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U.S. DEPARTMENT OF ENERGY

50 Years of Isotope Production via High Energy Accelerators at Brookhaven National Laboratory

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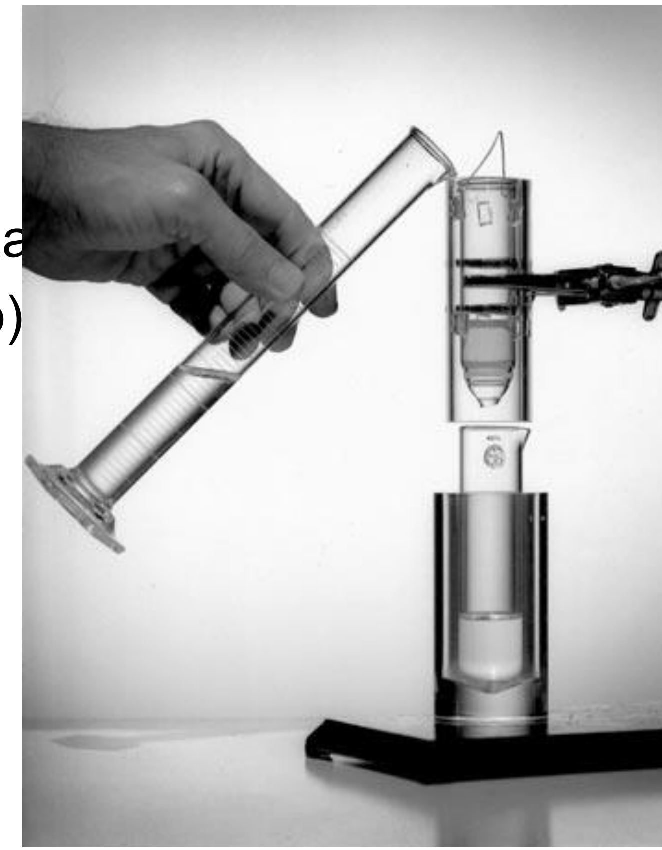
Role of the Department of Energy

The development of most, if not all, isotopes used in medicine was fostered by DOE or its predecessor agencies:

- C-14 (Oak Ridge National Lab)
- Mo-99/Tc-99m (Brookhaven National La
- I-131 (Lawrence Berkeley National Lab)
- Sr-90/Y-90 (ORNL)
- F-18 FDG (BNL)
- Pb-212/Bi-212 (Argonne National Lab)
- Sr-82 (Los Alamos National Lab)
- Ac-225/Bi-213 (ORNL)



The BNL Tc-99m Generator

DOE Isotope Program Mission

Produce and/or distribute radioactive and stable isotopes that are in short supply; includes by-products, surplus materials and related isotope services

Maintain and upgrade the infrastructure required to produce and supply priority isotope products and related service

Conduct R&D on new and improved isotope production and processing techniques which can make available priority isotopes for research and application. Develop workforce.

Ensure robust domestic supply chains. Reduce U.S. dependency on foreign supply to ensure National Preparedness.

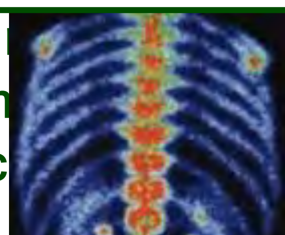
Isotopes are forms of the same element that contain equal numbers of protons but different numbers of neutrons in their nuclei, and hence differ in relative atomic mass but not in chemical properties; in particular, a radioactive form of an element.

Isotope Program Competencies

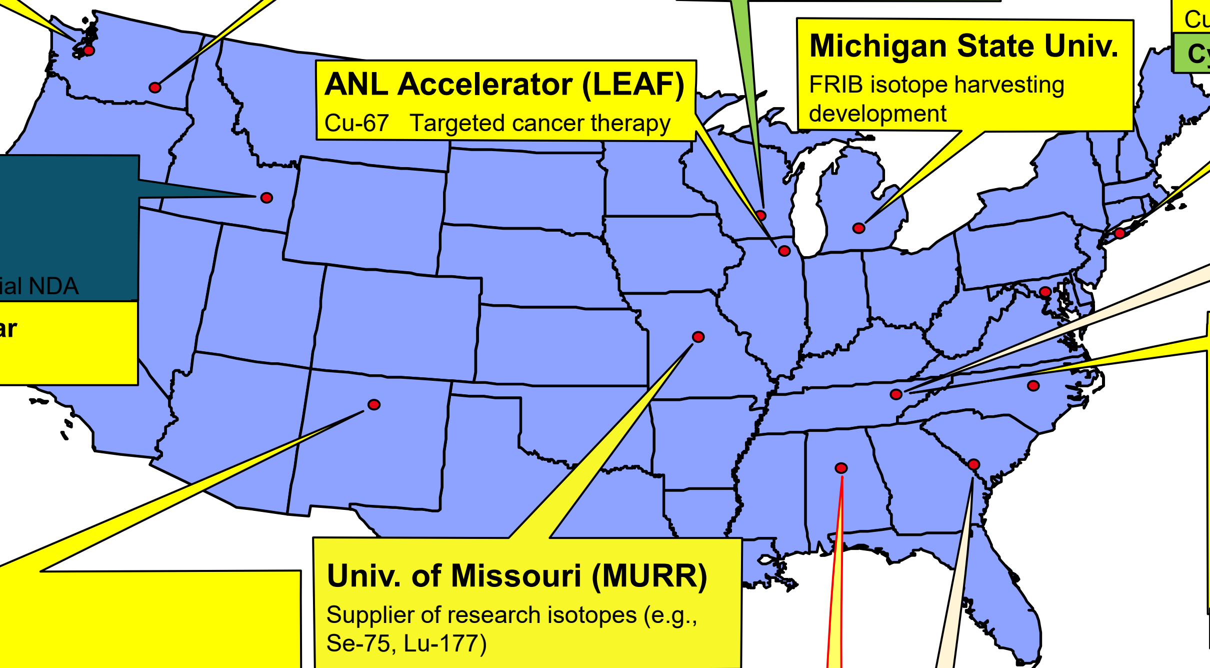
- Isotope Program in DOE has sole authority to produce isotopes for sale and distribution – labs may not embark on isotope production on their own.
  - **DOE IP not responsible for Mo-99 (NNSA), Pu-238 (NE) and SNM for weapons (NNSA)**

- DOE Isotope Program is the only Mission Essential Function in the Office of Science.
  - **Continued to operate during COVID-19 lab shutdowns**
  - **Stepped in when international supply chains at risk**

- Supports a wide variety of core competencies
  - **Nuclear Physics**
  - **Chemistry (Separations, Nuclear and radio-chemistry)**
  - **Bio-medical**


DOE Isotope Program Production Sites
DOE Mission Essential Function



Univ. of Washington
Supplier of research isotopes (e.g., At-211)

PNNL
Sr-90 Y-90 generator for cancer therapy

Univ. of Wisconsin
Supplier of research isotopes (e.g., Mn-52)

BNL
Accelerator (BLIP):
Ac-225 Targeted cancer therapy
Ti-44 Sc-44 generator for PET imaging
Y-86 PET imaging
Cu-67 Targeted cancer therapy
Cyclotron (TR-19)

Michigan State Univ.
FRIB isotope harvesting development

ANL Accelerator (LEAF)
Cu-67 Targeted cancer therapy

INL
ATR Reactor:
Co-60 Stereotactic radiosurgery, industrial NDA
Rad EMIS – nuclear forensics

Y-12 (NNSA Facility)
Li-6 Neutron detection
Li-7 Radiation dosimeters

ORNL
HFIR Reactor:
Ac-227 Cancer therapy
Se-75 Industrial NDA
Cf-252 Industrial sources
W-188 Cancer therapy
Radioisotopes Inventory:
Ac-225 Cancer therapy
Ra-223 Cancer therapy
RPF (Radioisotope Proc. Fac.)
Stable Isotopes Inventory:
E.g., Ca-48, Ga-69, Rb-87, Cl-37
Stable Isotope Production:
ESIPP
SIPF
SIPRC

LANL
Accelerator (IPF):
Ac-225 Targeted cancer therapy
Ti-44 Sc-44 generator for PET imaging
Cd-109 X-ray fluorescence analyses
As-73 Environmental tracer
Si-32 Oceanographic research
Plutonium Facility (PF-4):
Am-241 Oil and gas exploration

Univ. of Missouri (MURR)
Supplier of research isotopes (e.g., Se-75, Lu-177)

Univ. of Alabama Birmingham
Supplier of research isotopes (e.g., Mn-52)

SRNL (NNSA Tritium Facility)
He-3 Neutron detection
Fuel source for fusion reactors
Lung testing

Started with 6 in 2009

Strong communication with and impact on stakeholders

- White House Working Groups
- Inter-agency Working Groups
- Community Users Working Group (medical)
- Professional Society Meetings and Councils
- Commercial stakeholder meetings twice a year
- Annual Industrial Survey
- Annual Federal Workshops and Survey
- Sponsorship of workshops, symposium at conferences

National Isotope Development Center

- The Department of Energy NIDC includes the Isotope Business Office located at Oak Ridge National Laboratory
- Coordinates the distribution of all DOE isotope products and services available from DOE facilities.
- All contractual discussions with customers.
- Responsibilities:
  - transportation
  - Q&A
  - public relations (website, newsletter, booth)
  - cross-cutting technical topics
  - marketing strategy
  - Assessments
- Customers maintain technical discussions with sites.

www.isotopes.gov

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DOE Accelerator Facilities

BNL BLIP

- 200 MeV, 165 μA p+ beam
- Ac-225, Ti-44, Se-72, Be-7, Y-86, Rb-83, Zn-65
- New hot cells under development for processing of alpha emitting isotopes
- 19 MeV cyclotron for Ac-225
- Ops coordinated with RHIC

LANL IPF

- 100 MeV, 300 μA p+ beam
- Ac-225, Am-241, Al-26, As-73, NA-22, Zr-88, Y-88
- Ops parasitic with LANSCE
- New processing capability (joint NNSA/DOE IP)

ANL LEAF

- 20-55 MeV electron machine
- Cu-67: theragnostic radioisotope: therapy and diagnostic capabilities in a single isotope.
- Sc-47 and Ac-225 production is under development.

Newly refurbished hot cells for alpha-processing

Outstanding hands-on training in smaller facilities

Safe radioisotope processing during the COVID-19 pandemic

Drawing of the new a-Target Processing Facility to be located next to IPF

Diagnostic demonstration of Cu-67 in living mice, in collaboration with University of Alabama-Birmingham

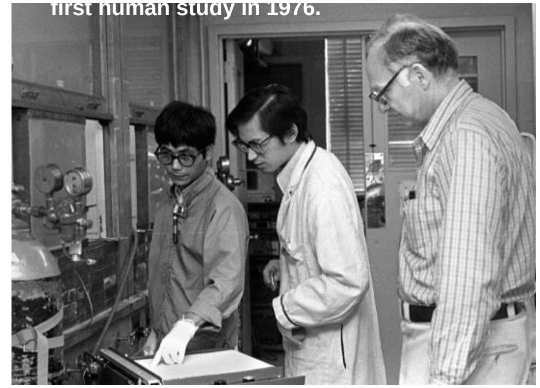
Hot cell processing of Cu-67

BNL is the Birthplace of Nuclear Medicine

- In the late 1950’s, BNL scientists Walter Tucker and Margaret Greene developed a generator system for producing Tc-99m and Powell Richards promoted its use for medical imaging. Tc-99m is now used in over 10 million patients/year in the U. S. alone.
- In the 1970's, scientists at BNL, U. Penn and NIH, combined chemistry, neuroscience and instrumentation to develop ^{18}FDG (fluorodeoxyglucose), revolutionizing the study of the human brain.
- In 1980, BNL scientists first reported high FDG uptake in tumors, leading to FDG/PET for managing the cancer patient.
- Many radionuclide generator systems developed at BNL: ^{132}Te/^{132}I; ^{90}Sr/^{90}Y; ^{68}Ge/^{68}Ga; ^{52}Fe/^{52m}Mn; ^{81}Rb/^{81m}Kr; ^{82}Sr/^{82}Rb; ^{122}Xe/^{122}I
- BNL pioneered the use of high energy proton beams for isotope production (BLIP)

P. Richards

first human study in 1976.



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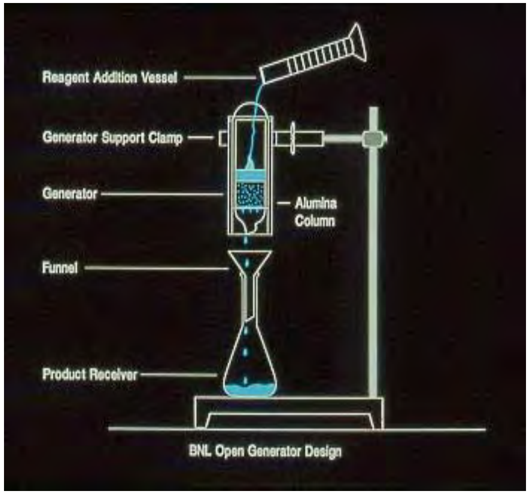
The Radioisotope Generator

A "generator" or cow is a practical, convenient method to transport and use (milk) very short-lived radioisotopes without having to produce them at each site

- long lived "parent" radioisotope decays into a short lived "daughter" radioisotope and
- the parent and daughter must be chemically separable

This technique has been of utmost importance to nuclear medicine

Milking cow analogy



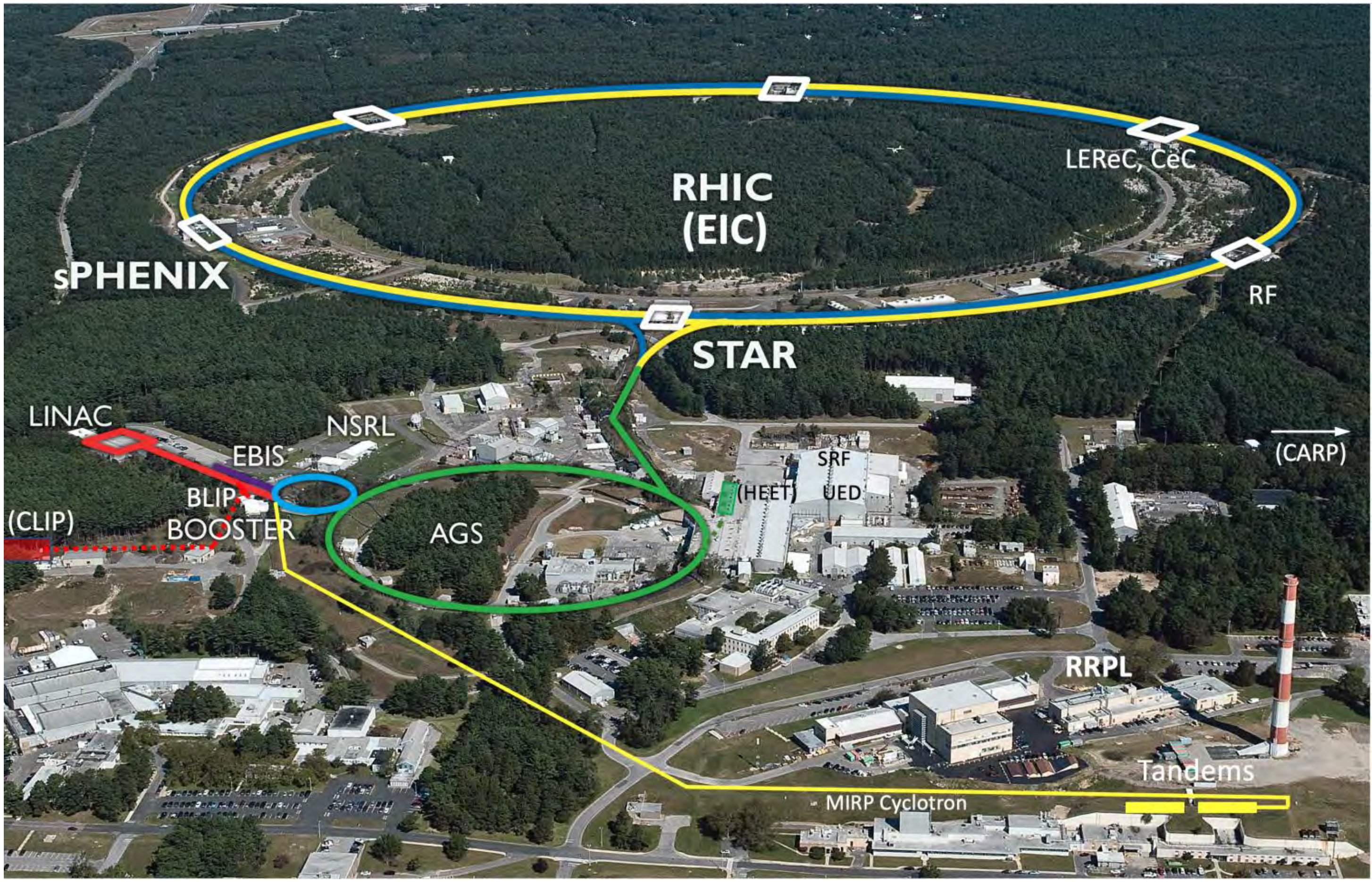
Collider-Accelerator Department facilities

Uniquely flexible and only hadron collider in US for exploration of QCD phase diagram and proton spin

Injectors also used for application programs:

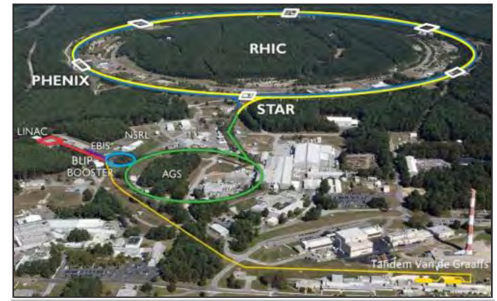
- Linac/BLIP for isotope production
- Booster/NSRL for space radiation studies
- Tandem for industrial/academic users

R&D for future facilities and application
sources, cooling, pol. beams, …



Brookhaven LINAC Isotope Producer

- BLIP utilizes the beam from the proton Linac injector for the Booster, AGS, and RHIC accelerator (nuclear physics)
- Excess pulses (~92%) are diverted to BLIP. Energy is incrementally variable from 66- 202 MeV.
- The BLIP beam line directs protons up to 165μA intensity to targets; synergistic operation with nuclear physics programs for more cost-effective isotope production.
- Target Processing laboratories contains hot cells and radiochemistry labs GMP compliant
- Key production isotopes Sr-82, Ge-68; R&D isotopes Ac-225, Sc-44, Cu-67, As-72, Re-isotopes



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http://www.bnl.gov/cad/Isotope_Distributionsodistoff.asp

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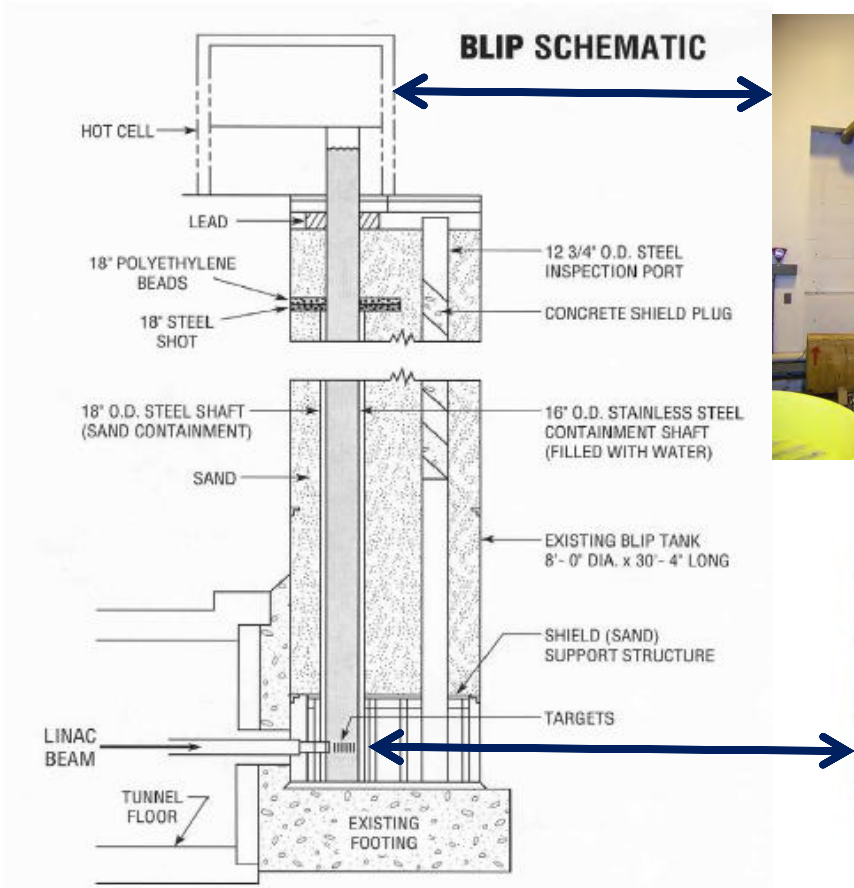
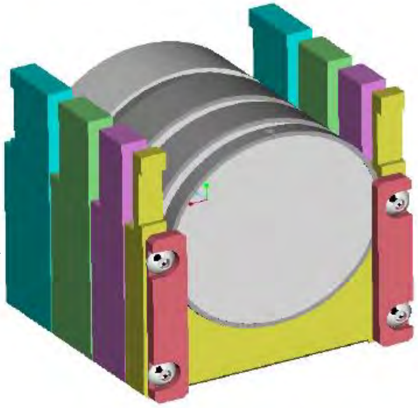
Brookhaven Linear Isotope Producer (BLIP)





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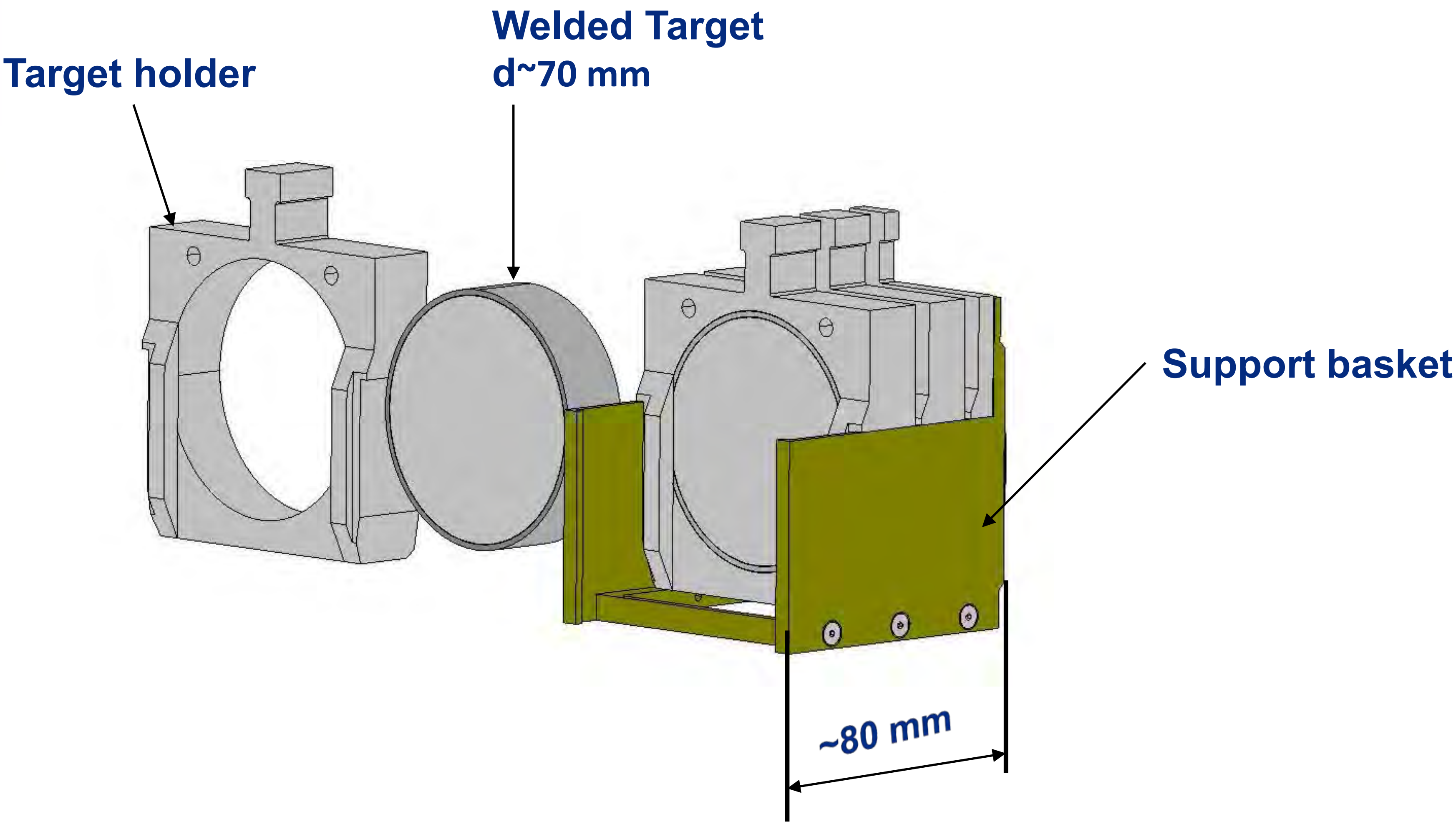
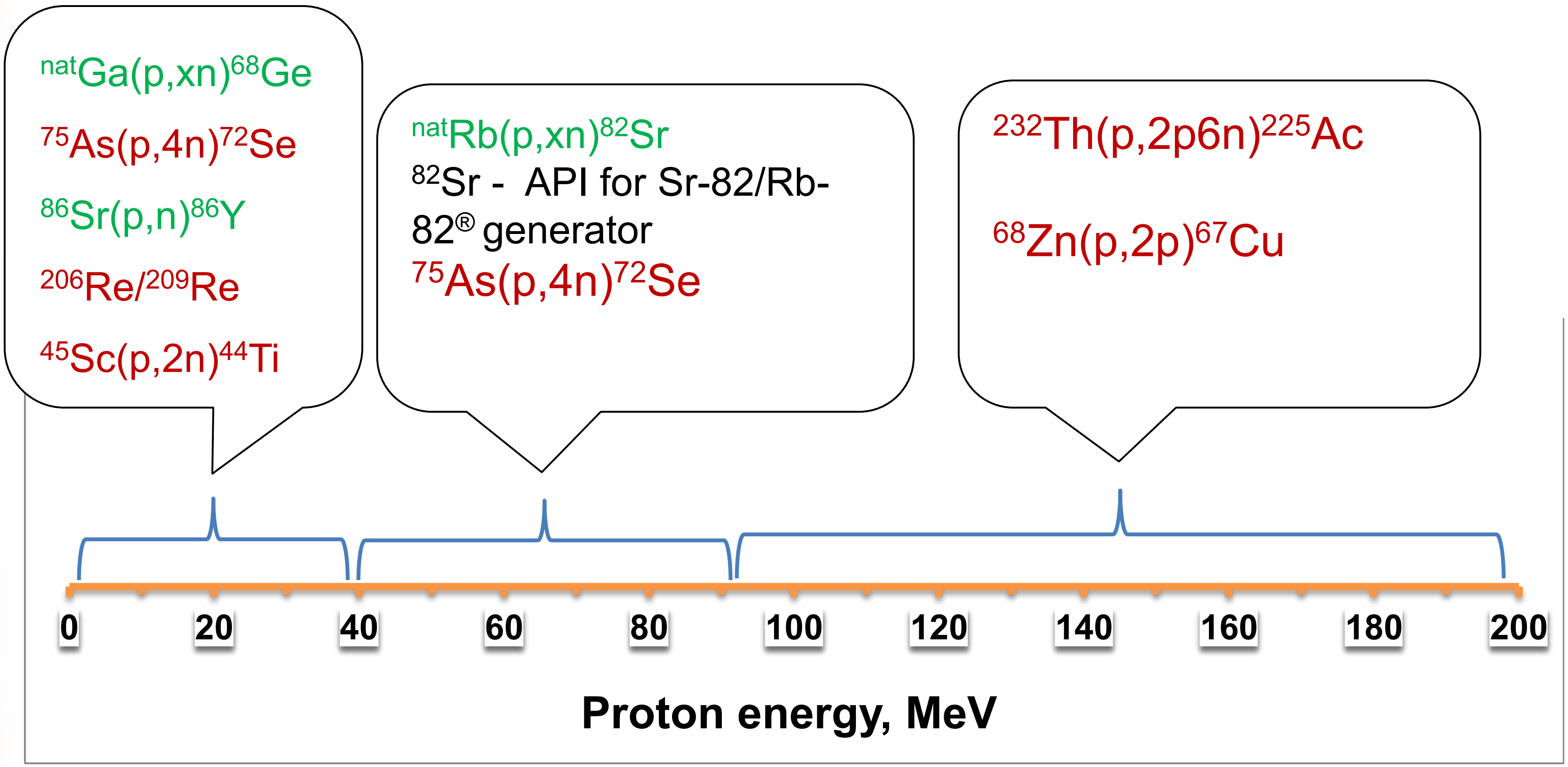
BLIP target assembly



For high energy irradiation 2 baskets can be irradiated at the same time one after another resulting 160 mm long target stack

Opportunities for Isotope Production and R&D at BLIP

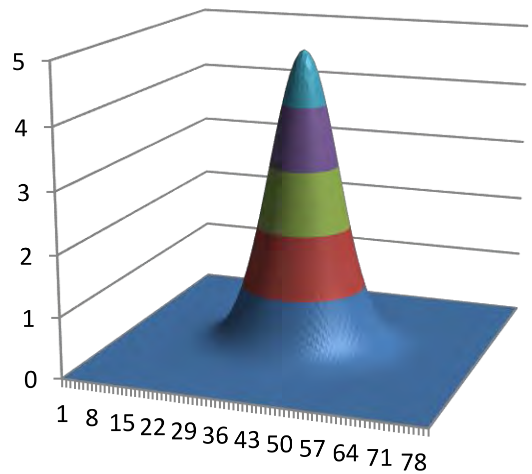


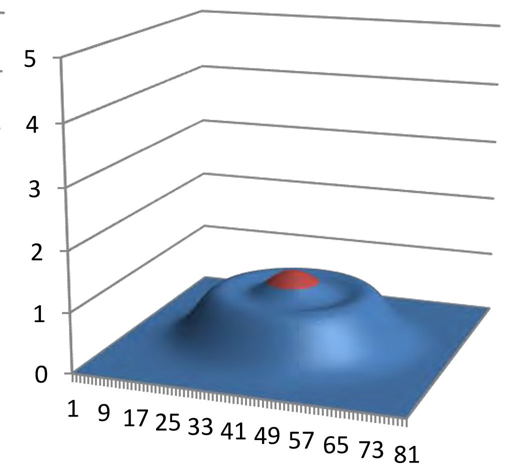
BLIP Beam Enhancements

BLIP beam raster system

Reduction in localized target heating

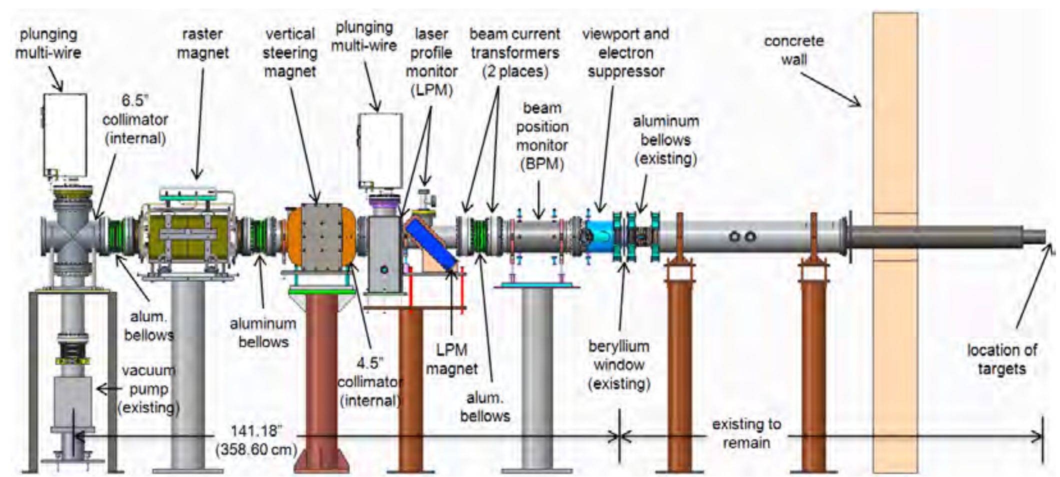
- Enables increase in beam current from 100 μA to 165 μA (greater isotope yields)
- Greatly lowers possibility of target failures





Linac intensity upgrade

- Phase 1 increased current to 165 μA
- Phase 2
  Will increase current to 250 μA by increasing pulse length



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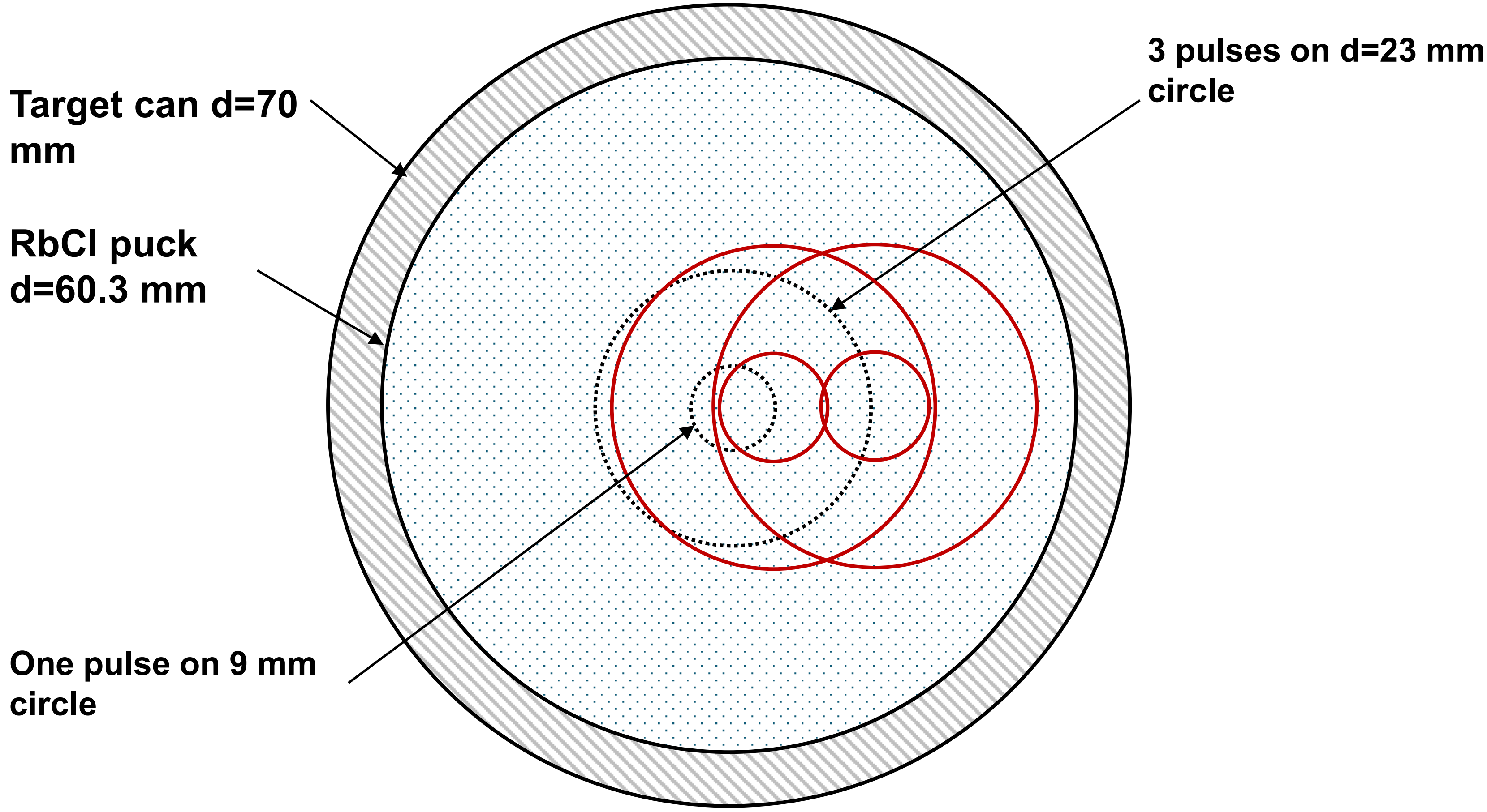
Raster pattern



Red donut depicts horizontal projections of FWHM and FWTM

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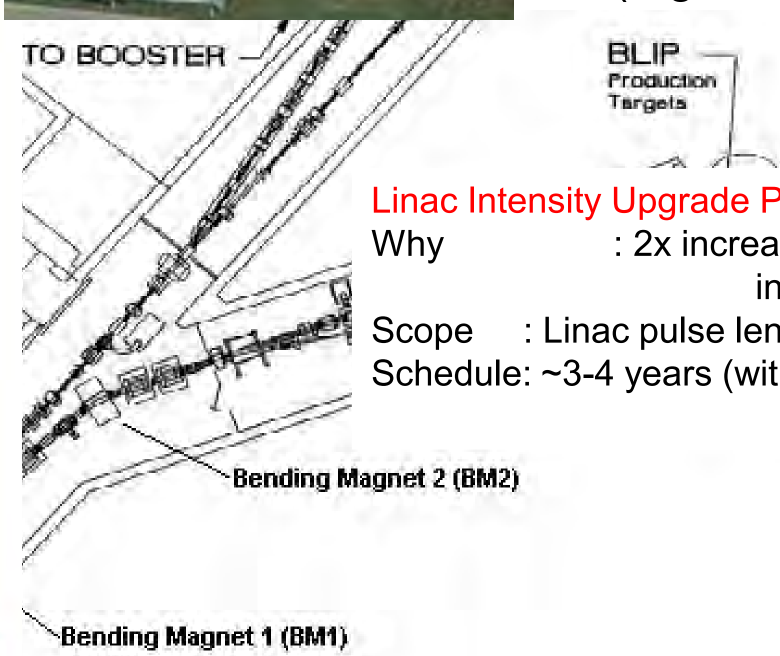
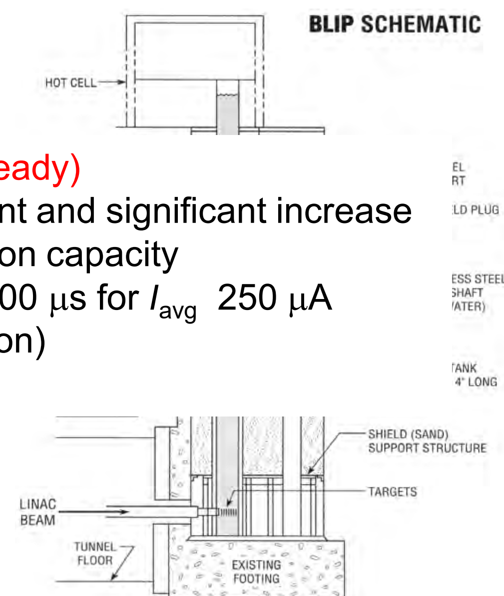
200 MeV H- beams LINAC/BLIP

Contact: D. Raparia

- First beam: fall 1972
- 85-100% of all Linac pulses go to BLIP
- Target irradiation with 66 – 200 MeV, 165 μA
- Radioisotope production for diagnostic (e.g., ^{82}Sr, ^{68}Ge) and therapeutic (^{225}Ac) use





Linac Intensity Upgrade Phase II (shovel-ready)

Why : 2x increase in beam current and significant increase in isotope production capacity

Scope : Linac pulse length doubling to 900 μs for I_{avg} 250 μA

Schedule: ~3-4 years (with cost minimization)

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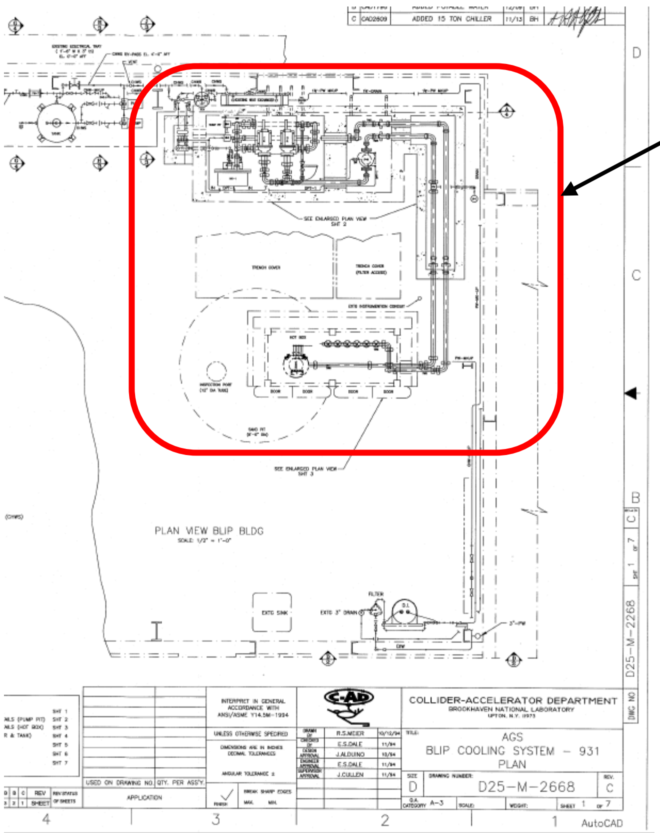
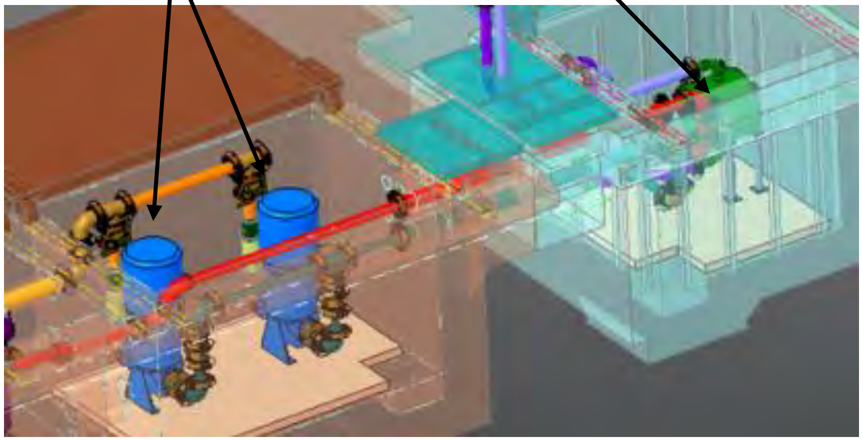
Design for the cooling system upgrade



Remove and replace pumps and heat exchanger to achieve 4X the flowrate, and approximately 3X the cooling capacity of the water flow over the target faces

New, vertical pumps

New, heat exchanger



Alpha Therapeutic Agents

Alpha Emitters

- Ability to deliver target-specific radiation dose due to short & well-defined track length (<100 μm)
- High linear energy transfer (LET) properties of alpha can be therapeutically effective in cells with low sensitivity to low-LET radiation (Quality factor = 5)
- Also effective against dormant tumor cells in G_o phase
- Cytotoxicity at both high and low-dose rates
- Works in hypoxic tissues
- Overcome required resistance
- ***Limited use due to availability, complexation chemistry needs development, requires specialized facilities for handling***

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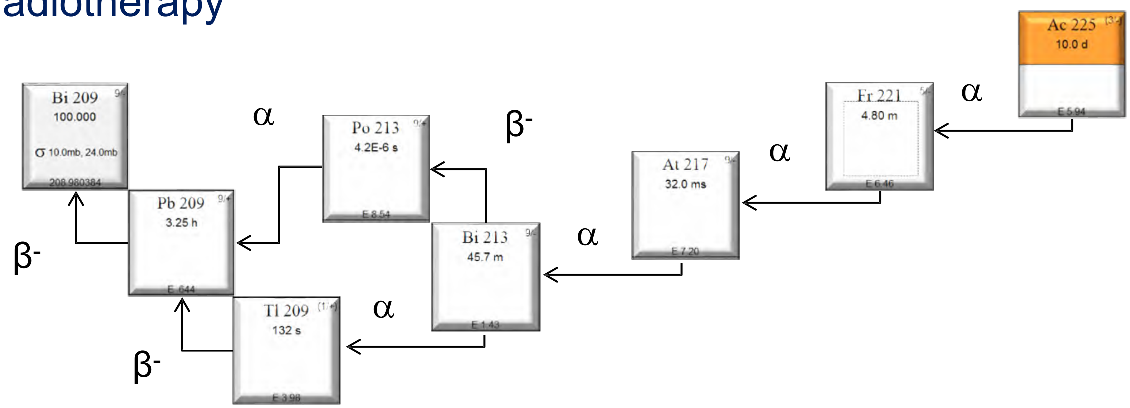
Actinium-225 nuclear data and applications

- Ac-225 is an alpha emitter, $T_{1/2}$=9.92 d, that decays, producing 4 alpha particles – suitable nuclide for alpha radiotherapy



- Ac-225 is a parent nuclide for Bi-213 ($T_{1/2}$=45.7 min) in a Ac-225/Bi- 213 generator pair. Bi-213 radiotherapeutic alpha emitter; also emits gamma ray suitable for SPECT imaging $E\gamma$=440 keV, 27.3%

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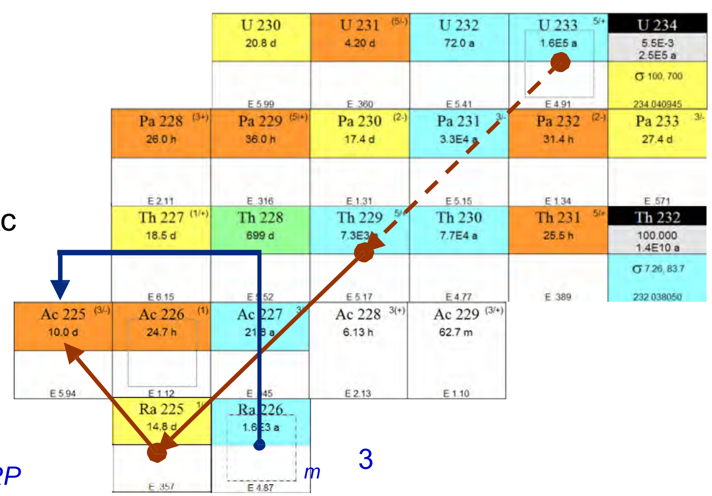
Pre-2013 ^{225}Ac production routes

- Decay from Th-229
  - ~100 mCi of Ac-225 is separated from 130 mCi of Th-229 stock at ORNL every 8 months *(Ball et al, 2005, JARI. 62(5) p 667)*
  - ~40 mCi available from the Institute for Transuranium Elements, Karlsruhe, Germany *(Apostolidis et al, J.Label.Compd. Radiopharm. 2001, 44(S1), p S806)*
- Cyclotron production through the Ra-226(p,2n)Ac-225 reaction
  - Radioactive target material *(Apostolidis et al, 2005, JARI, 62(3), p383)*

^{226}Ra(p,2n)^{225}Ac



D. Medvedev. 2019 MIRP Science and Tech targetry update

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Addressing the Supply Chain: Various $^{225}Ac/^{229}Th$ Production Routes

Facility	Nuclear Reaction
Reactor (thermal neutrons)	$^{226}Ra(3n,g)^{229}Ra \rightarrow ^{229}Ac \rightarrow ^{229}Th$ (plus ^{228}Ra target)
Accelerator (electrons)	$^{226}Ra(g,n)^{225}Ra \rightarrow ^{225}Ac$
Accelerator (low energy particles)	$^{226}Ra(p,2n)^{225}Ac$ $^{226}Ra(a,n)\ ^{229}Th$ $^{226}Ra(p,pn)\ ^{225}Ra$ $^{232}Th(p,x)\ ^{229}Th$
Accelerator (high energy particles)	**$^{232}Th(p,x)^{225}Ac$** $^{232}Th(p,x)^{225}Ra \rightarrow ^{225}Ac$
Accelerator (high energy neutrons)	$^{226}Ra(n,2n)\ ^{225}Ra$
Hot Cell Facility (^{233}U processing)	^{229}Th decay to ^{225}Ac

Basis of the Tri-Lab Effort:

Leveraging Unique Isotope Program Facilities, Capabilities, and Expertise to Address ^{225}Ac Supply

ORNL - Approximately 25 years of experience in the isolation of ^{225}Ac from fissile ^{233}U via ^{229}Th

LANL Isotope Production Facility (IPF) at LANSCE; 100 MeV incident energy up to 275 μA for routine production

BNL Linac at the Brookhaven Linac Isotope Producer (BLIP) 165 μA intensity to targets at incident energies ranging from 66-202 MeV

Front Face of the All Inclusive (AP) Production Hot Cells

- Refurbished all windows
- Replaced all manipulators
- Replaced all wiring and electronics
- Installed new ventilation and monitoring
- Installed new target introduction system
- Developed new system to remove samples

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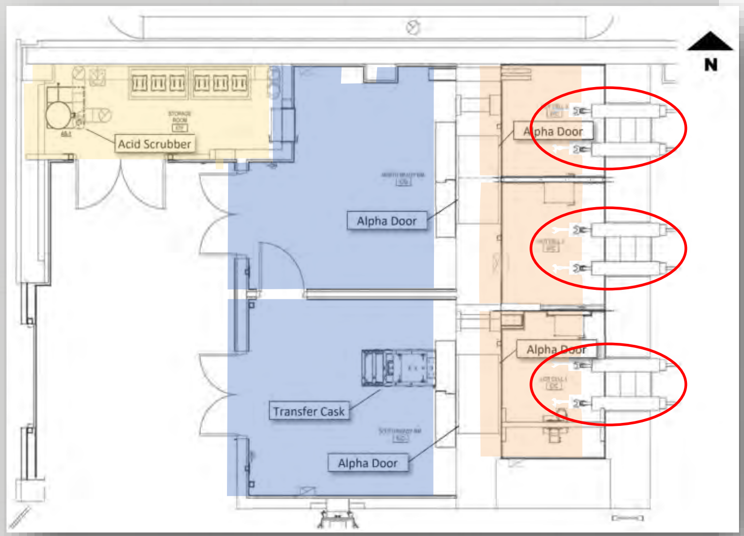
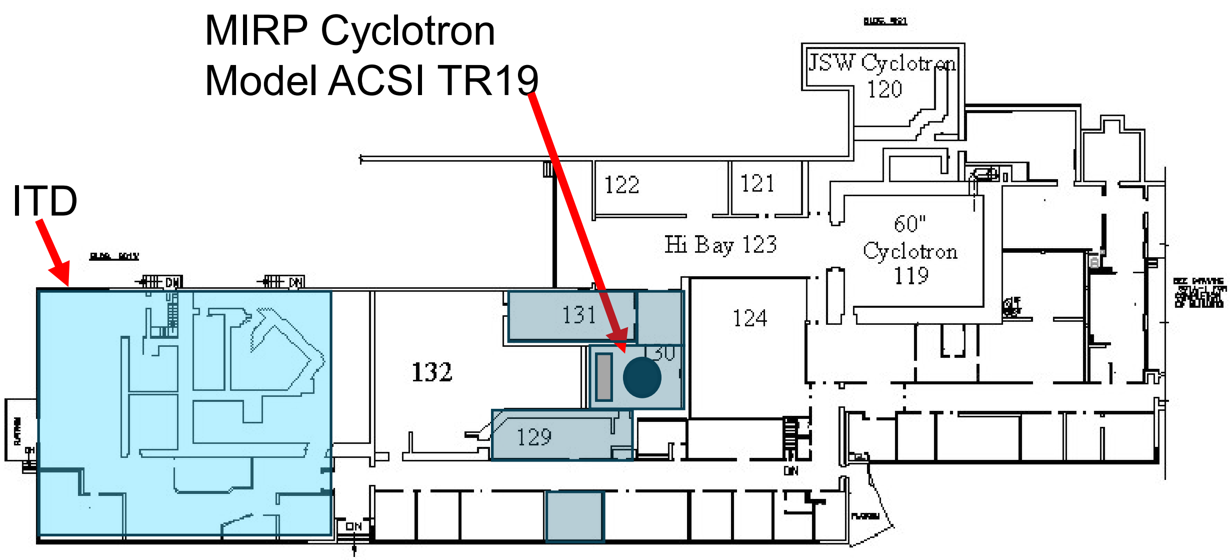
Description of the AP Hot Cells

- Three shielded enclosures
- Two ready rooms
- Storage room
- Six master-slave manipulators
  - Three nitrogen-filled windows
- Walls constructed of 3-ft. thick concrete with 3/8” steel plate
- Personnel access to ready rooms through electronically locked doors



Cyclotron in Building 901

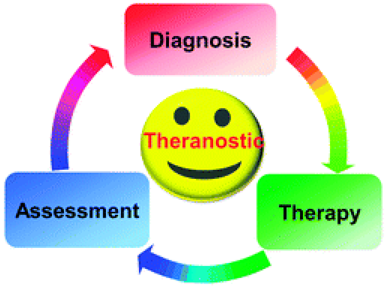


Low Energy Cyclotron

- Production of ^{225}Ac from ^{226}Ra at low energies free from ^{227}Ac (single port)
- Radiometal production for theragnostic applications: $^{44,\,47}$Sc, $^{186/189}$Re, ^{72}As, ^{86}Y, ^{109}Cd (secondary port) without beam energy degradation
- Add lab space near the cyclotron

Theragnostics

- Aim to treat the right patient with the right drug at the right time at the right dose.
- Proposed process of diagnostic therapy for individual patients to test the for possible reaction to taking new medications and to tailor a treatment plan for them based on the test results
- Therapeutic product followed by diagnostic
  - ➢eg: a drug that shows efficacy, but not for all; new diagnostics used to identify the patients for whom it will work
- Diagnostic product followed by therapeutic
  - ➢Diagnostic that distinguishes patients or disease type and allows selection of ther



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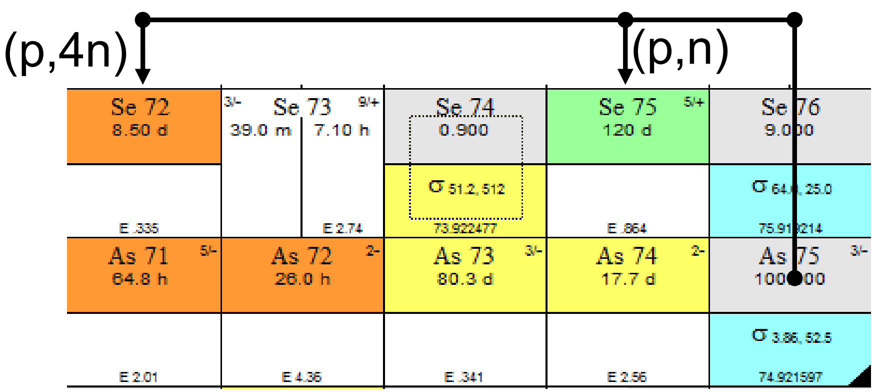
High Specific Activity ^{72}As – theragnostic pair to ^{77}As *(with University of Missouri and University of Washington)*

Imaging Isotope ^{72}As ($T_{1/2}$= 26 h)

- Positron energy comparison

Isotope	^{89}Zr (3.27 d)	^{68}Ga (67.7 m)	^{124}I (4.18 d)	^{72}As (26 h)
Mean E_{β^+}, keV	396 (22.7%)	829.5 (88.9%)	870 (22.7%)	1170 (87.8%)

- No-carrier added As-72 can be obtained from ^{72}Se/^{72}As generator
- Accelerator production of ^{72}Se from ^{nat}RbBr(p,x) at high energy and ^{75}As(p,4n) at intermediate energy has been reported
- We are interested in ^{75}As(p,4n) production route for which excitation functions up to 45 MeV have been reported



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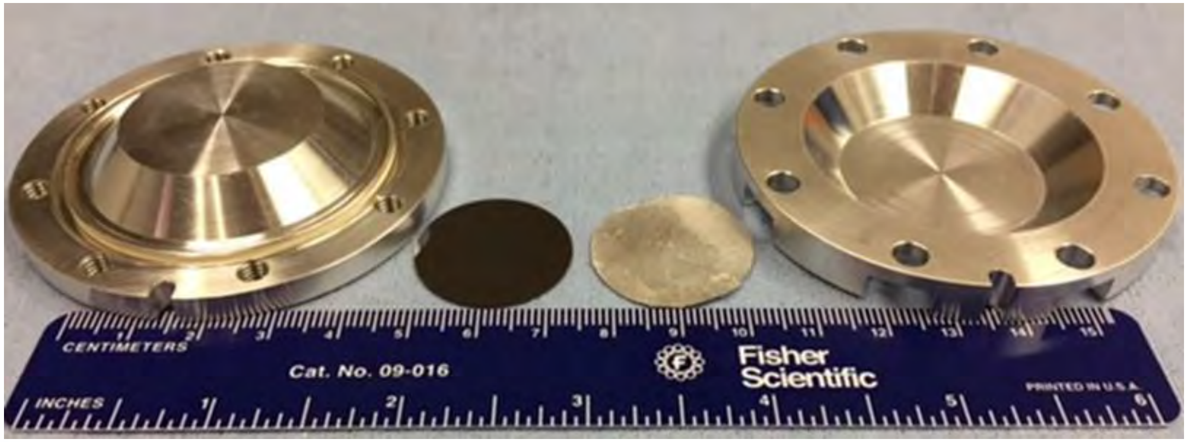
Measurements of ^{75}As(p,x) excitation functions above 45 MeV*

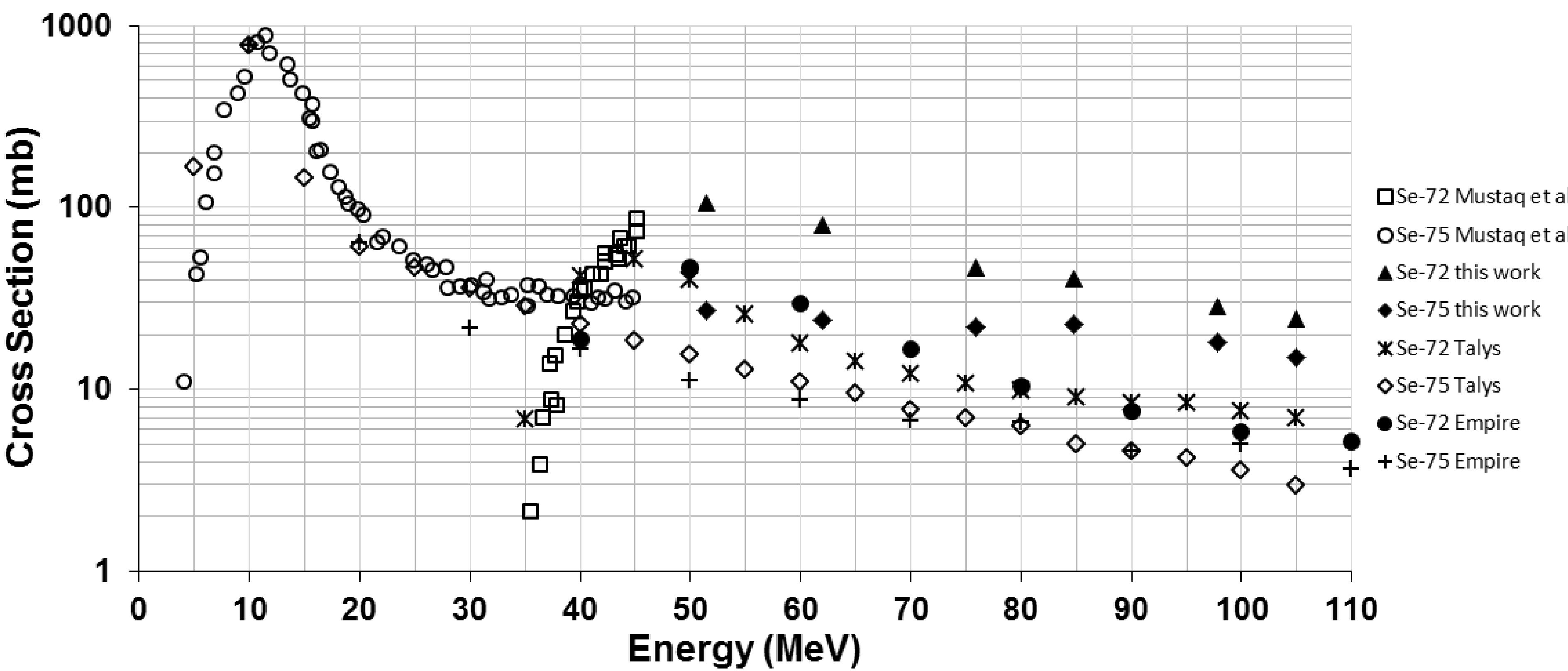


Work done by Dr. Anthony DeGraffenreid

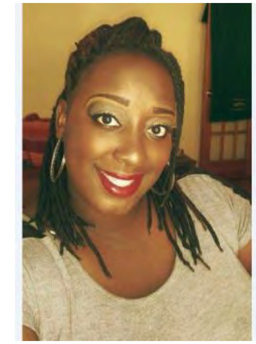
Irradiation conditions:

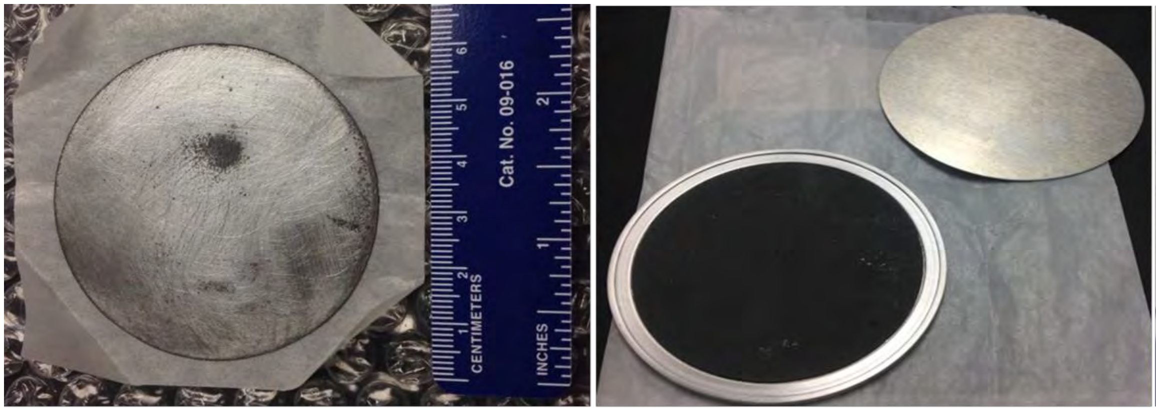
- Target material: GaAs foil, d×h=2.5×0.00254 cm
- Beam current: ~30 μA, focused beam
- Irradiation time: 2 h
- Incident energy: 117 MeV incident, lower points achieved by degradation with Al degraders
- Aluminum foil used for beam monitoring

Excitation functions for Se-75 and Se-72 production from As

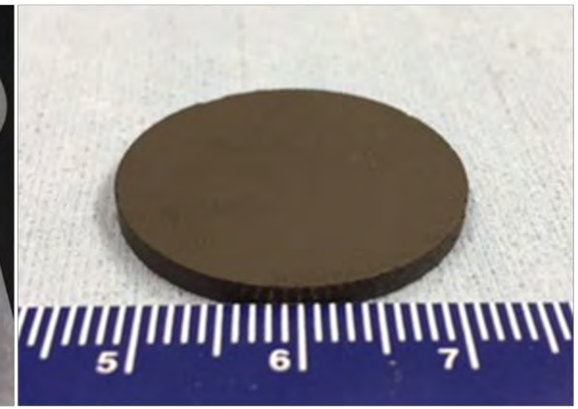


Large scale production of ^{72}Se at 105-103.5 MeV





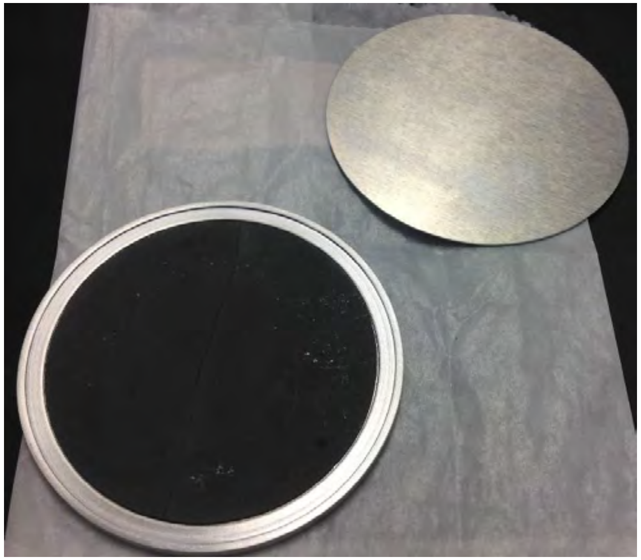
Arsenic Metal Sputtering

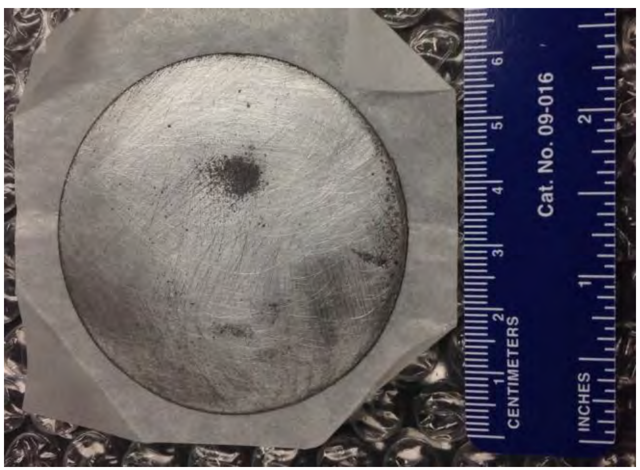


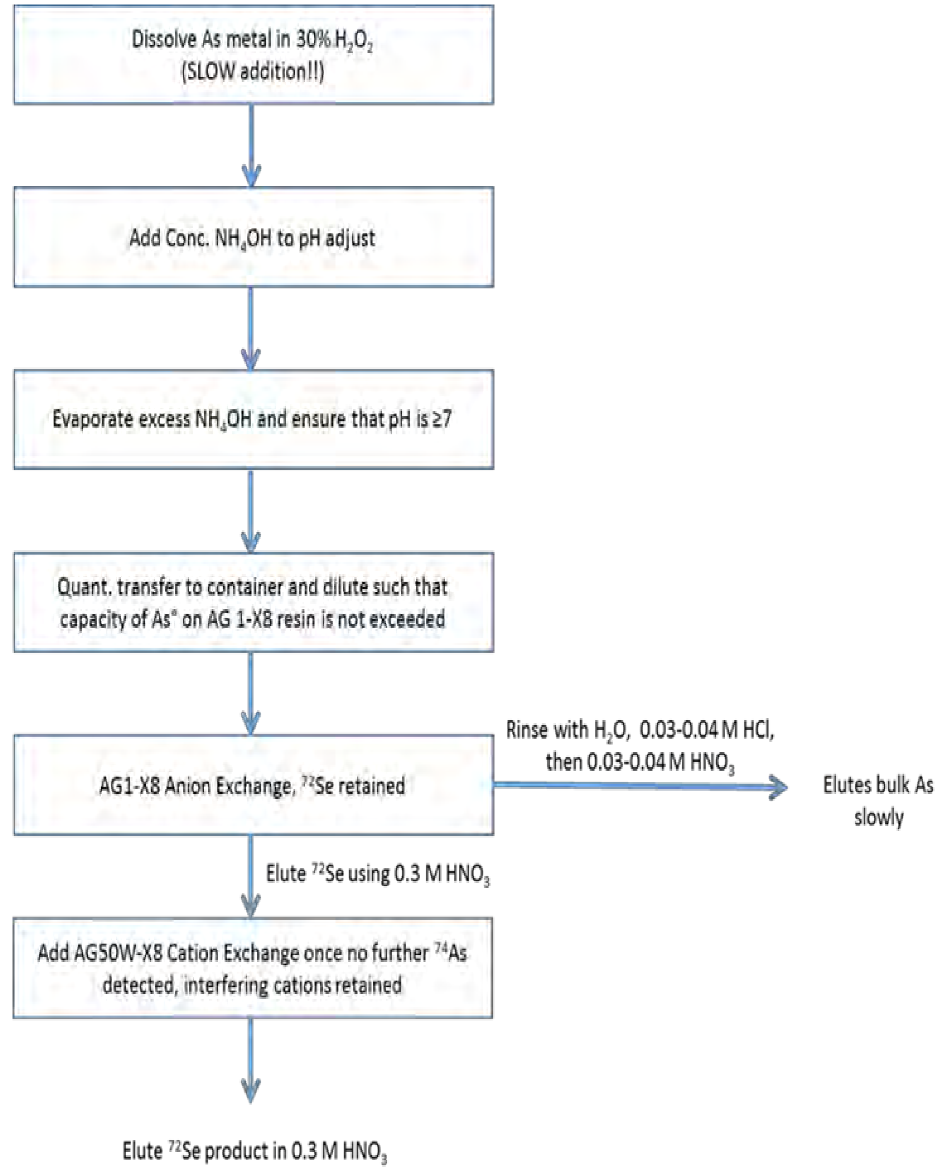
Pressed Arsenic Metal

BNL ID	Design	Material; Mass, g	Exit-Incident Energy, MeV	Beam time, d	Beam Current, µA	Activity Produced, mCi	^{72}Se Production Rate, µCi/µAh	^{75}Se Production Rate, µCi/µAh	^{72}Se/^{75}Se Ratio
BXA	Welded Al	GaAs; 7.6	103.7-105	4.85	136.4, rastered	101.6	6.4	0.35	18.3
BXI	Welded Al	Sputtered As; 9-10	46.1-50.2	2.87	163.2, rastered	373.4	32.5	1.8	18.1
BXR	Welded Al	Sputtered As; 9.5	103.3-104.9	11.3	152.1, rastered	394.5	9.6	0.72	13.3
CCD	Bolted Al	Pressed As; 5.0	53.7-61.1	0.79	86.4, focused	309.5	189.9	3.84	49.4
CCE	Bolted Al	Pressed As; 5.0	49-56.8	0.76	118, focused	343.7	158.6	2.95	53.8

Chemical Processing







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$^{72}Se/^{72}As$ Generator

Anion exchange

AG1-X8 (200-400 mesh)

- 5 mL BV

Load in 0.3 M NH_4OH

Rinse H_2O

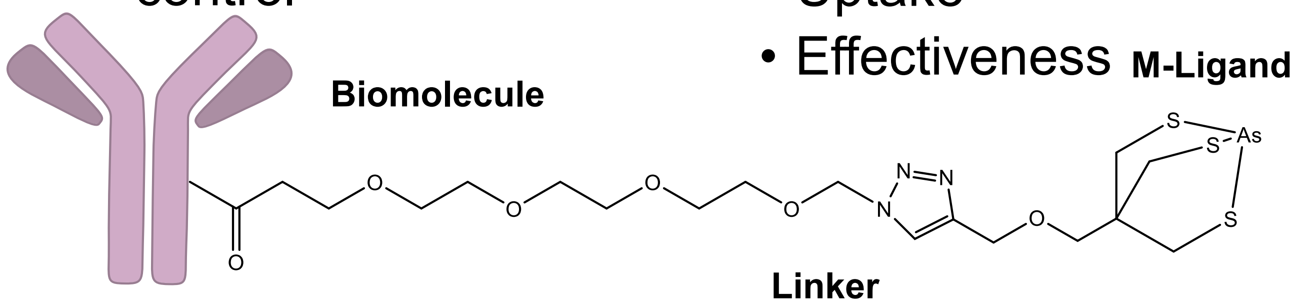
Rinse dilute HCl

Collect each fraction to determine percent loaded

^{72}As-Monoclonal Antibodies

- Trastuzumab (Herceptin)
  - 2mg/mL/rxn
- Daratumumab
  - 1mg/mL/rxn
  - control

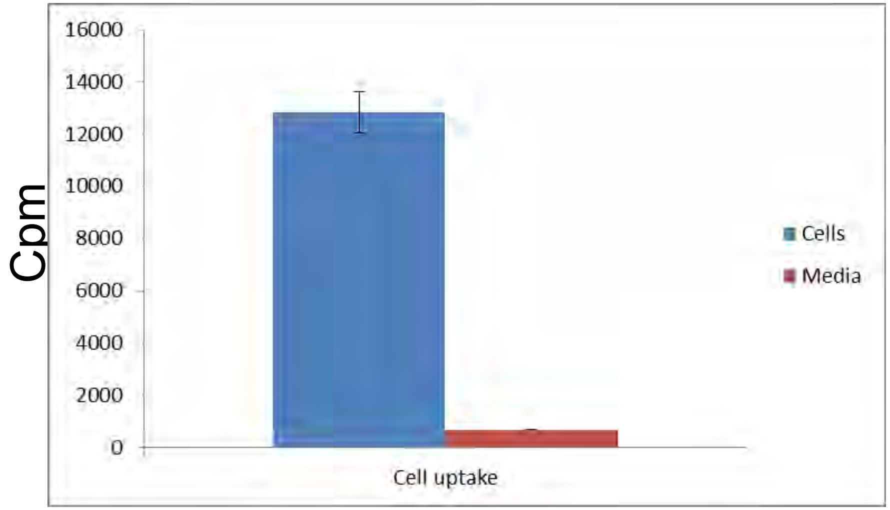
- Test against patient specific tumor models
- To visually observe
  - Drug sensitivity
  - Uptake
  - Effectiveness



^{72}As-mAb Cell Studies

- ^{72}As-trastuzumab is incubated with gastric cancer cell lines for a 24 hour period
- Cells are separated from the media and analyzed for radioactivity

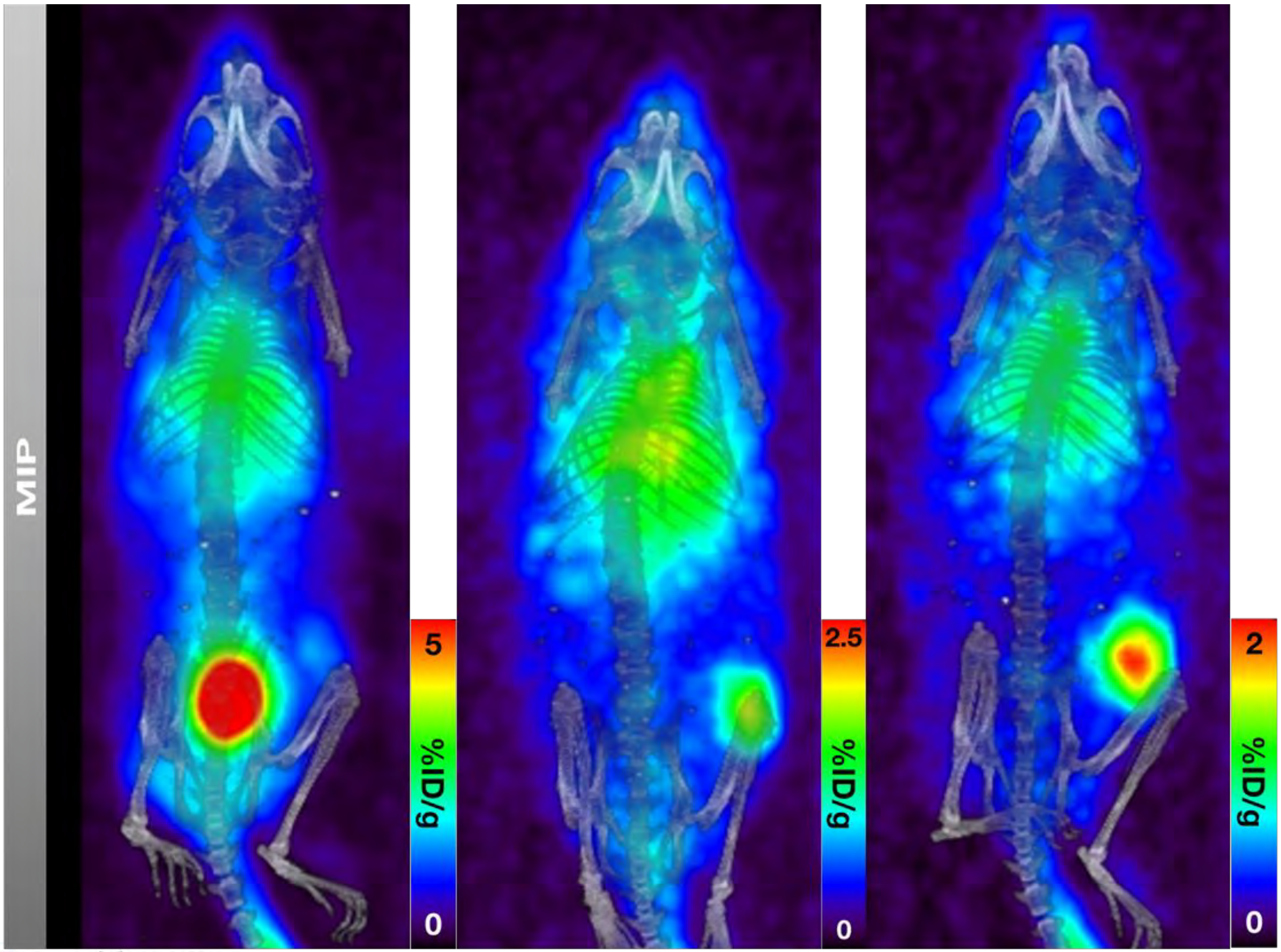
Gastric Cancer Cell



18.5 times uptake in cells!!!

Completed at Stony Brook University

^{72}As-Trasztuzumab in NCI-N87 gastric cancer xenografts



8 Hour 24 Hour 72 Hour

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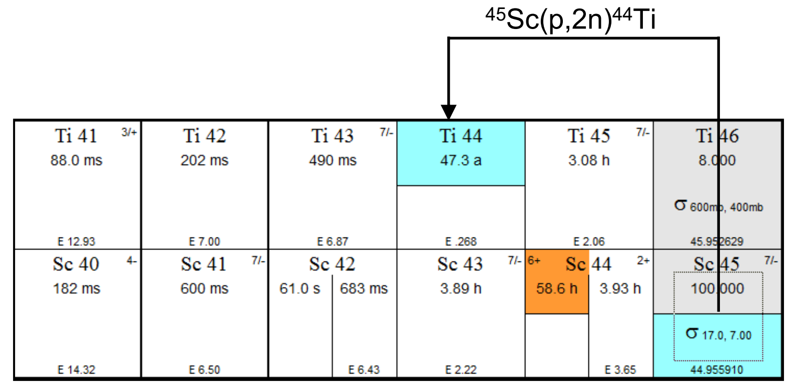
Production at < 30 MeV: Ti-44 (59.1y) parent of Sc-44 (3.97 h)

Scandium-44

- Decays by electron capture to Ca-44 (stable), mean $E_{\beta+}$=632 keV, Eγ=1157.02 keV (99.9%)
- Metallic isotope that offers intermediate half-life of 3.97 h (Ga-68 – 67.7 min, Zr-89 – 78.41 h)
- Offers theragnostics opportunities
  - Pretherapeutic dosimetry evaluation for M^{3+}-radiopharmaceuticals
  - Excellent compatibility with biological half-life of peptides
  - Diagnostic pair for therapeutic Sc-47

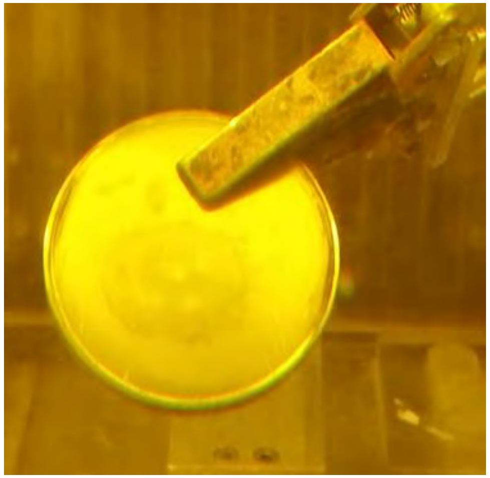


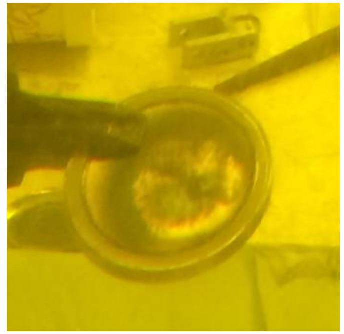
Can be supplied on a generator* ^{44}Ti(59.1 years)→ ^{44}Sc(3.97 h)

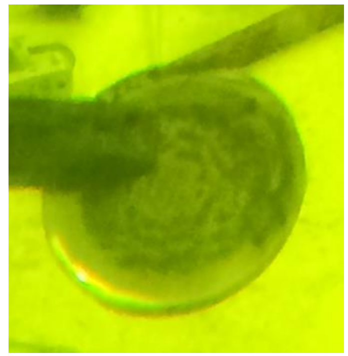
Ti-44 production requires long irradiations: dedicated irradiations are not economically viable

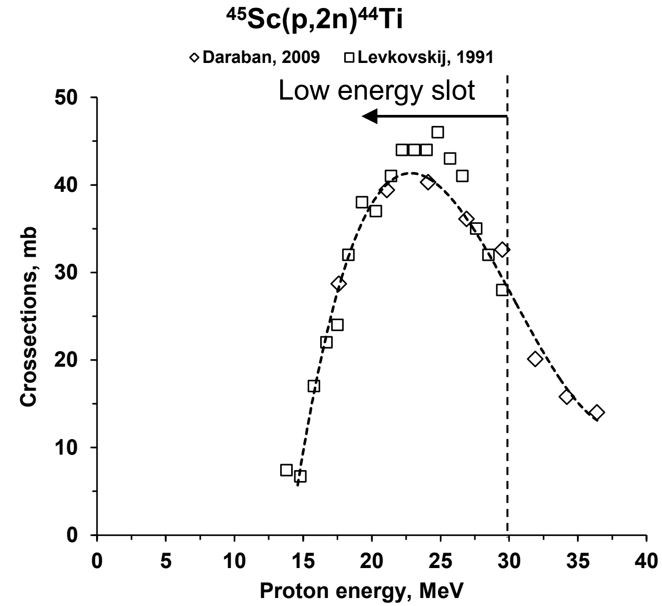
*Filosofov et al, Rad. Acta. 2010, 98(3), 149-156

Natural Scandium target after irradiation









Target development and irradiation status

BNL ID	Cladding	Time period	Accumulated µA-h	Beam current, µA	Irradiation yield, Ti-44
BXF	Inconel	2016	32774.79	131.5	0.96 mCi
BXG	Inconel	2016-2017	160277.67	~150	4.7 mCi*

*projected yield

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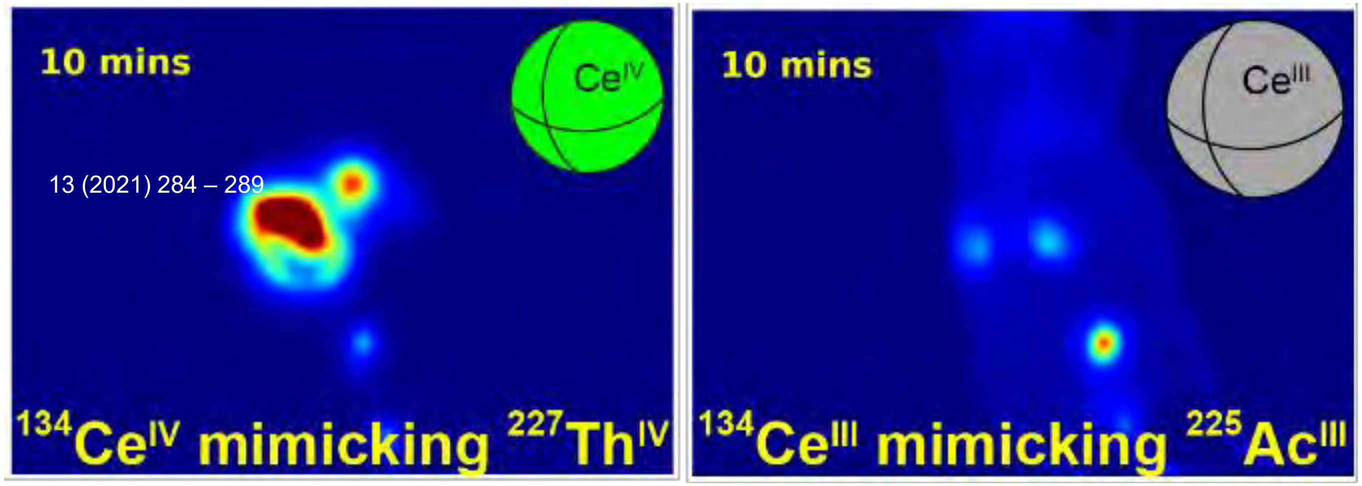
^{134}Ce and ^{134}La; Promising PET imaging Isotopes



- Demonstrated the production, purification, and potential application of cerium-134. This isotope decays into lanthanum-134, an isotope useful for positron emission tomography (PET) imaging.
- The results show that cerium-134, through its lanthanum-134 decay product, could serve as a diagnostic partner for medical treatments based on actinium-225 or thorium-227.

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ARTICLES

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Summary

BLIP routinely receives proton beam from LINAC at 200-66 MeV and average current 165 µA

Future upgrades will increase intensity to 300 µA and significantly enhance cooling

A total of 160 mm of target space is available both for research and production

Generic target array comprised of 4 slots (80 mm total)

Beam is rastered for production targets; can be focused for cross section measurements and enriched targets' irradiations

Additional production capability exists upstream and downstream of production targets and used for production of Se-72, Y-86, Ti-44 and other targets.

For high energy irradiation target space is available downstream

Questions

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Se-72/As-72

University of Missouri: Silvia Jurisson, Tim Phelps, Matt Gott

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Ti-44/Sc-44

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