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U.S. DEPARTMENT OF ENERGY

Accelerator Production of Medical Radionuclides

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August 12, 2022 NAPAC 2022

Radiopharmaceuticals

- Radiopharmaceuticals - Drugs that contain radioactive atoms
- Radiopharmaceuticals are used for imaging and therapy
- Diagnostic radiopharmaceuticals have no pharmacological effect
  - Examples:
    - Heart disease (e.g., ^{99m}Tc, ^{18}F, ^{82}Rb)
    - Cancer (e.g., ^{18}F, ^{68}Ga)
- Therapeutic radiopharmaceuticals deliver radiation therapy directly to a lesion
  - Examples:
    - Seeds for prostate cancer therapy (^{192}Ir)
    - Targeted therapy (^{90}Y, ^{131}I, ^{223}Ra, ^{177} Lu)
- More than 20 million nuclear medicine procedures are performed each year in the US, ~ 50% of the global market
- Nuclear medicine is ~ $2 billion USD/year industry
- **The health benefits and economic impact are enormous**

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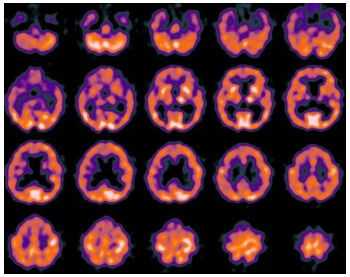
What Is Molecular Imaging?

What Is Molecular Imaging?

Visualization



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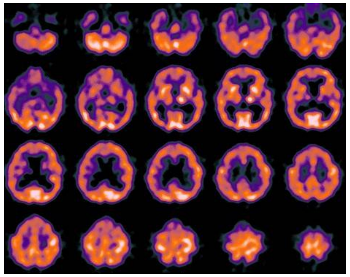
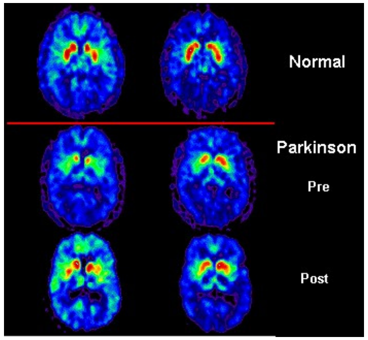


Characterization



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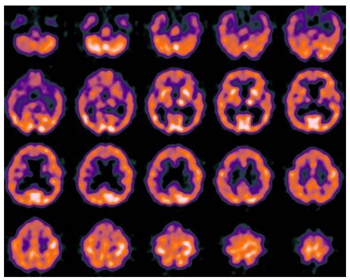

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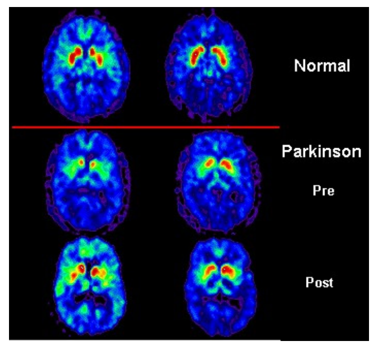
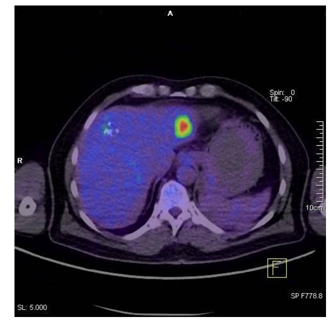
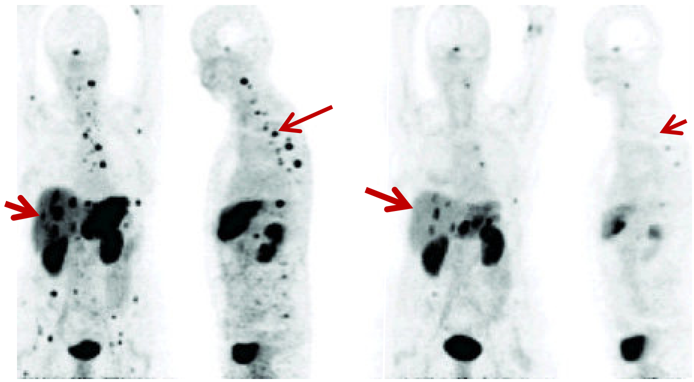


Measurement

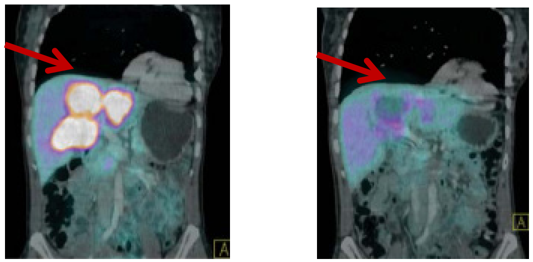


of biological processes at the molecular and cellular levels in humans and other living systems

"Remarkable response to Bi-213-DOTATOC observed in tumors resistance to previous therapy with Y-90/Lu-177-DOTATOC"



Case I: Shrinkage of liver and bone metastases after i.a. therapy with 11 GBq ^{213}Bi DOTA-TOC



Case II: Response of multiple liver lesions after i.a. therapy with 14 GBq ^{213}Bi DOTA-TOC

- Abbreviated decay chain: ^{225}**Ac**→ ^{221}Fr→ ^{217}At→ ^{213}**Bi**
- GEP-NET = Gastroenteropancreatic neuroendocrine tumors
- Ref. Morgenstern et al. J. Nucl Med 2012; 53 (Supplement 1): 455.

High publicity: Study awarded Society of Nuclear Medicine Image of the year in 2012

SNMMI press release June 11, 2012

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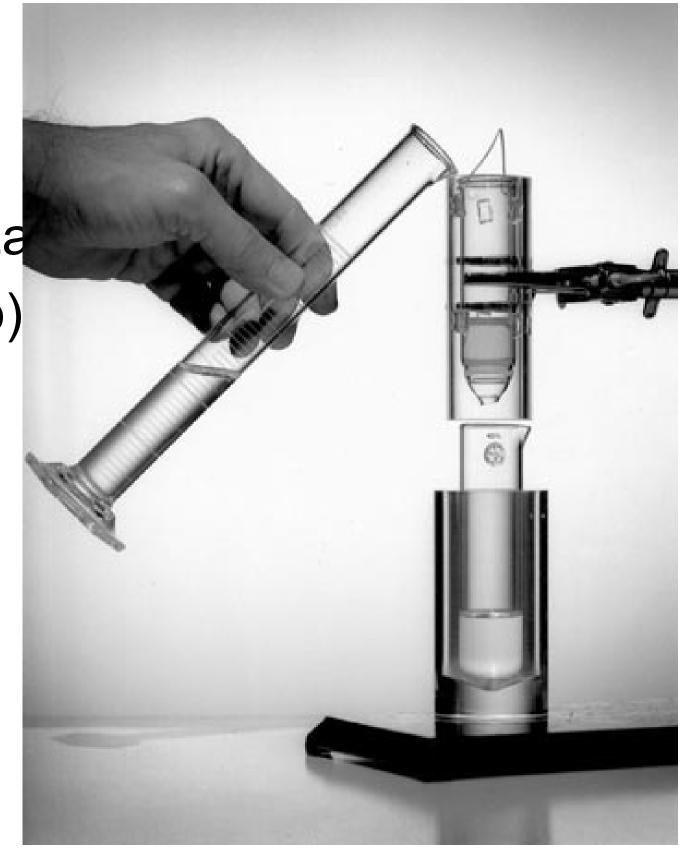
Role of the Department of Energy

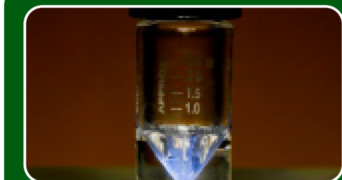
The development of most, if not all, isotopes used in medicine was fostered by DOE or its predecessor agencies:

- 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)

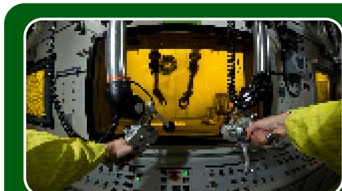


The BNL Tc-99m Generator

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.

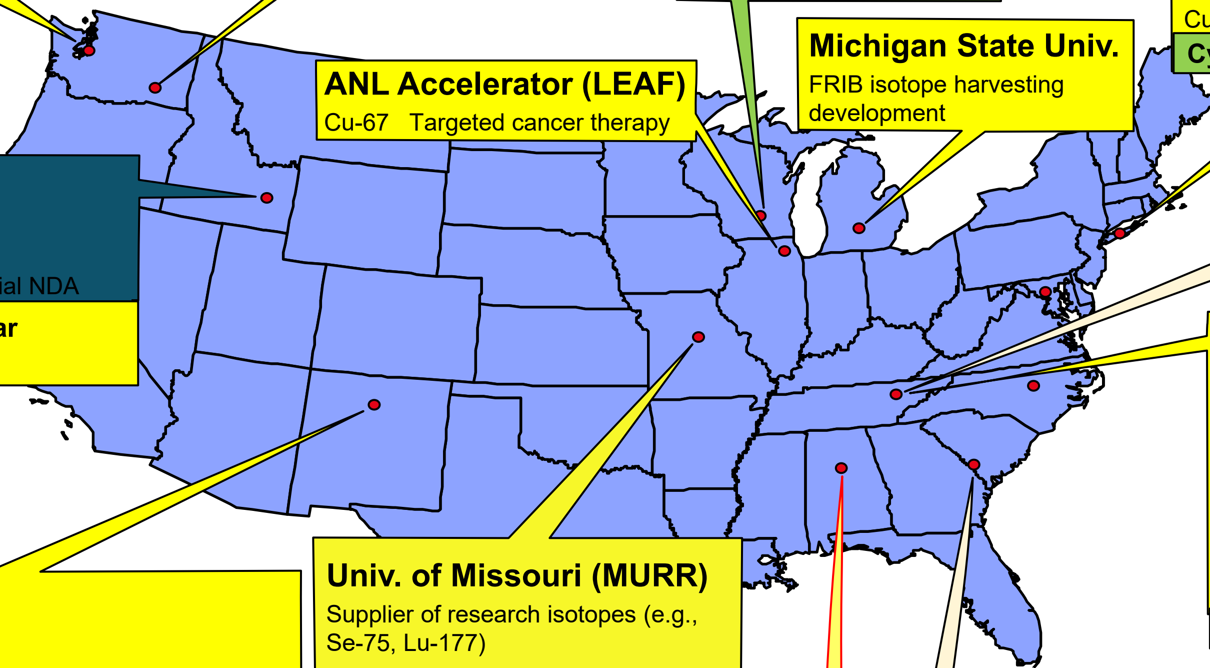
Isotope Program Competencies

- **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)

ANL Accelerator (LEAF)
Cu-67 Targeted cancer therapy

Michigan State Univ.
FRIB isotope harvesting development

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

How are accelerator radiopharmaceuticals produced?

1200 +

Cyclotrons

5600+

PET Scanners

IAEA Accelerator Knowledge Portal

iMAGiNE

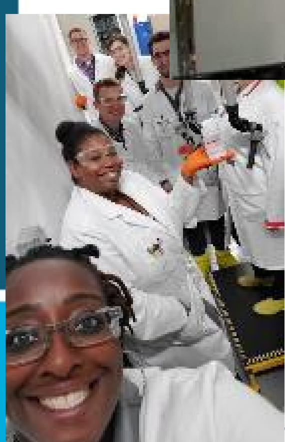
DOE Accelerator Facilities

BNL BLIP
- 200 MeV, 165 mA 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 mA 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.

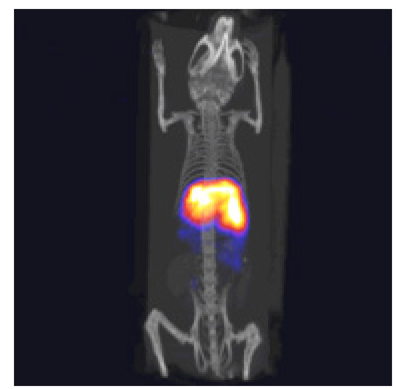
Newly refurbished hot cells for alpha-processing



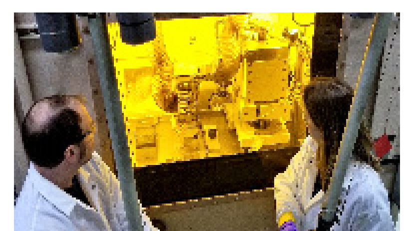
Outstanding hands-on training in smaller facilities

Safe radioisotope processing during the COVID-19 pandemic

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

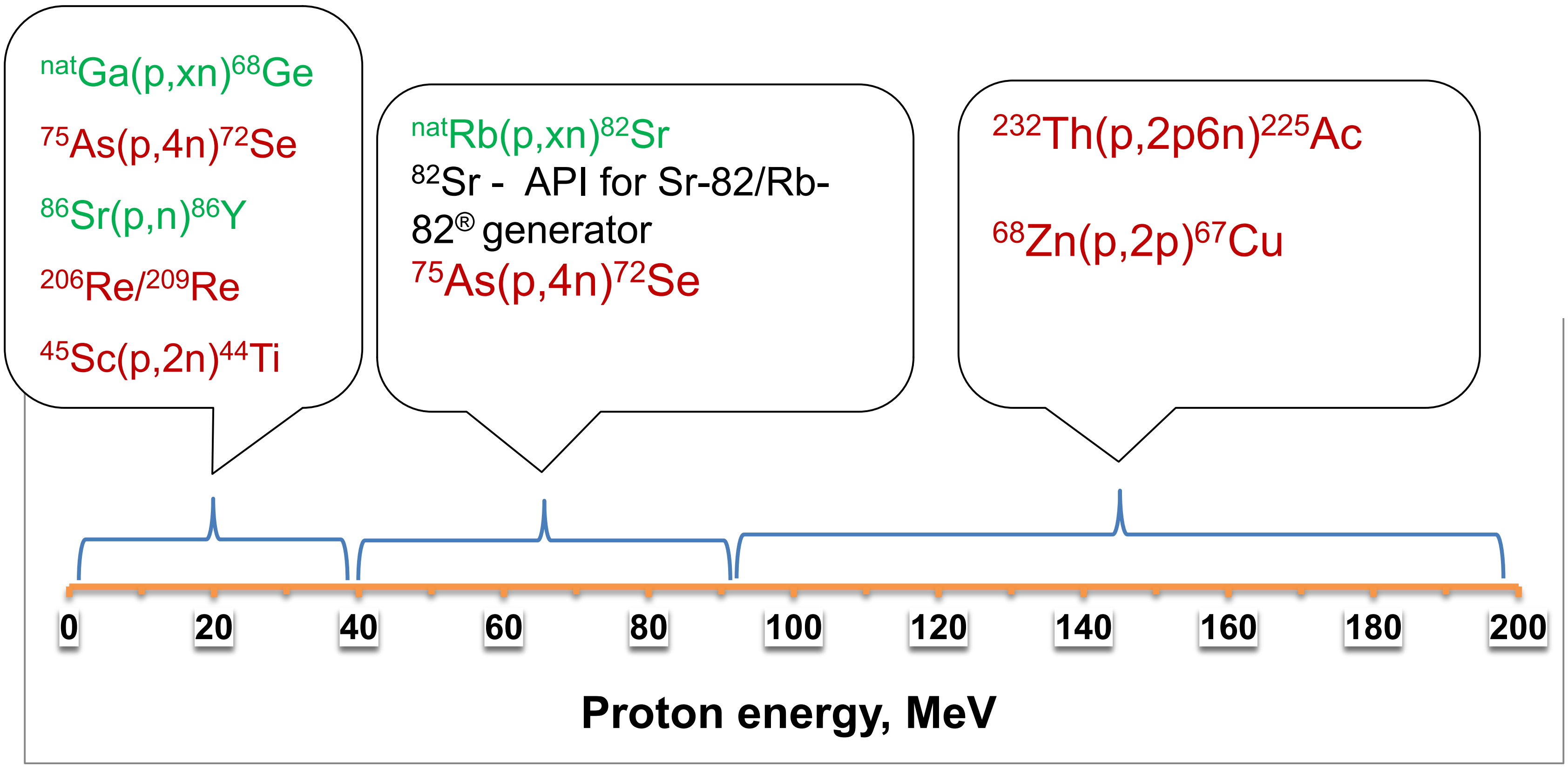


Diagnostic demonstration of Cu-67 in living mice, in collaboration with University of Alabama-Birmingham



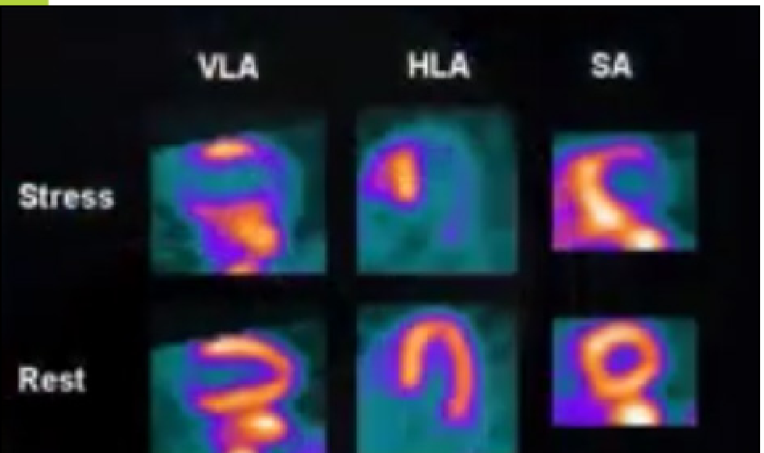
Hot cell processing of Cu-67

Opportunities for Isotope Production and R&D at BLIP

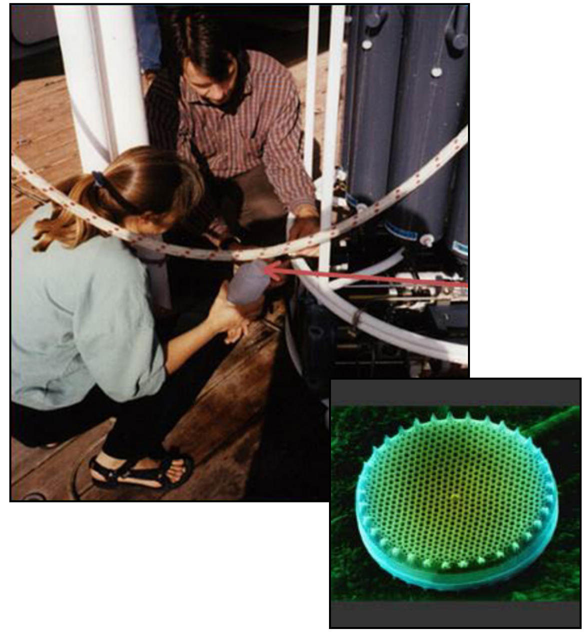


Applications – Accelerator Isotopes

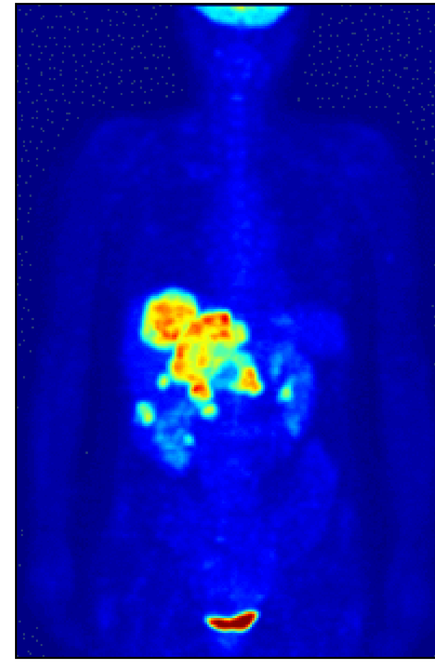
Sr-82/Rb-82: Generator- cardiac imaging



Si-32: Environmental applications

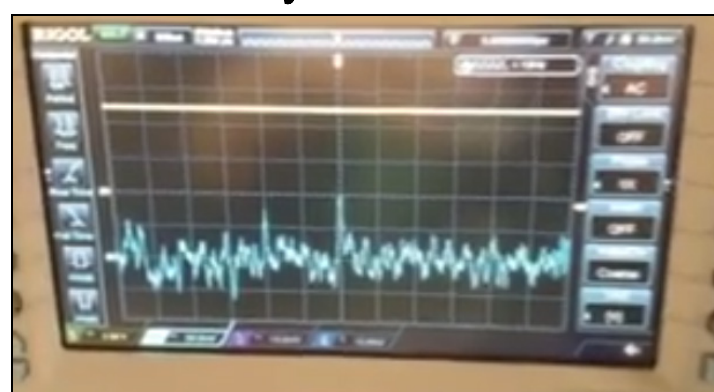


Ge-68/Ga-68: Generator- cancer imaging

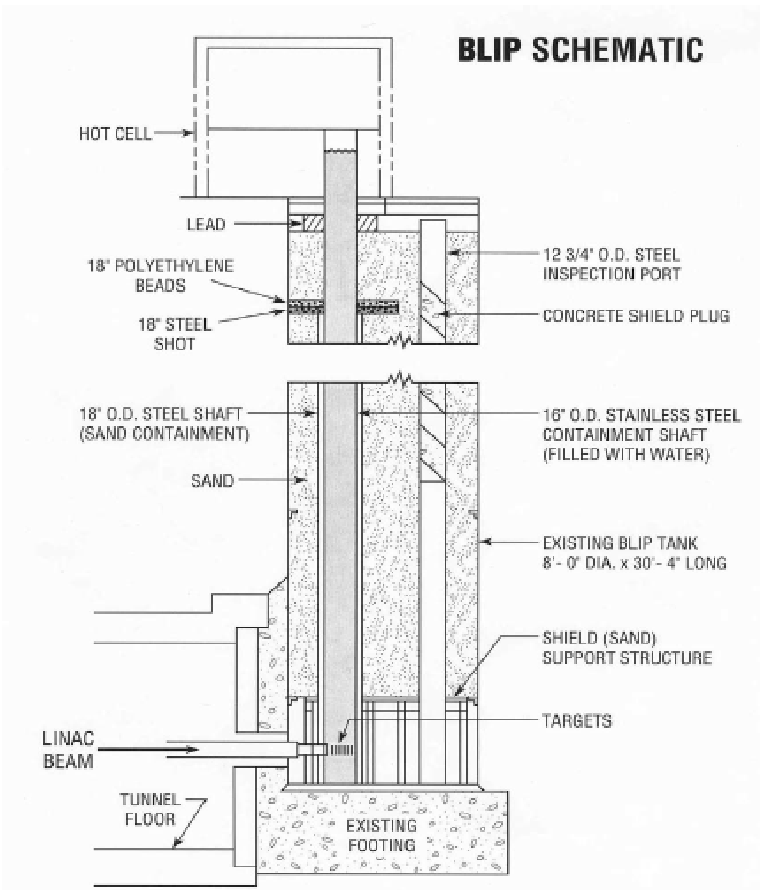


Na-22: Source for PET imaging

Cd-109: X-ray fluorescence source



Brookhaven Linear Isotope Producer (BLIP)



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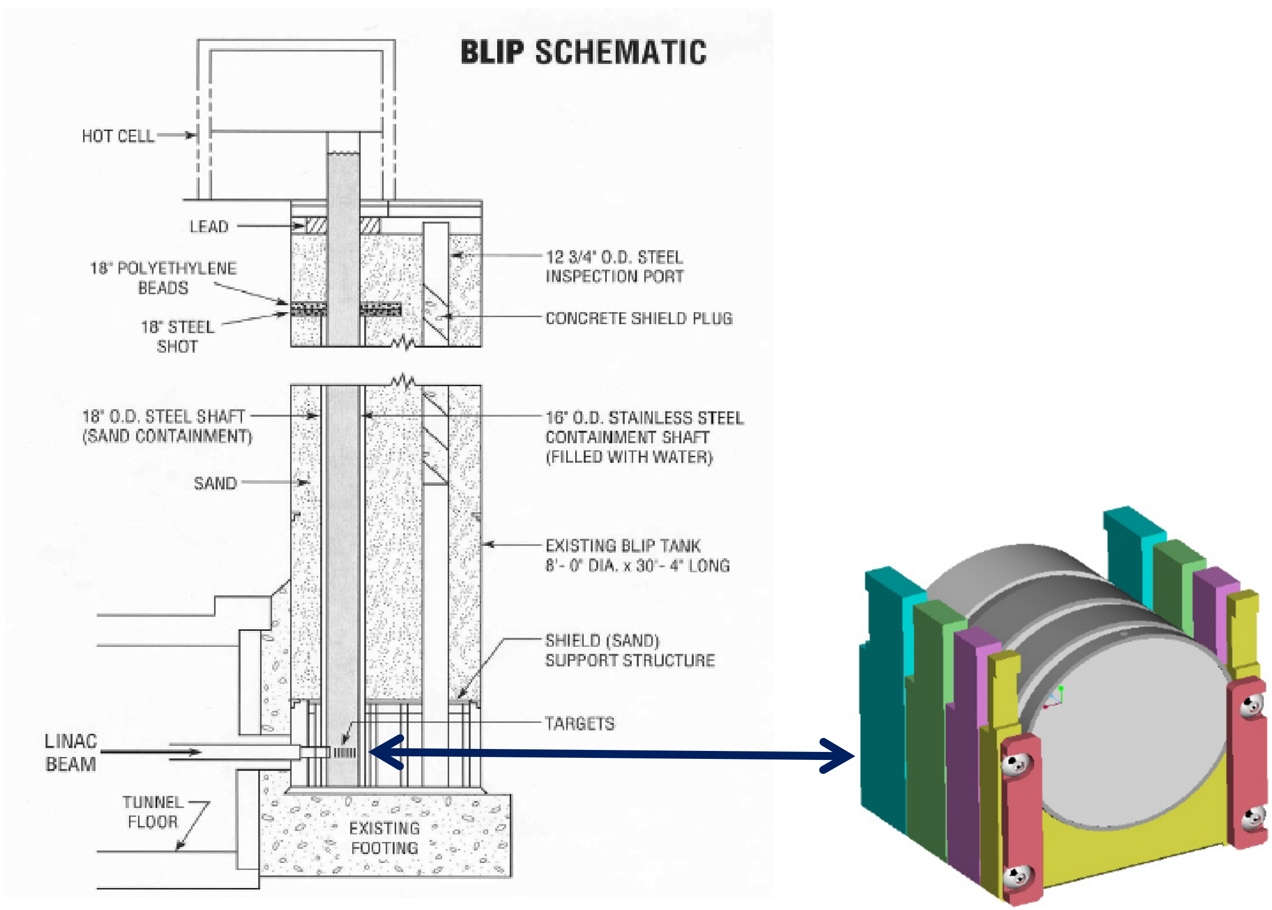

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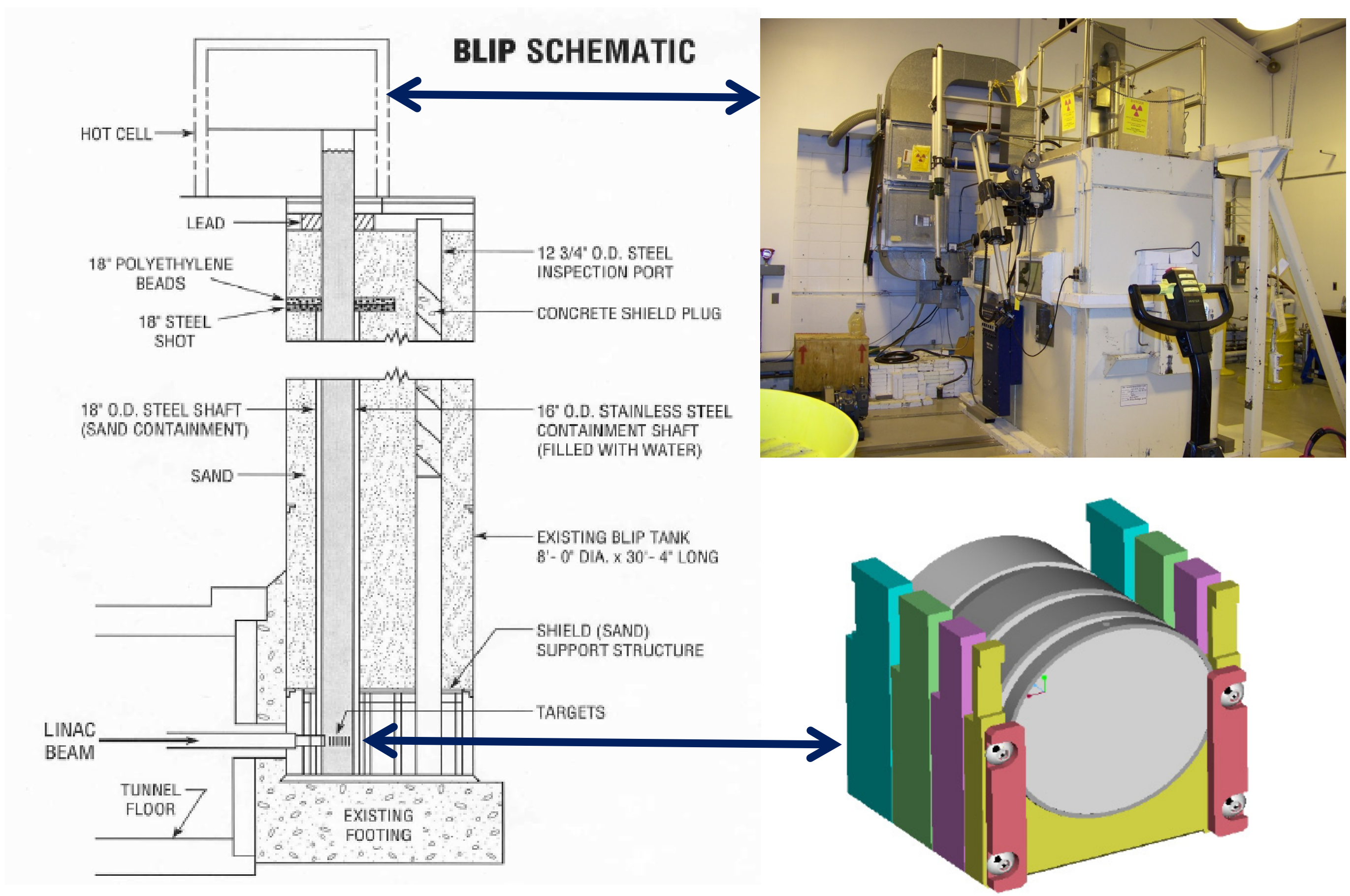
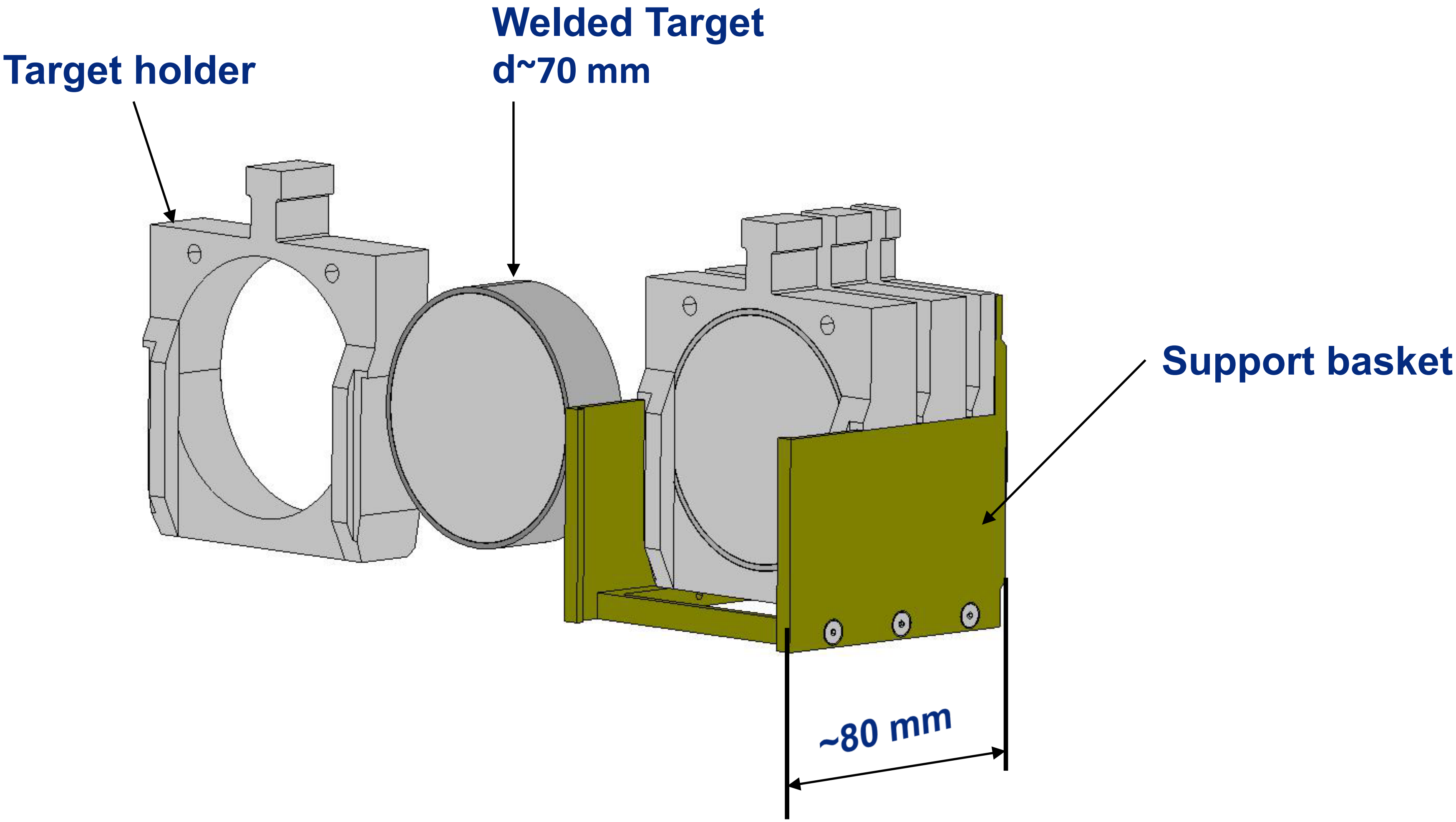


BLIP target assembly



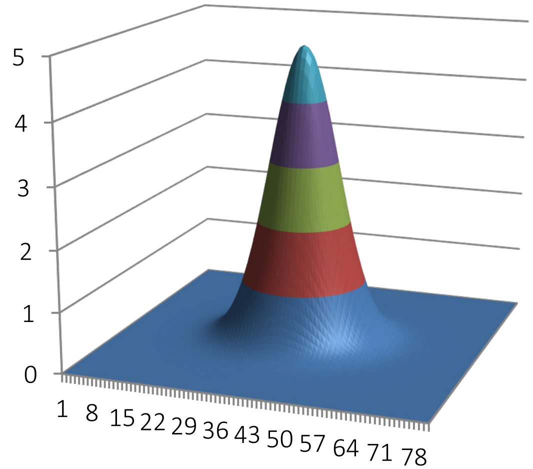
For high energy irradiation 2 baskets can be irradiated at the same time one after another resulting 160 mm long target stack

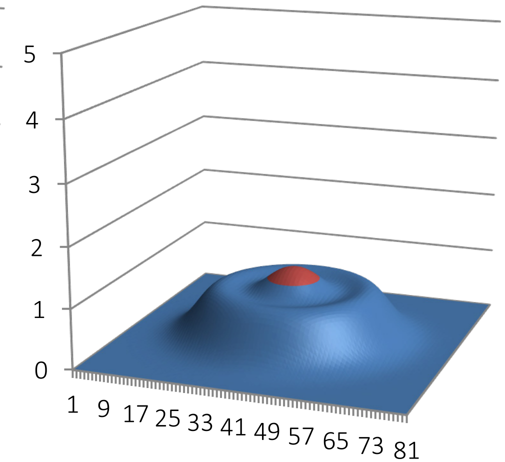
BLIP Beam Enhancements

BLIP beam raster system

Reduction in localized target heating

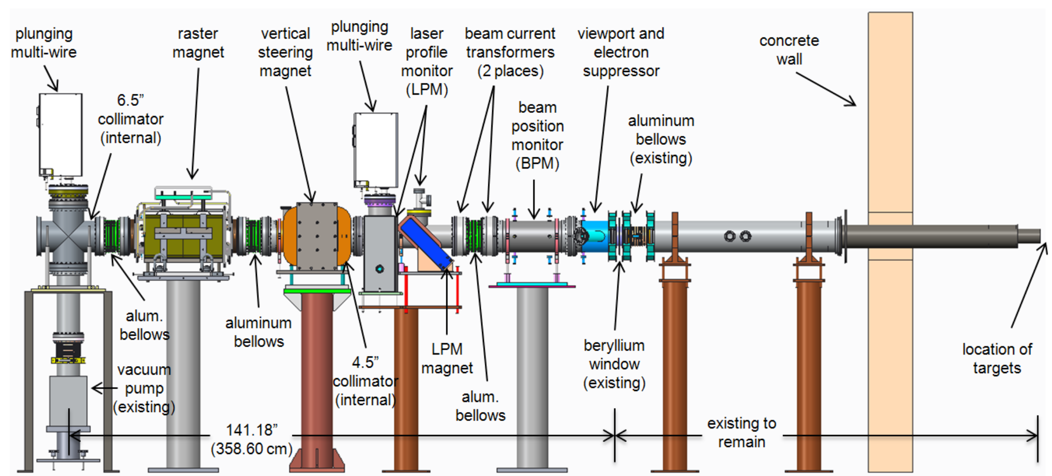
- Enables increase in beam current from 100 μA to 165 μA (greater isotope yields)
- Greatly lowers possibility of target failures





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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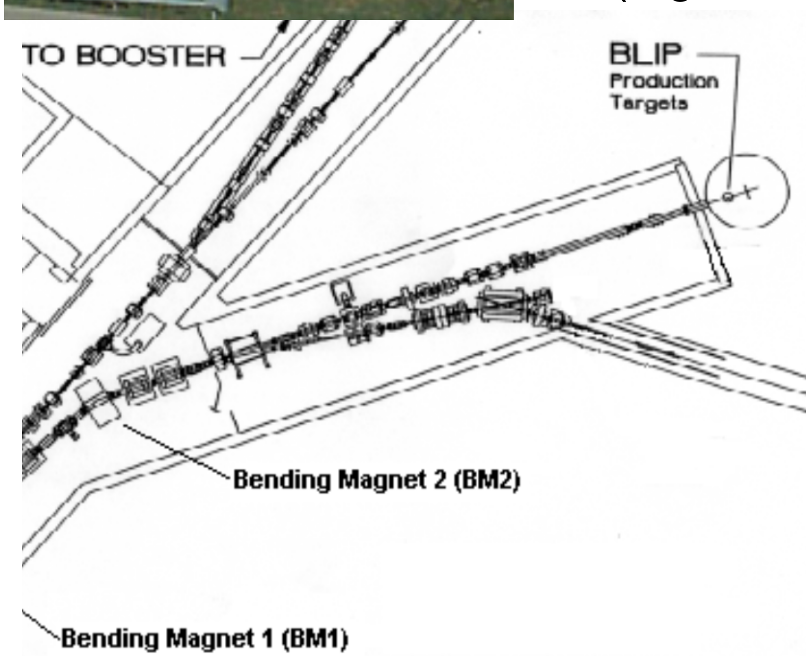
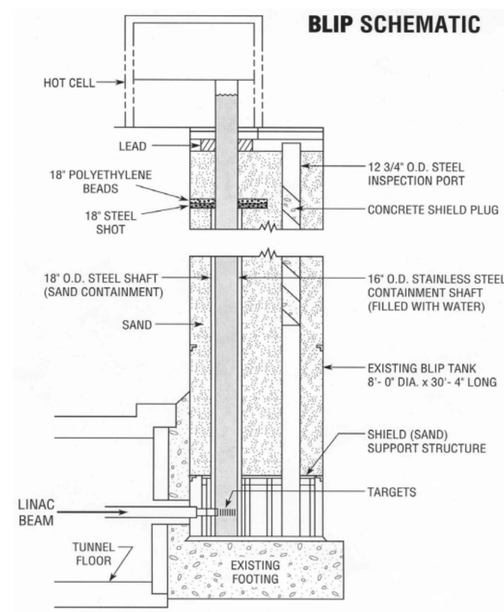
200 MeV H- beams LINAC/BLIP

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

Contact: D. Raparia





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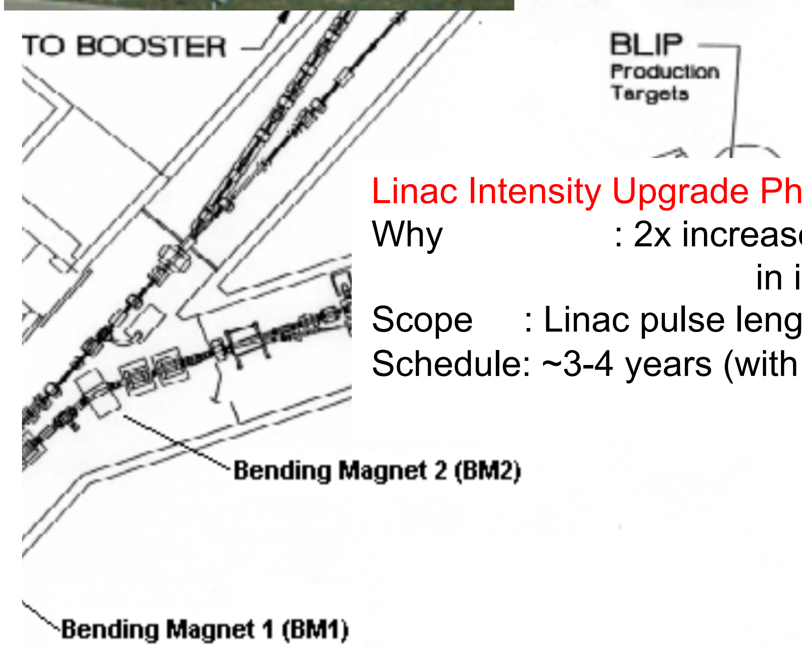
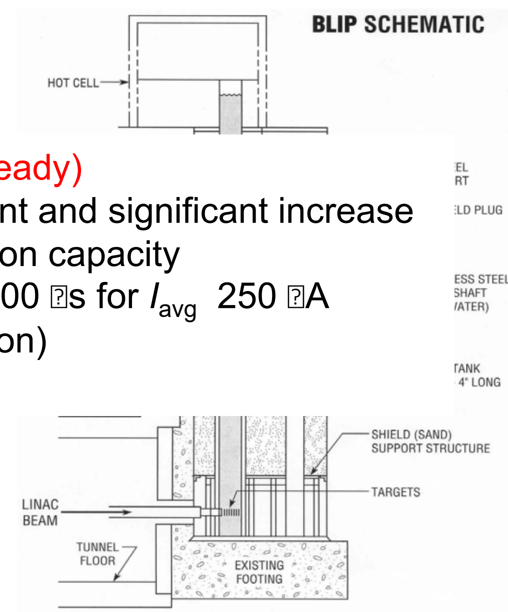


Linac Intensity Upgrade Phase II (shovel-ready)

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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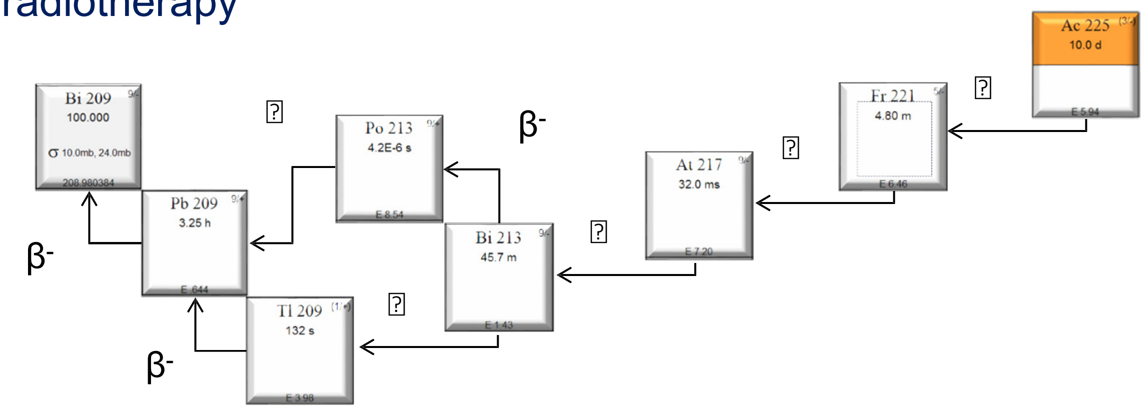
Alpha Therapeutic Agents

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***

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▯=440 keV, 27.3%

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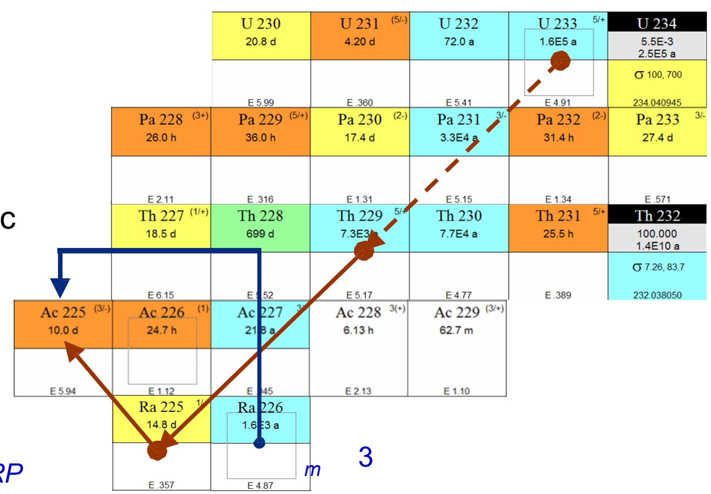
Pre-2013 ^{225}Ac production routes

- 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



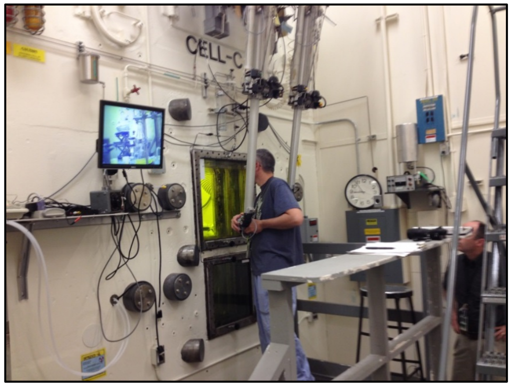
D. Medvedev. 2019 MIRP
Science and Tech targetry update

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



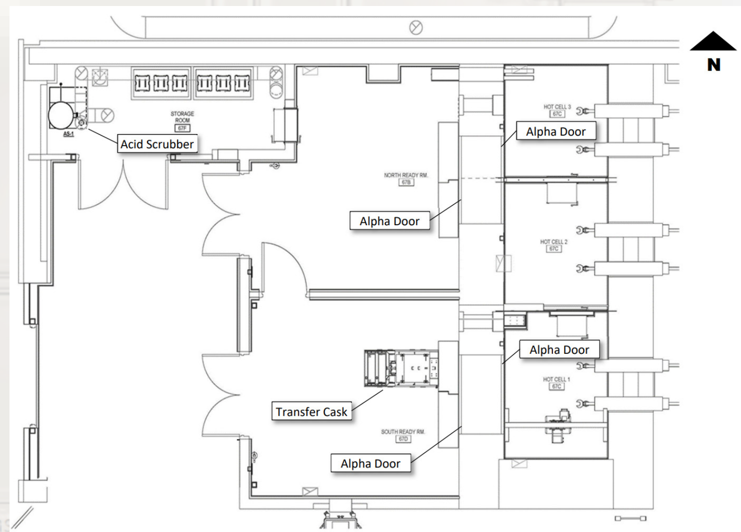
ORNL - Approximately 25 years of experience in the isolation of ^{225}Ac from fissile ^{233}U via ^{229}Th

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

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

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



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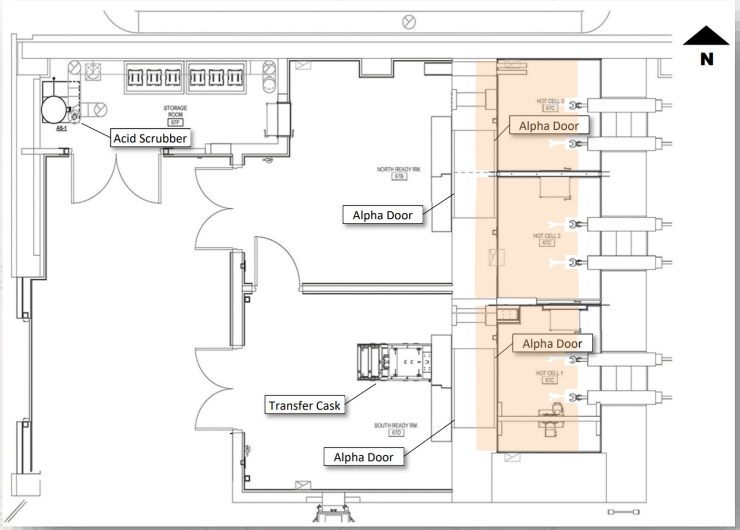

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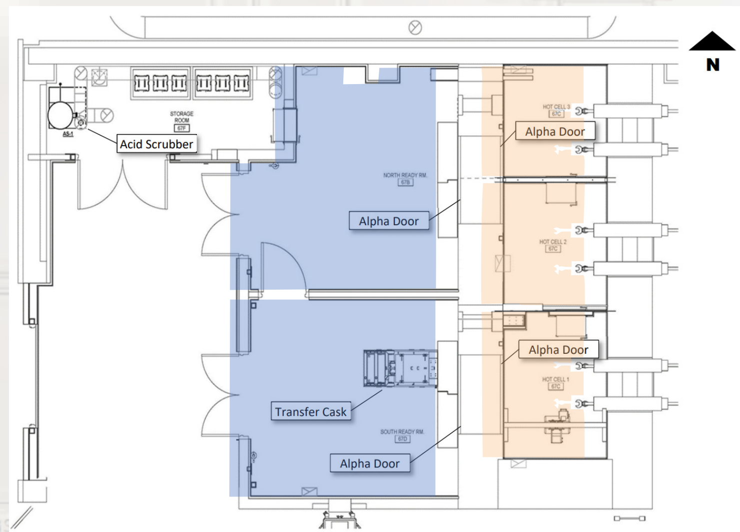

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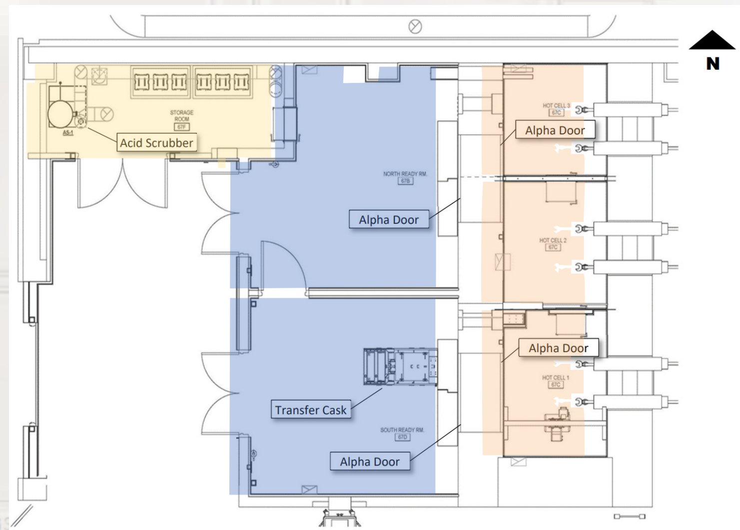

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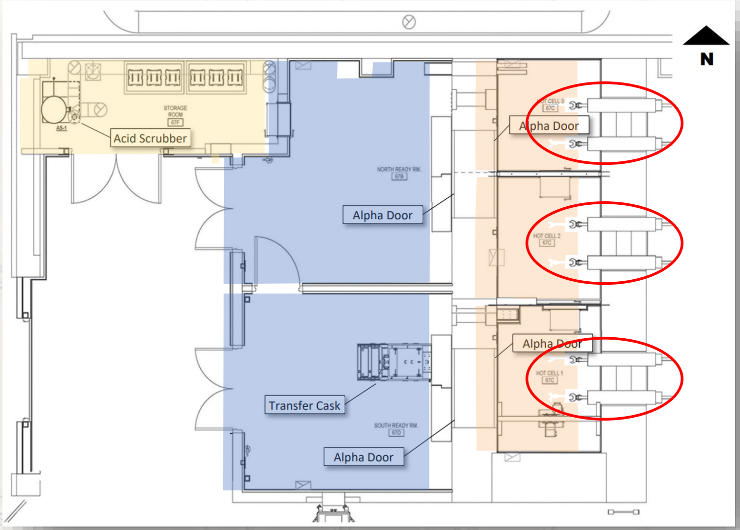

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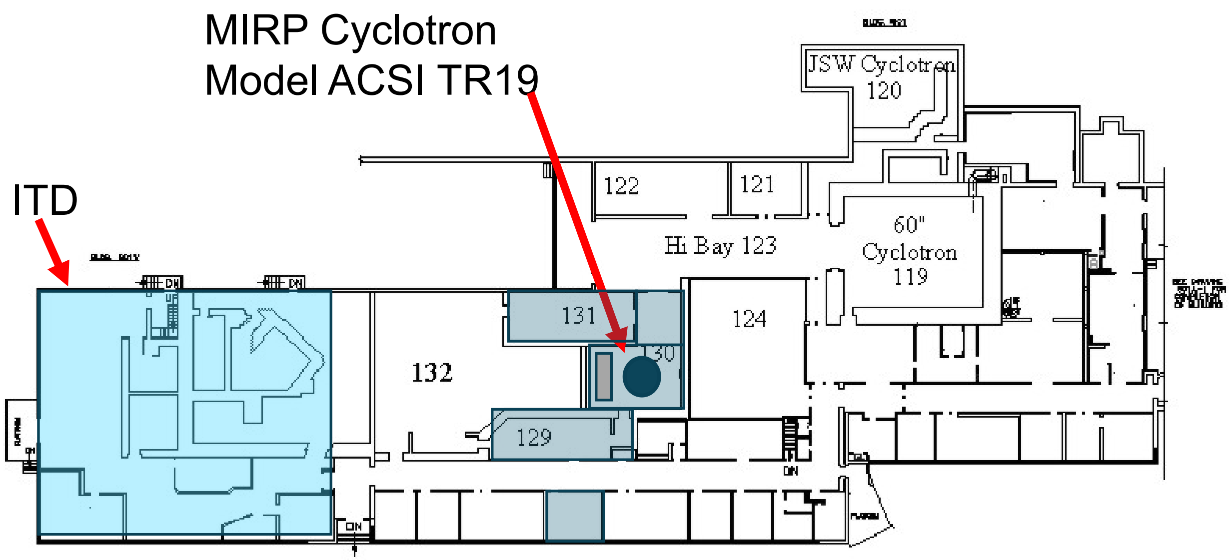
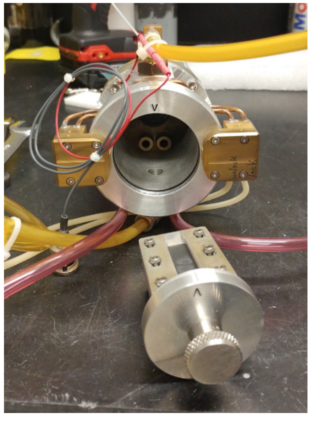
Cyclotron in Building 901



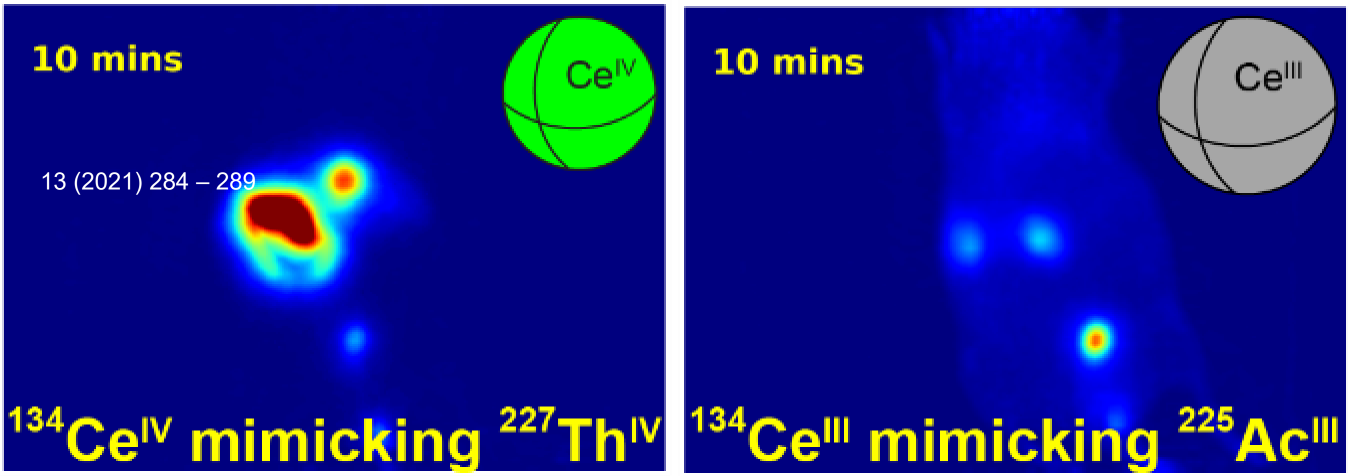
Low Energy Cyclotron

- 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



Brookhaven National Laboratory

^{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.

nature chemistry

ARTICLES

https://doi.org/10.1038/s41557-020-00598-7

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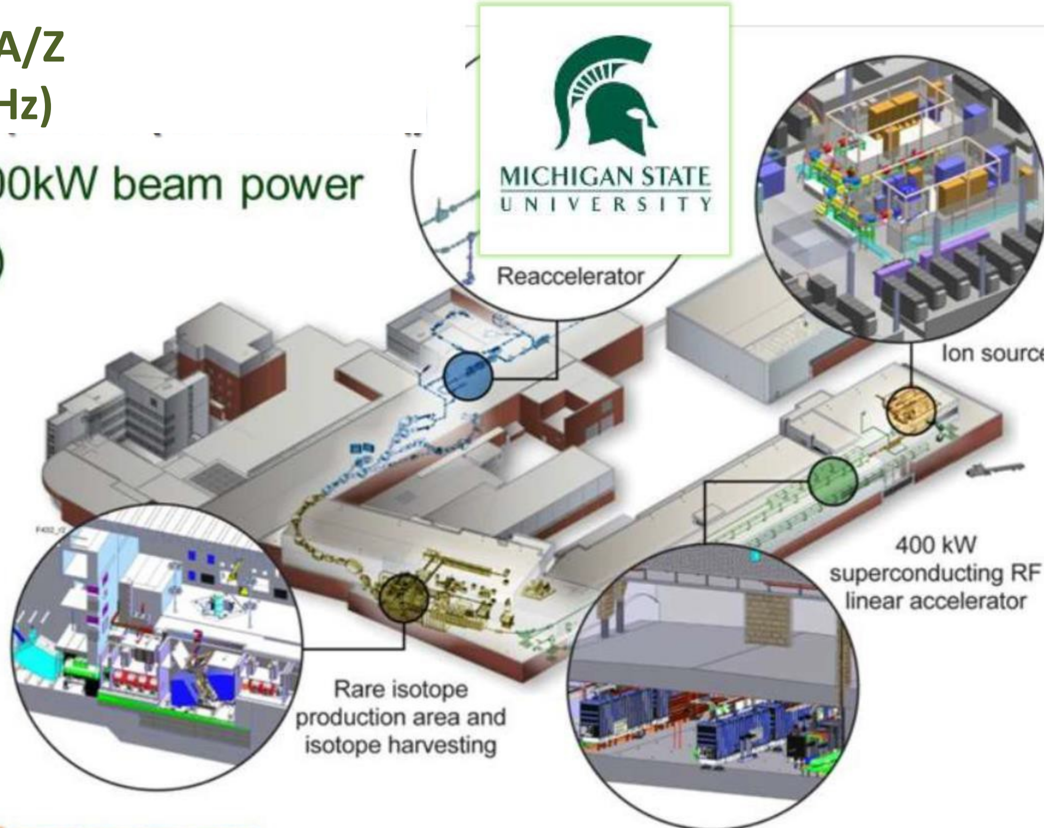
Brookhaven National Laboratory

Facility for Rare Isotope Beams (FRIB) -

- 200 AMeV, verity A/Z
  SC RF (80- 322 MHz)
- Key Feature is 400kW beam power
  ($5x10^{13}$ ^{238}U/s)

Apr. 2021:
all 46 CMs
212 MeV/u

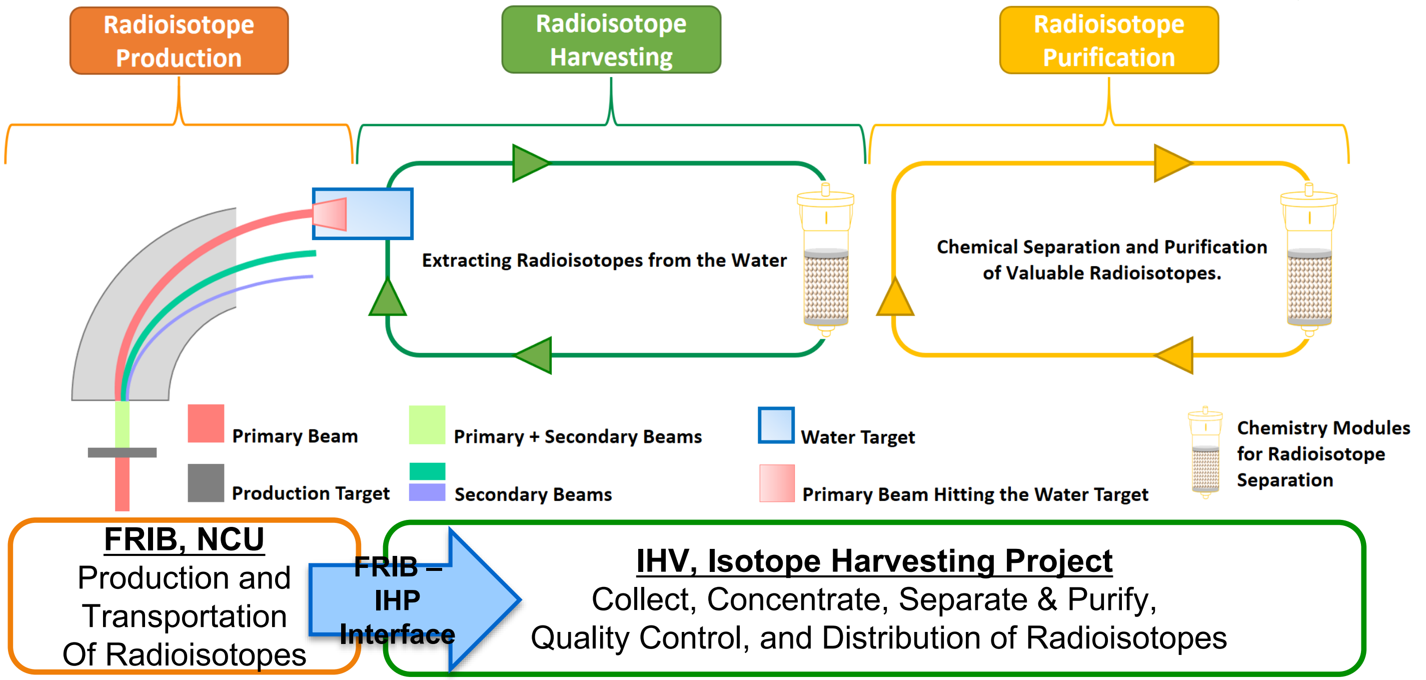


Separation of isotopes "In-flight"

Suited for all elements and short half-lives

Fast, stopped, and reaccelerated radioactive beams

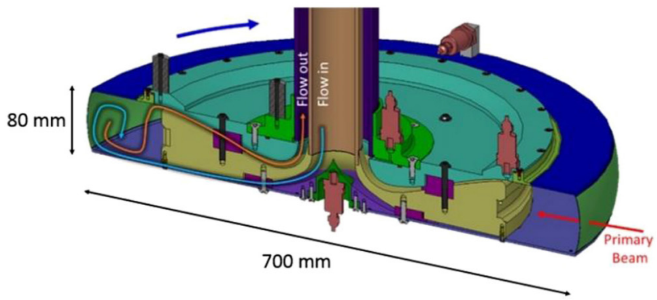
02 IHP OVERVIEW



High Level Requirements

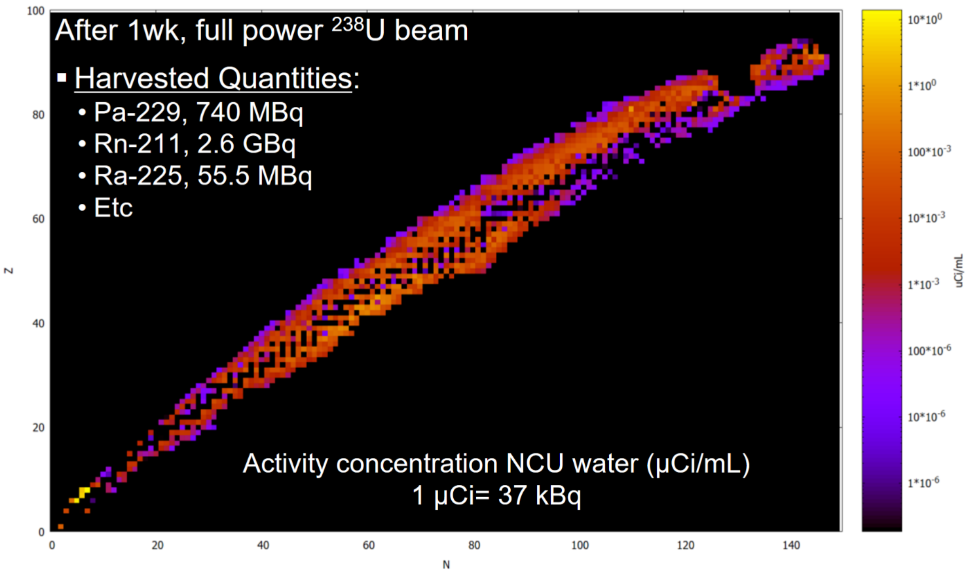
- Radioactive gas and water transportation: Piping and facility modifications
- Radioactive handling equipment and shielding: Radiation shielding, radiation monitoring, QA/ QC, controls

02 BEAM DUMP AND RADIOISOTOPE PRODUCTION



*FRIB Beam Dump

Ti–6Al–4V: low density, high strength, good corrosion resistance, and good fatigue performance
Primary ion beams: From ^{18}O to ^{238}U
Beam power: ~400 kW
Energy: 200MeV/u
Total volume of water: 7000 L



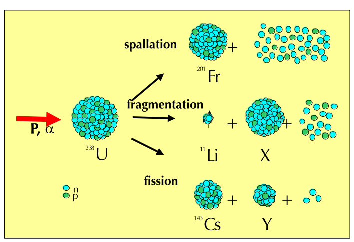
†Beams	^{48}Ca	^{64}Zn	^{78}Kr	^{238}U
†Radioisotopes	$^{47}Ca \rightarrow ^{47}Sc$	$^{62}Zn \rightarrow ^{62}Cu$	$^{77}Kr \rightarrow ^{77}Br$	$^{211}Rn \rightarrow ^{211}At$
†Production Rates of Mother	370.0 GBq/d	118.3 GBq/d	247.9 GBq/hr	15.9 GBq/d

*M. Avilov, A. Aaron, A. Amroussia, et al.; Thermal, mechanical and fluid flow aspects of the high power beam dump for FRIB; Nucl Instrum Methods Phys Res B; 376 (2016) 24–27.
†E. P. Abel, M. Avilov, V. Ayres, et al.; Isotope Harvesting at FRIB: Additional Opportunities for Scientific Discovery; J Phys G: Nucl Part Phys; 46 100501 (2019) 1 – 33.

How to supply “novel” radionuclides with mass separation

PRISMAP proposes to federate a consortium of high energy cyclotrons, research reactors, and isotope mass separation facilities in Europe.

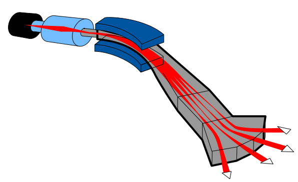
Accelerator



$I_{[pps]} \sim F_{[pps]}\, S_{[barn]}\, N_{[g/cm2]}$ production rate

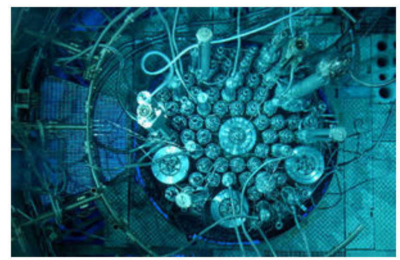
10^{10}pps 100µA (6.10^{14}) 1mbarn 1g/cm^2 for A_{target}=30g/mol

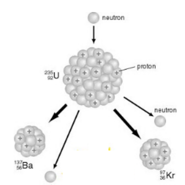
Isotope mass separation



$I_{[pps]} \sim F_{[pps]}\, S_{[barn]}\, N_{[g/cm2]}\, e_{[\%]}$

Research reactor





$$\frac{dN'}{dt} = nv\sigma_{act} N_T$$

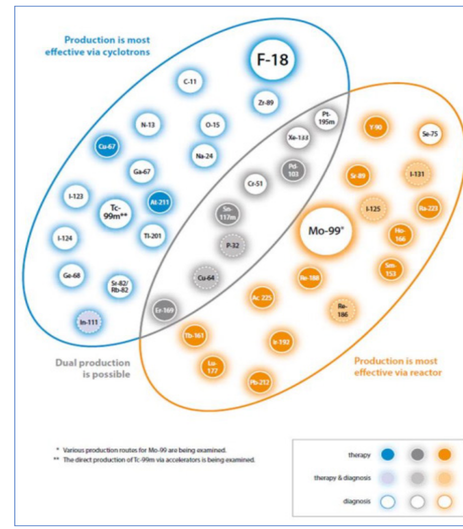


Figure 31 : Main medical radioisotopes production process

European Commission ENER/17/NUCL/SI2.755660 (2018)

Summary

Acceleratorsplay a huge role in supplying radioisotopes for a variety of applications.

Internationally the placing of small cyclotrons in remote areas increases patient access

The next stage of needed radionuclides such as alpha emitters require complex targetry, separations and facilities for their production

DOE is building facilities to enhance production and availability of stable and radioactive radionuclides.

National Laboratories around the world are enhancing their facilities to increase the energies they can provide as well as adding mass spec capabilities to provide isotopes that otherwise would not be available. These promise to dramatically increase availability to support applications work.