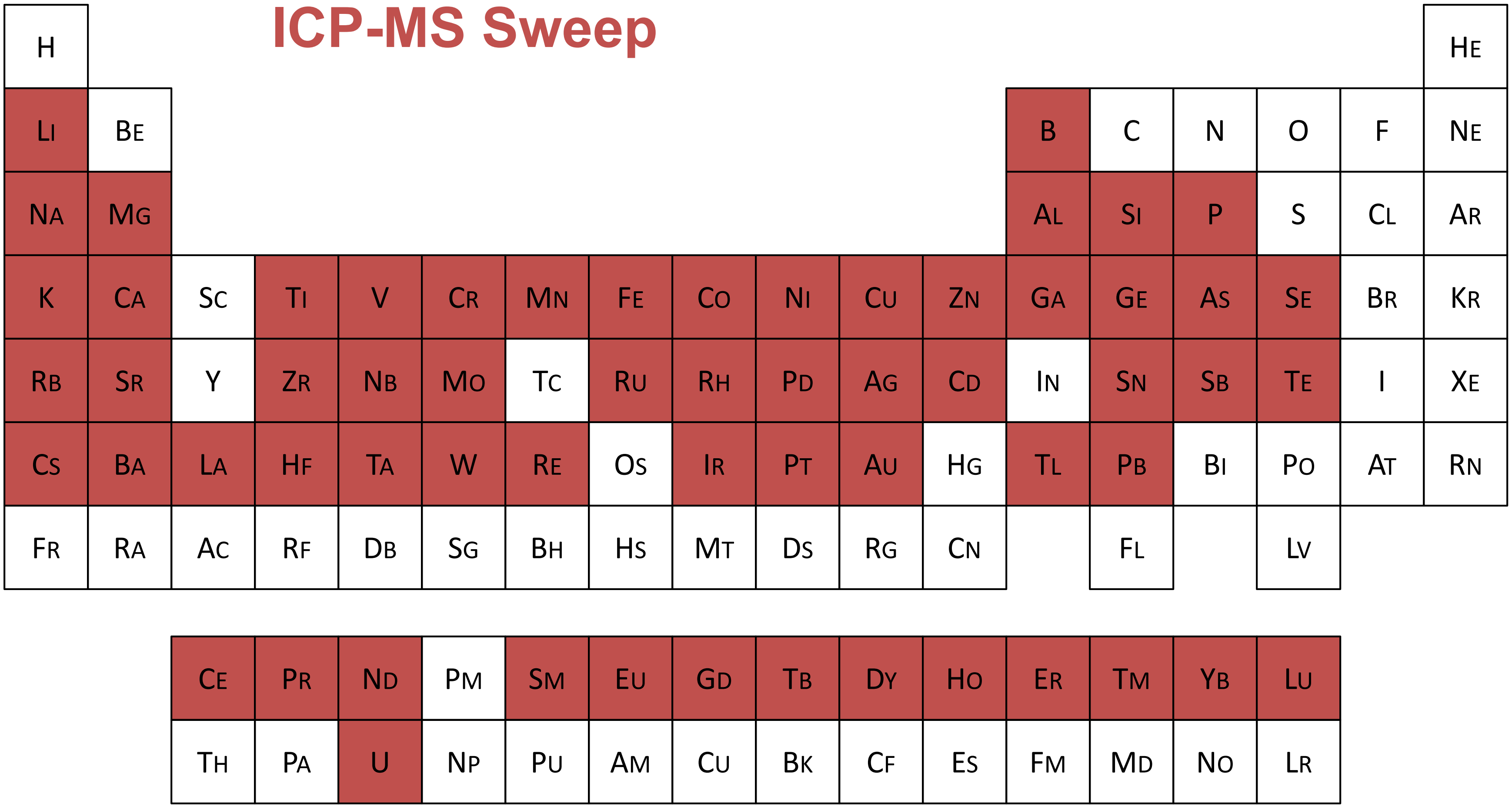


Purity Considerations:
Final Product

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn		Fl		Lv		
		Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu		
		Th	Pa	U	Np	Pu	Am	Cu	Bk	Cf	Es	Fm	Md	No	Lr		

Purity Considerations: Final Product

ICP-MS Sweep



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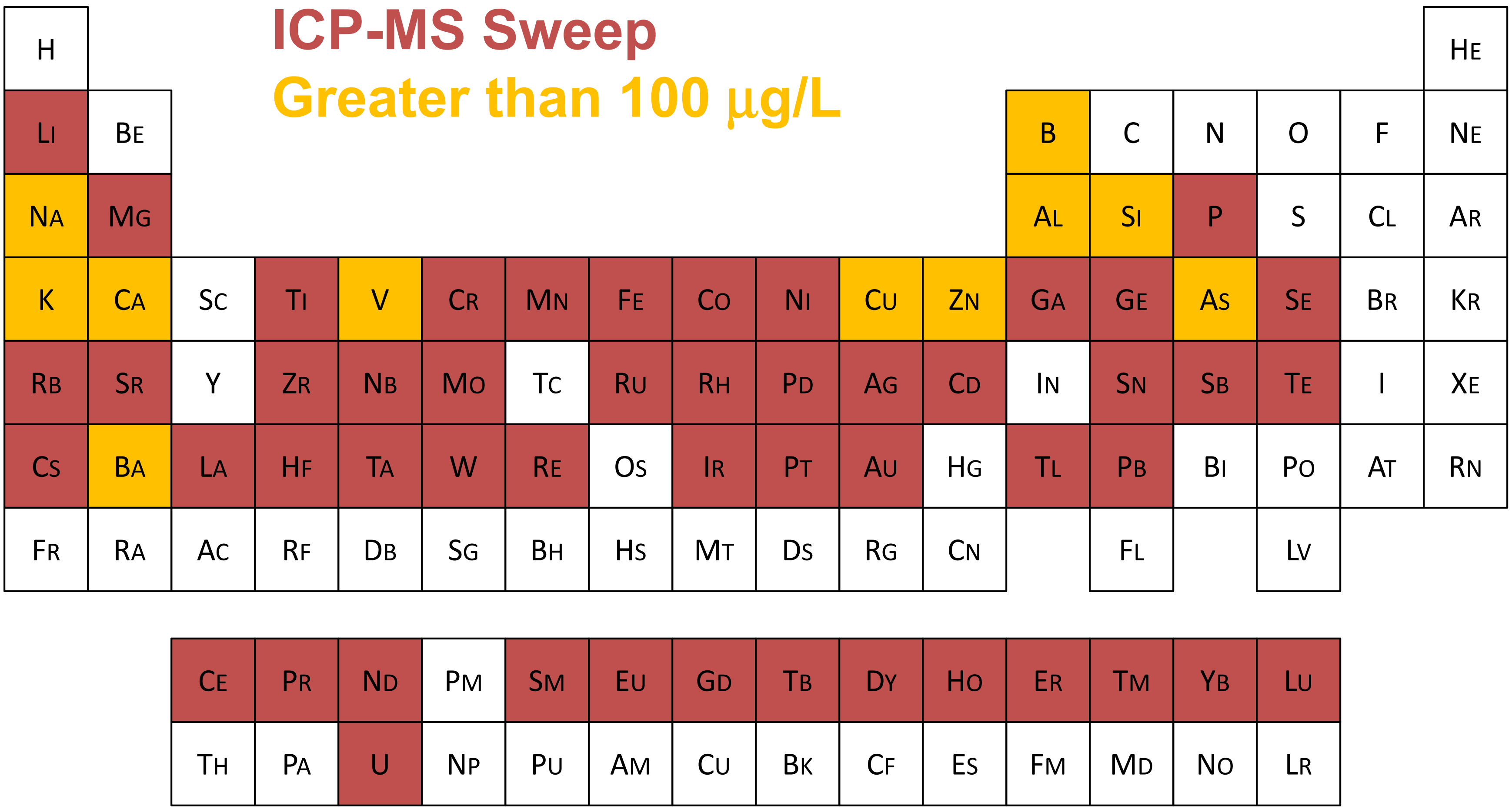

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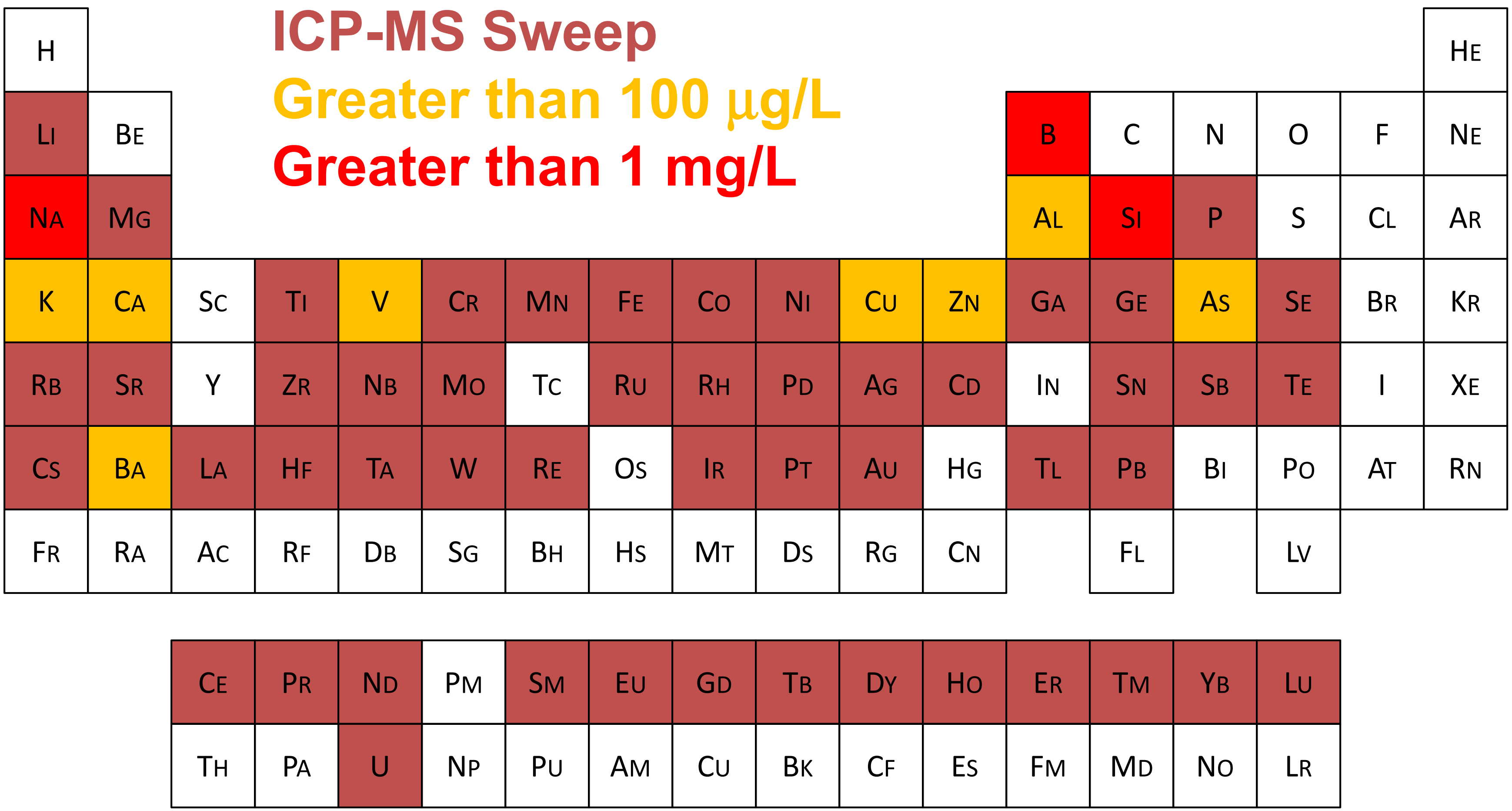
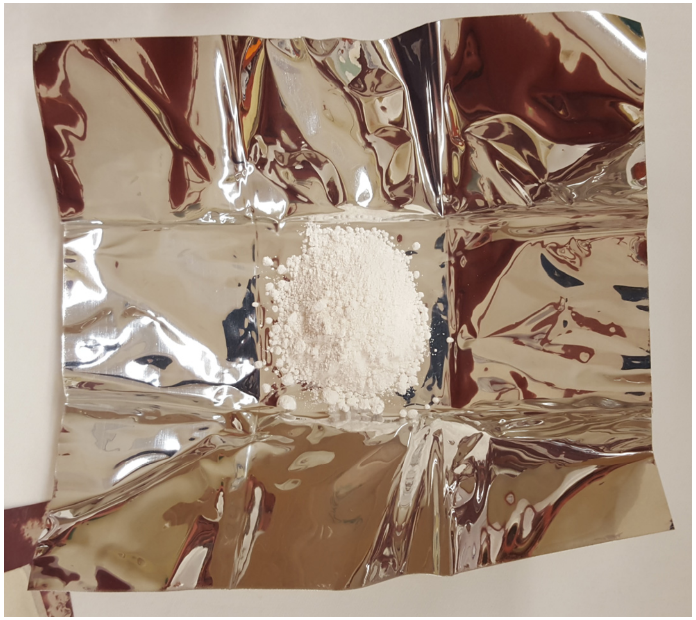
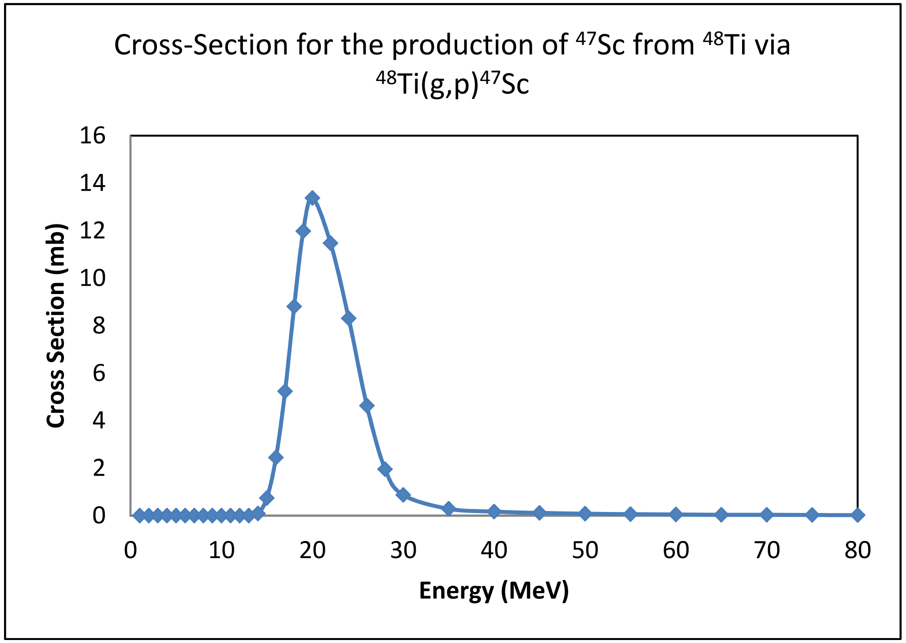


Scandium-47

- Similar to ^{67}Cu production
  - Bremsstrahlung: $^{48}Ti(\gamma,p)^{47}Sc$
  - “Clean” production with enriched target (^{48}Ti – 73.7%)

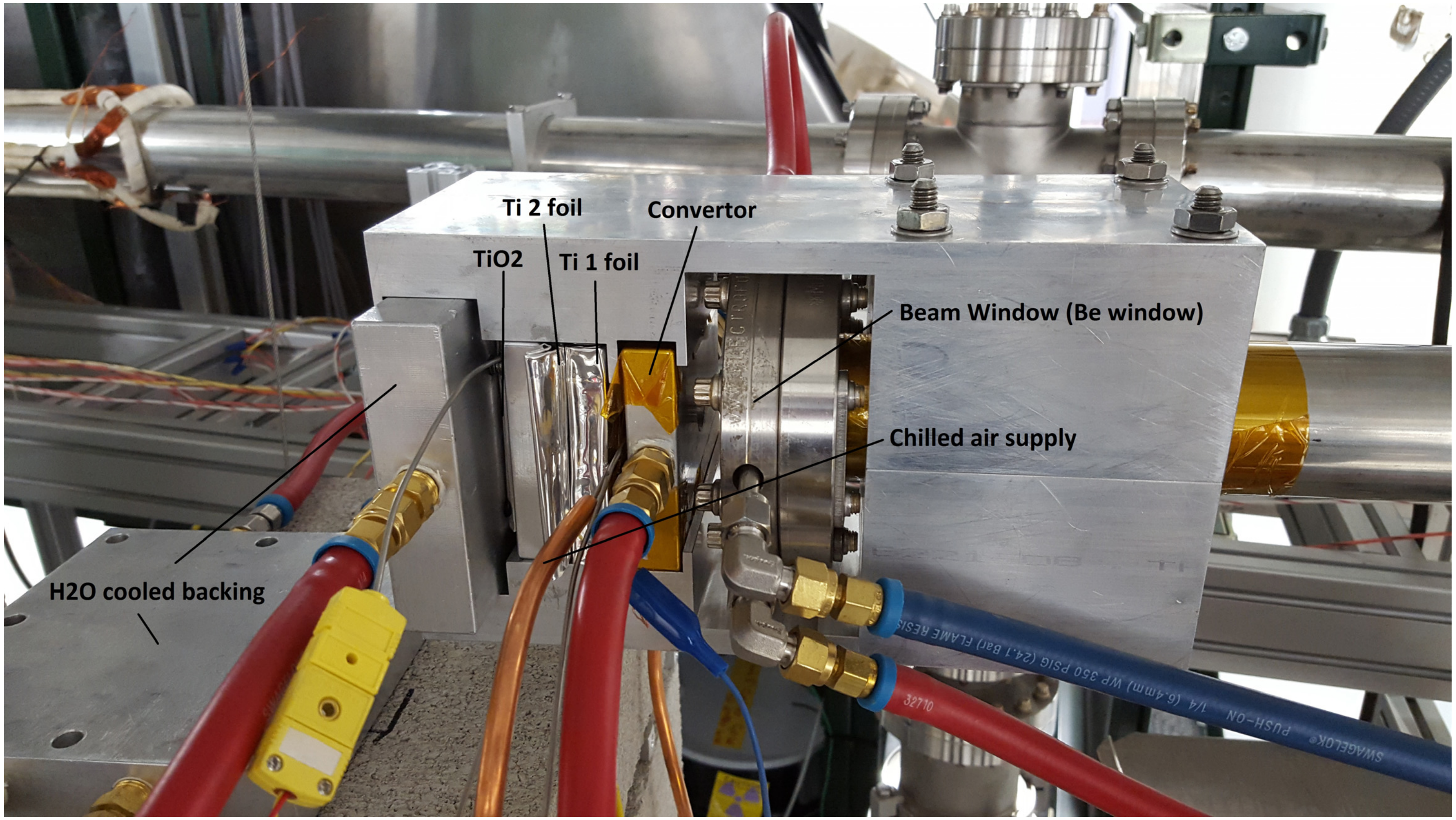


- Requires a mid to high energy linac
- ^{47}Sc reaction has a threshold at ~15 MeV and a peak at ~22 MeV
- Enriched targets will virtually eliminate co-produced isotopes



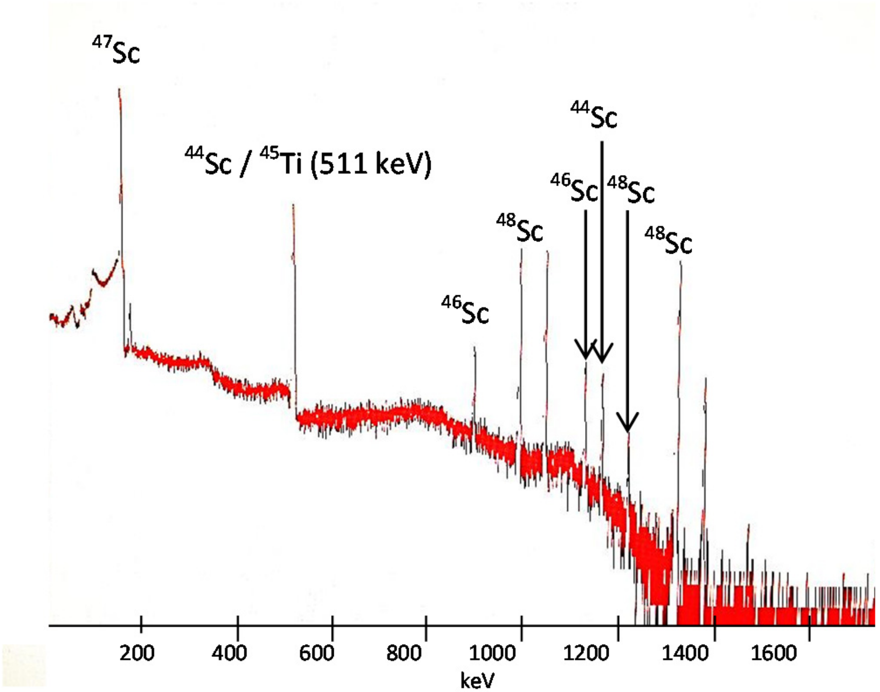
Nat-Titanium Irradiations

- Beam Parameters
  - Energy: 35 MeV
  - Power: 2 kW
  - Frequency: 22 Hz
  - Irradiation time: 2 hrs



Nat-Titanium Irradiations

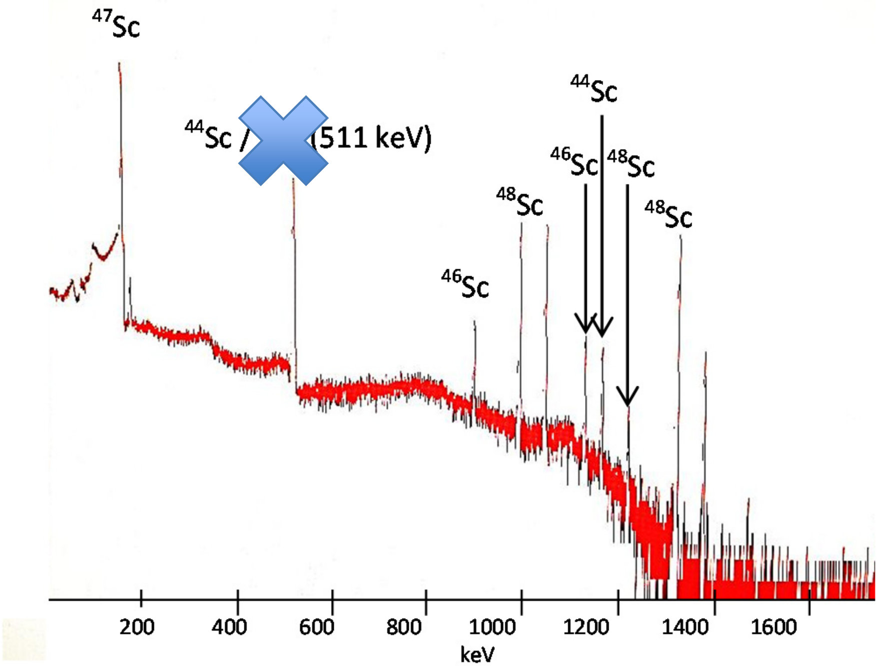
- Beam Parameters
  - Energy: 35 MeV
  - Power: 2 kW
  - Frequency: 22 Hz
  - Irradiation time: 2 hrs



Isotope (% abun.)	Pathway	Isotope	Ti foil 1 (μCi)	Ti foil 2 (μCi)	TiO_2 (μCi)
^{46}Ti (8.25)	(γ,pn)	Sc-44	1.85 E2	2.18 E2	1.27 E2
^{47}Ti (7.44)	(γ,p)	Sc-46	9.87	1.11 E1	5.70
^{48}Ti (73.72)	(γ,p)	Sc-47	1.31 E3	1.53 E3	7.16 E2
^{49}Ti (5.41)	(γ,p)	Sc-48	1.15 E2	1.33 E2	6.78 E1

Nat-Titanium Irradiations

- Beam Parameters
  - Energy: 35 MeV
  - Power: 2 kW
  - Frequency: 22 Hz
  - Irradiation time: 2 hrs



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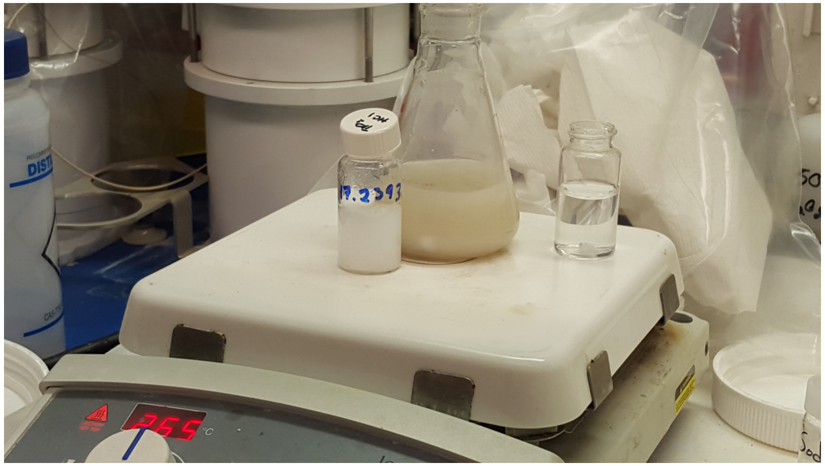
Scandium-47
Chemical Processing

- Dissolution of TiO_2
  - H_2SO_4 with excess SO_4^{-2} salt
- Dilute sample
- Perform Column Chromatography
  - Initial experiments used a syringe with commercially available slip-tip column



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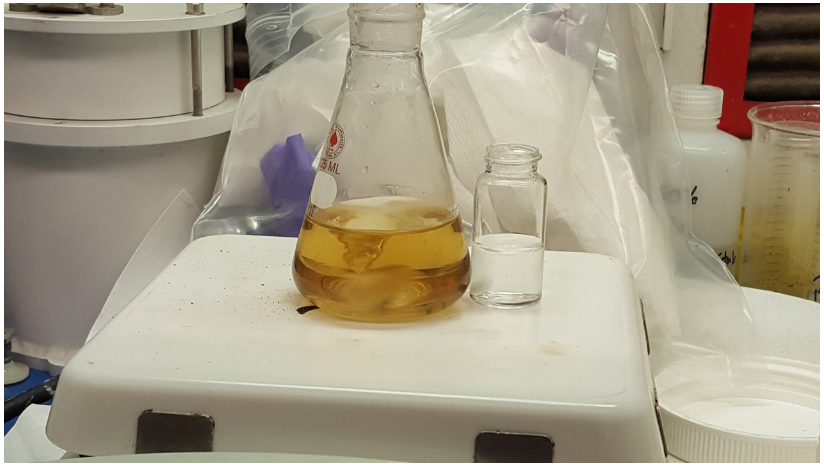

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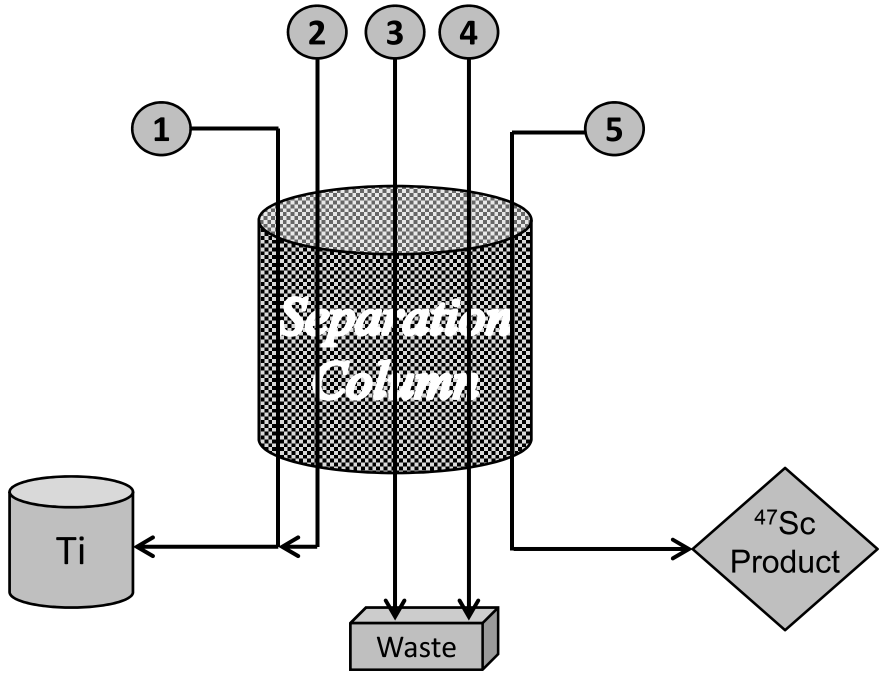
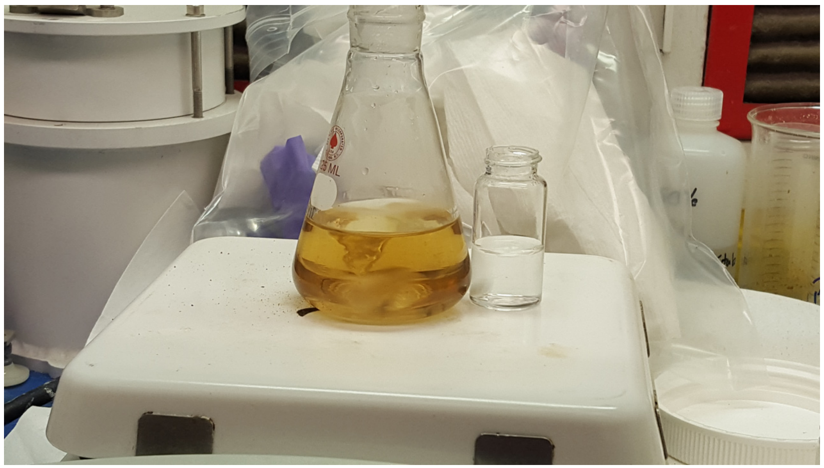
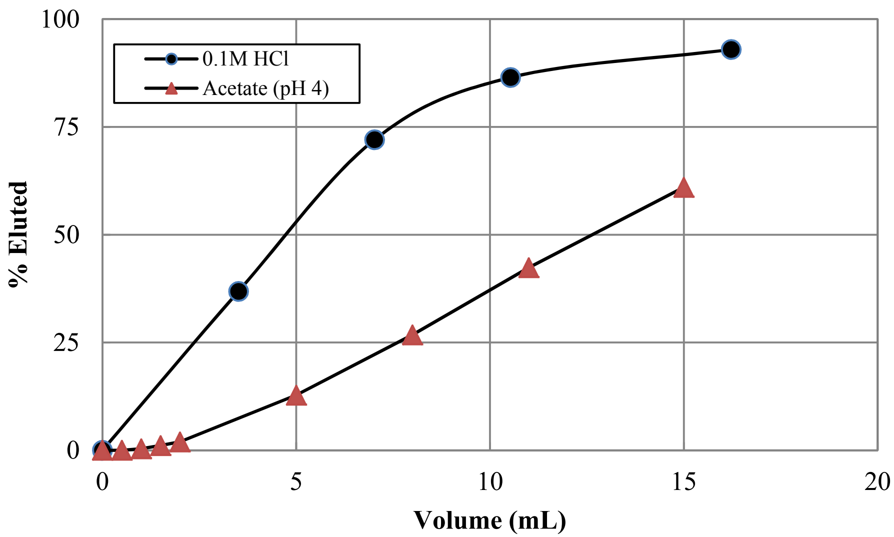




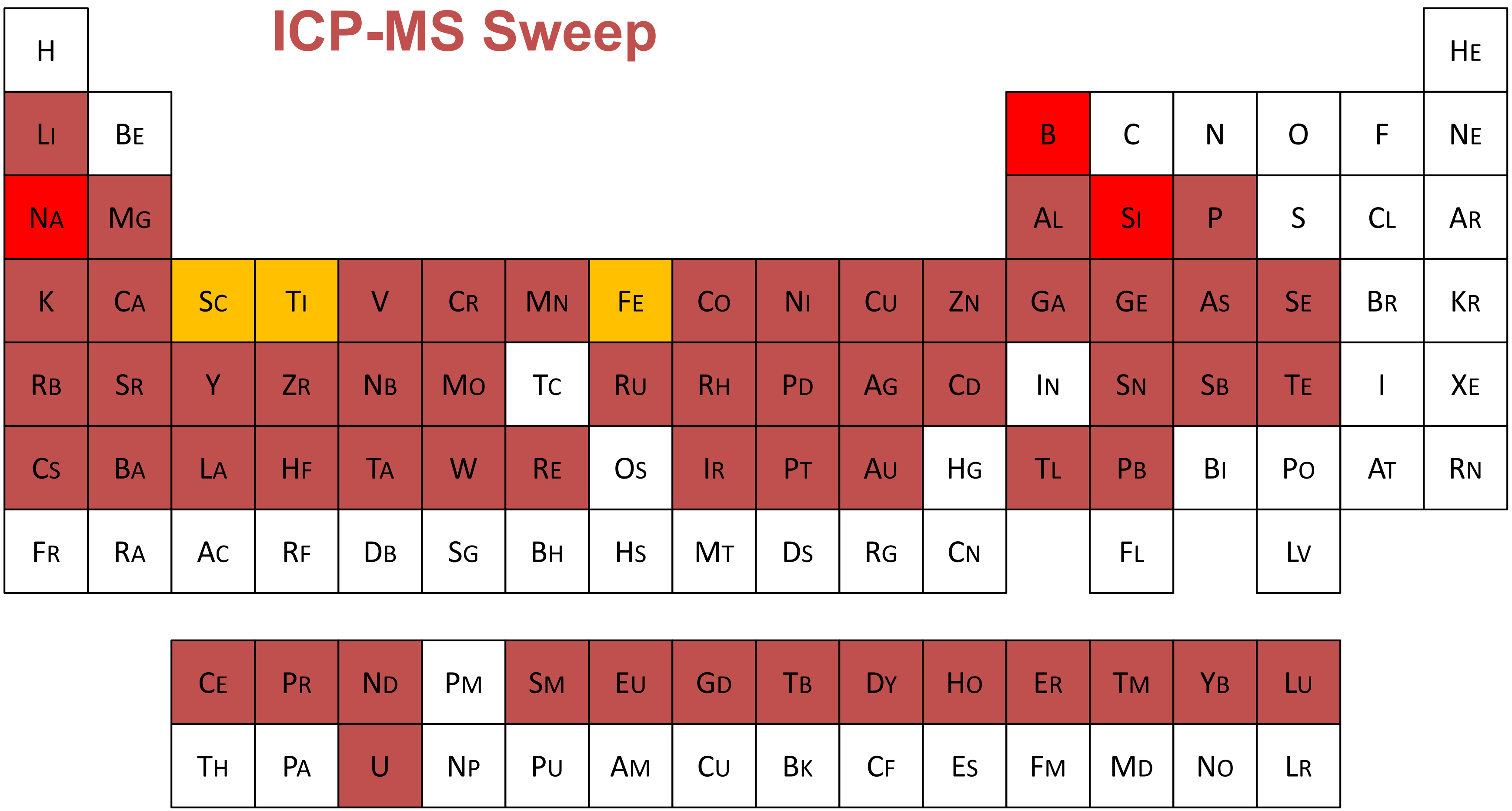


Purity Considerations:
Final Product

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn		Fl		Lv		

Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Th	Pa	U	Np	Pu	Am	Cu	Bk	Cf	Es	Fm	Md	No	Lr

Purity Considerations: Final Product



Purity Considerations: Final Product

ICP-MS Sweep

Greater than 100 µg/L

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn		Fl		Lv		

Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
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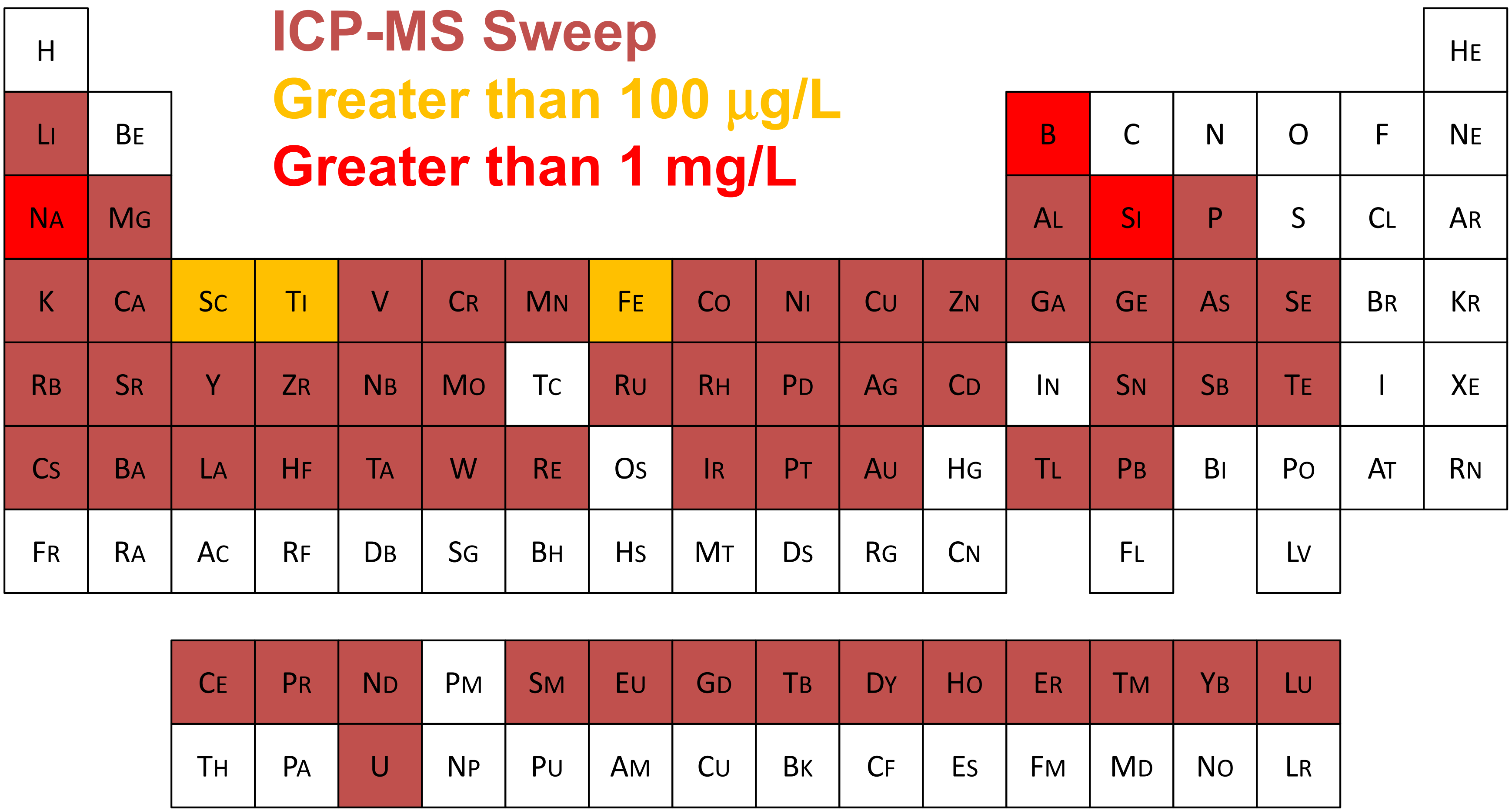
Purity Considerations: Final Product



Current Isotope Development Highlights

Sub Critical Fission – ^{99}Mo

-Produced and purified Mo-99 from sub-critical fission on UO_2SO_4

- Mo-99 has **met purity specifications**

-Developed separation methods

- **>95% recovery on initial recovery column**
- **>95% recovery on concentration column**
- **>85% recovery from LEU-modified Cintichem processing**

-Developed specialized equipment for remote processing

- Gas analysis
- Separations
- Full system monitoring
- Hot Cell operations

-Studied radiation effects

- Bubble formation
- Uranyl peroxide formation
- Mo-ABO stability

-Shipped Mo-99 to GE Healthcare and Lantheus for testing PASSED

-Fits into existing supply chain

-Moving on to Phase II

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^{100}Mo(γ,p) – ^{99}Mo

-Produced Mo-99 from solid targets

- Meets purity specs

-Developed processing of targets

- Dissolution of Mo metal
- Conversion to molybdate

-Optimization of large-scale dissolution conditions

-Recycle process to recover >95% pure and valuable enriched ^{98}Mo and ^{100}Mo

- Precipitation routes
- Solvent extraction routes

-Radiation stability studies at VDG

- Generator system components

-PAT study for the Dispensing unit

-Shipped Mo-99 to NorthStar for generator trials

Current Isotope Development Highlights

Sub Critical Fission – 99Mo

-Produced and purified Mo-99 from sub-critical fission on UO2SO4
- Mo-99 has met purity specifications

-Developed separation methods
- >95% recovery on initial recovery column
- >95% recovery on concentration column
- >85% recovery from LEU-modified Cintichem processing

-Developed specialized equipment for remote processing
- Gas analysis
- Separations
- Full system monitoring
- Hot Cell operations

-Studied radiation effects
- Bubble formation
- Uranyl peroxide formation
- Mo-ABO stability

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^{67}Cu

-Cu-67 was produced with **Specific Activity of 100 mCi/mg ($^{67}Cu/Cu$) for 2-4 mCi**

-Separation of 2-4 mCi of ^{67}Cu within 60 hours of irradiation with a high radiological purity

-Main separation removes >99% of target material

-Sublimation of ~100 g of irradiated zinc metal using alumina tube sublimation apparatus

-Standardization of sublimation step is under investigation

-Demonstrated >99% recovery of metallic zinc from sublimation apparatus
- Vital for economical use of enriched targets

-Manipulator-friendly apparatuses are designed and being tested

-Isotope Program funding to develop production and distribution of ^{67}Cu

Current Isotope Development Highlights

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-Developed processing of targets

- Dissolution of Mo metal

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^{47}Sc

- **^{47}Sc was produced** from **Ti foils and TiO_2 solid targets**
- **TiO_2 targets processed**
  - Proof-of-principal separations have been performed
  - **^{47}Sc isolated** with a **high radiological and chemical purity**
    - **Specific Activity of 996 mCi/mg (^{47}Sc/Sc) was achieved for <1 mCi ^{47}Sc production**
    - **Specific Activity of 7102 mCi/mg (^{47}Sc/Sc) was achieved for 5 mCi ^{47}Sc production**
  - Separation removes >99% of target material
- **Processing time <2 hrs**
- Final separation optimization underway (Batch Studies)
- Recovery of Titanium from dissolved solutions underway (recycling)
- Target optimization underway

Acknowledgments

- ^{99}Mo
  - George Vandegrift
  - Sergey Chemerisov
  - Mark Williamson
  - Mandy Youker
  - Peter Tkac
  - John Krebs
  - Mike Kalensky
  - Jim Grudzinski
  - Art Gelis
  - M. Alex Brown
  - Andy Hebden
  - Thad Heltemes
  - Dominque Stepinski
  - Jim Byrnes
  - Jim Jerden
  - Megan Bennett
  - Bill Ebert
  - Candido Pereira
  - Marty Steindler
  - Del Bowers
  - Roman Gromov
  - Chuck Jonah
  - Vakho Makarashvili
  - Brad Micklich
  - Lohman Hafenrichter
  - Kurt Alford
  - Ken Wesolowski
  - Kevin Quigley
  - Jim Baily
  - Del Bowers
  - Jackie Copple
  - Momen Abdul
  - All ACL Staff
  - HP Support Staff

- ^{67}Cu
  - Dave Ehst
  - Del Bowers
  - Nick Smith
  - Sergey Chemerisov
  - M. Alex Brown
  - Roman Gromov
  - Jim Grudzinski
  - George Vandegrift
  - Jerry Nolen
  - HP Support Staff

- ^{47}Sc
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  - John Greene
  - Roman Gromov
  - Megan Bennett
  - Holly Dinkel
  - George Vandegrift
  - HP Support Staff

- Mo-99 work supported by the U.S. Department of Energy, National Nuclear Security Administration's (NNSA's) Office of Material Management and Minimization, under Contract DE-AC02-06CH11357.

- Cu-67 work was supported by the U.S. Department of Energy's Office of Science, Isotope Development and Production for Research and Applications (IDPRA)

- This work was performed by UChicago Argonne, LLC, Operator of Argonne National Laboratory ("Argonne"). Argonne, a U.S. Department of Energy Office of Science laboratory, is operated under Contract No. DE-AC02-06CH11357.