BNL Medical Isotope Research and Production Program

Cathy Cutler

April 13th, 2015

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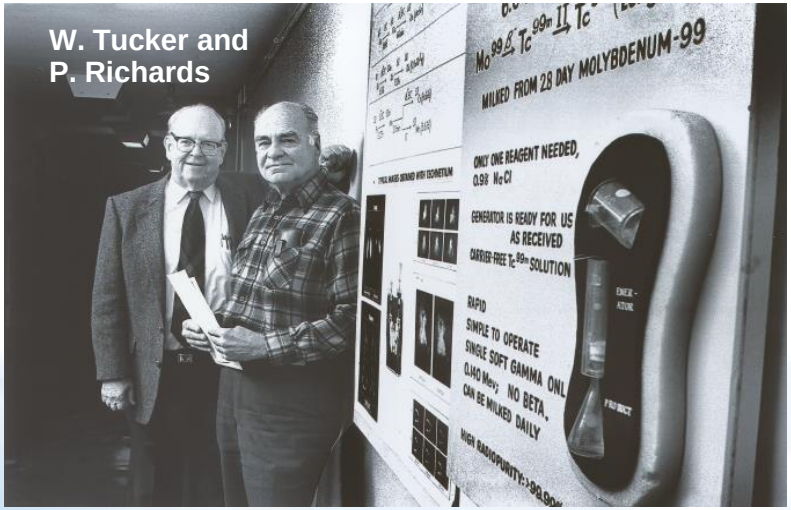
BROOKHAVEN NATIONAL LABORATORY

a passion for discovery

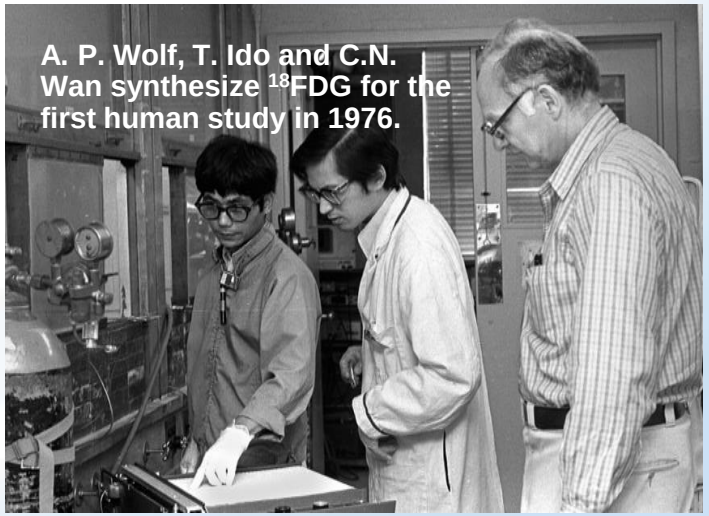
Office of Science

BNL is the Birthplace of Nuclear Medicine

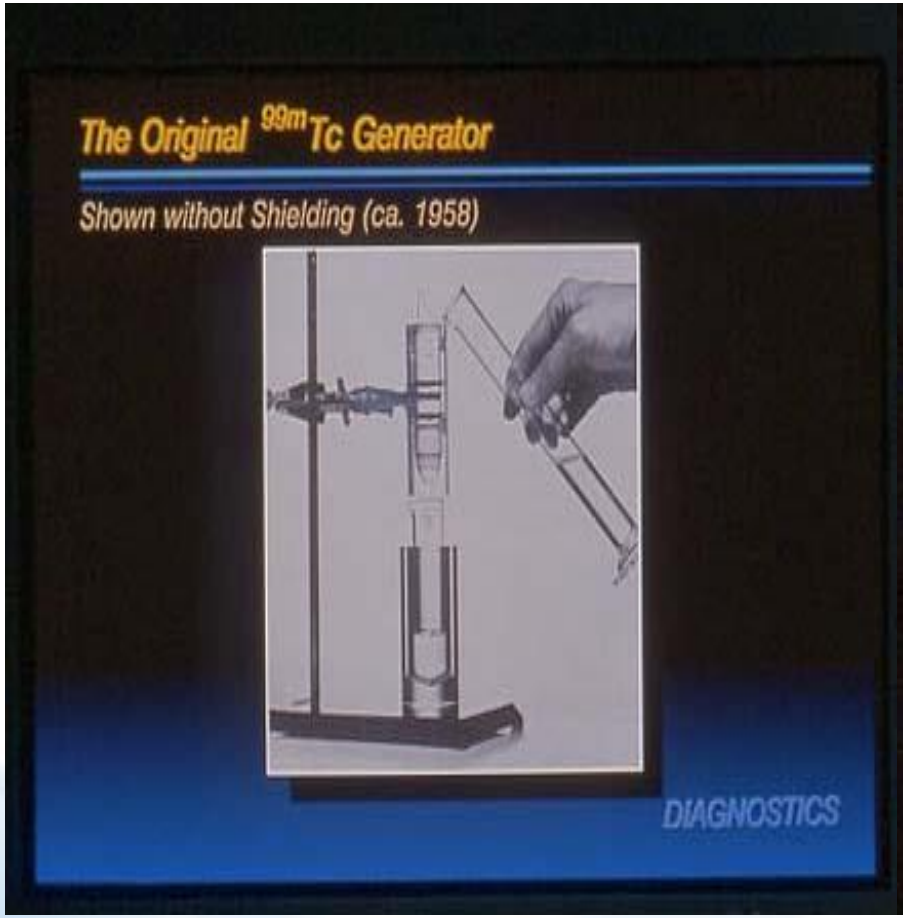
- 1950s: BNL scientists Walter Tucker and Powell Richards developed a generator system for producing Tc-99m and suggested its use for medical imaging. Tc-99m is now used in over 10 million patients/year in the U. S. alone
- 1970s: BNL pioneered the use of high energy proton beams for isotope production (BLIP)
- 1970s: 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

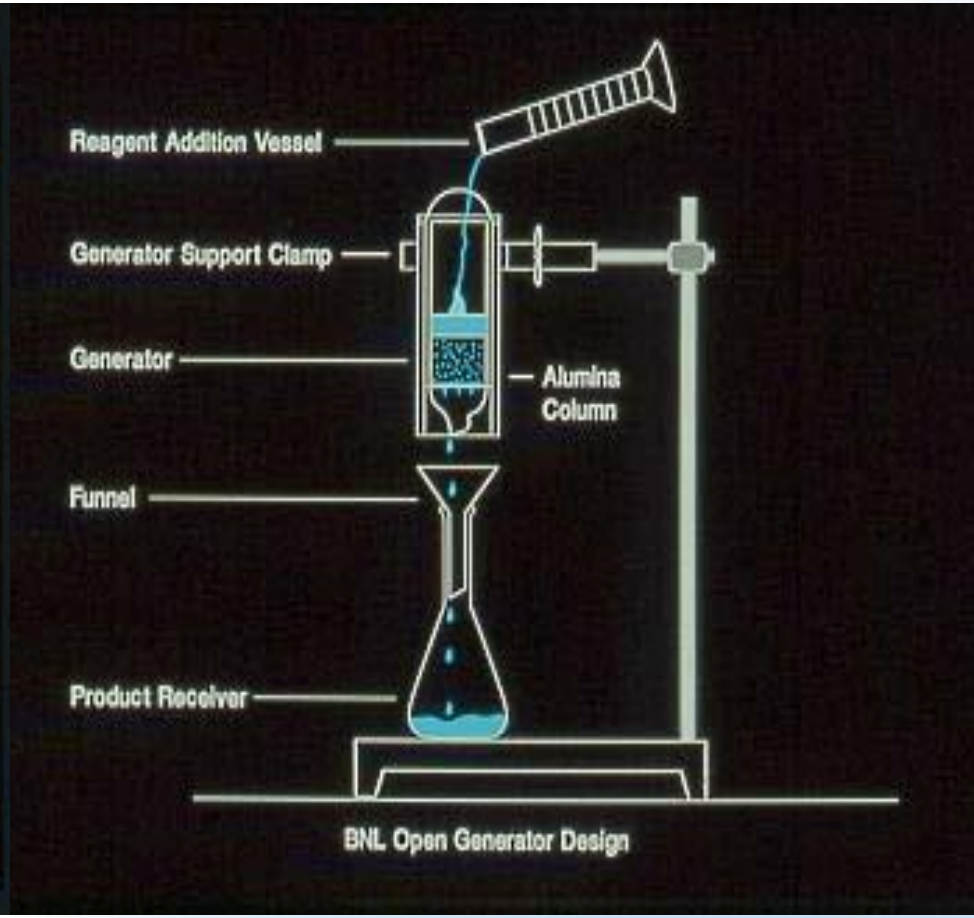


W. Tucker and P. Richards

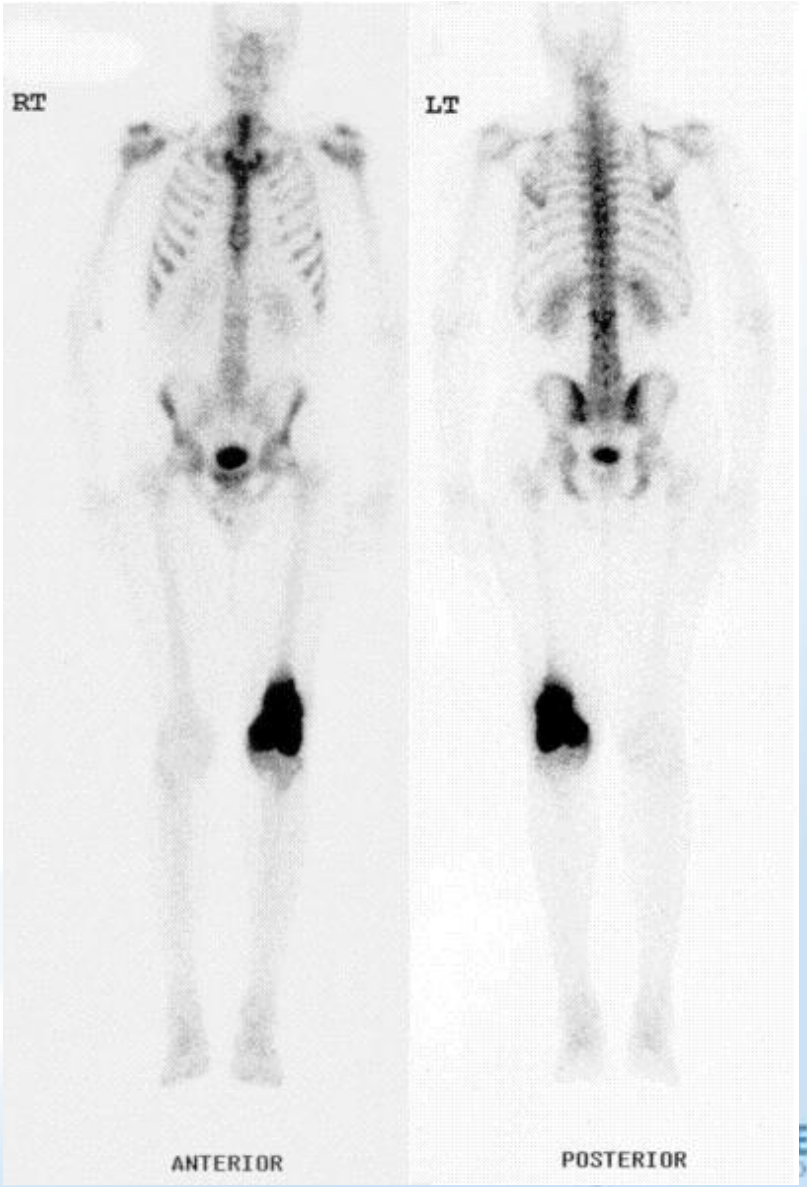

A. P. Wolf, T. Ido and C.N. Wan synthesize ^{18}FDG for the first human study in 1976.

BNL Open Generator Design: Column Chromatography



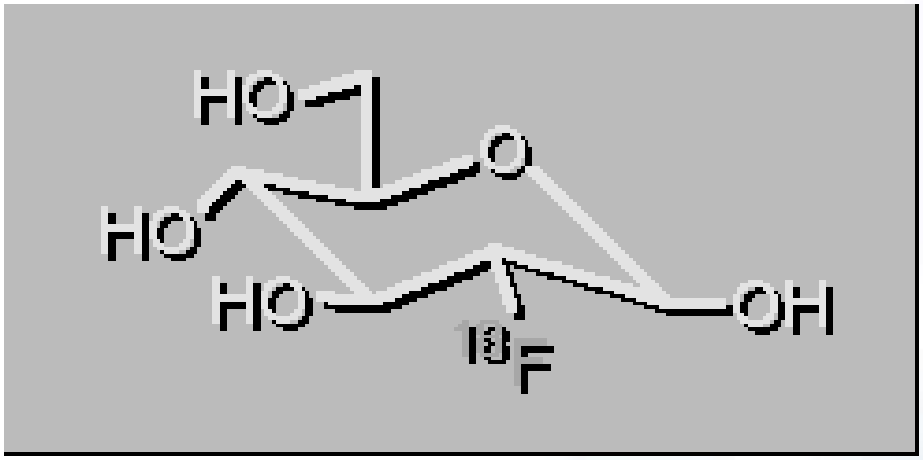


Anatomic vs Physiologic Imaging



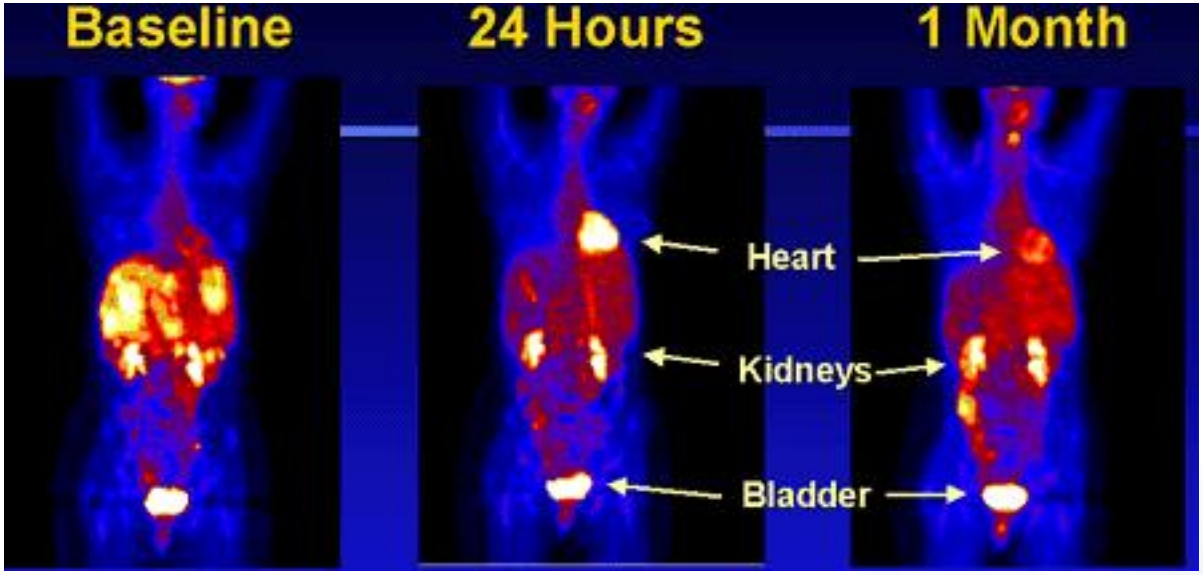
What Are Molecular Imaging Agents?

Molecular imaging agents are probes used to visualize, characterize, and measure biological processes in living systems.



- FDG is an analogue to glucose that easily crosses the blood-brain barrier and other highly selective membranes in the body

Before and after Gleevec: Monitoring Drug Success with FDG



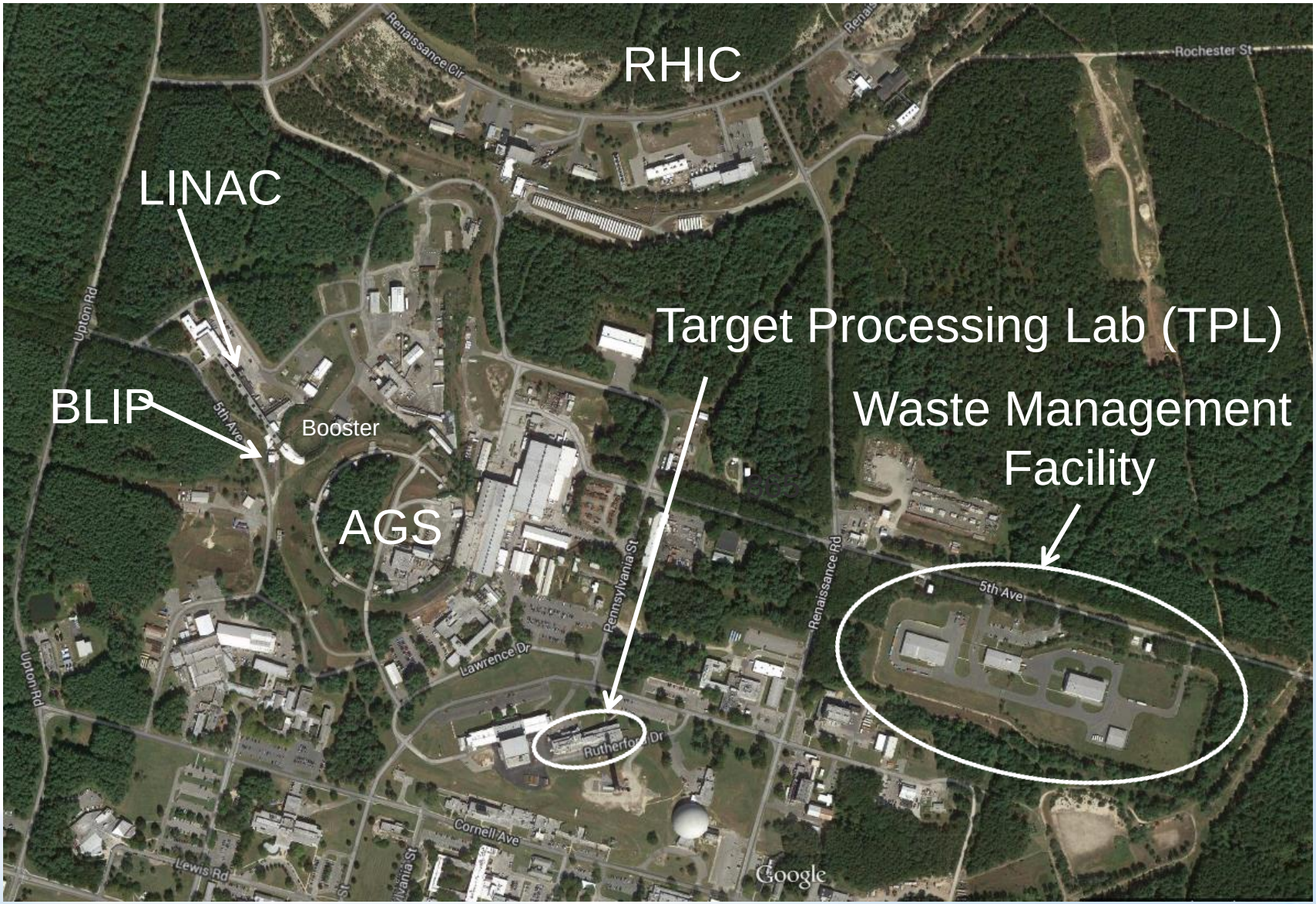
Isotope Program Missions

- Produce and/or distribute radioactive isotopes that are in short supply, including valuable by-products, surplus materials and related isotope services
- Maintain the infrastructure required to produce and supply isotope products and related services
- Conduct R&D on new and improved isotope production and processing techniques which can make available new isotopes for research and applications

Attributes:

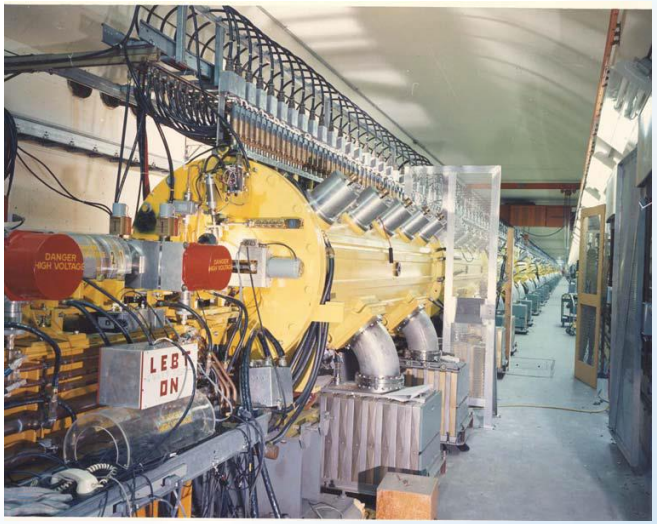
- Core R&D where there are programmatically stewarded activities
- Competitive R&D
- SBIR/STTR, Early Career Award Program
- Nuclear and Radiochemistry Summer School, Workforce Development

BNL Isotope Program - Aerial View



Brookhaven Linac Isotope Producer (BLIP)

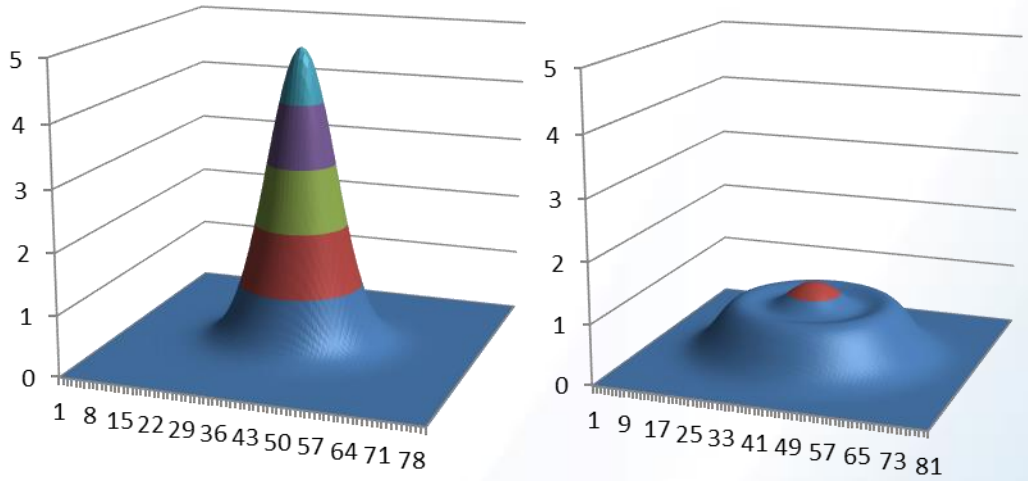
- First to use a high energy proton accelerator to produce isotopes (1972)
- BLIP utilizes the beam from the 200-MeV Linac that injects the Booster, which leads to AGS and RHIC accelerators (nuclear physics)
- Excess Booster pulses (~90%) are diverted to BLIP. Energy is incrementally variable from 66-202 MeV
- The BLIP beam line is a parasitic operation with nuclear physics programs for more cost effective isotope production
- In 2016, implemented beam rastering and increasing linac current to increase isotope production capabilities



BLIP Beam Enhancements

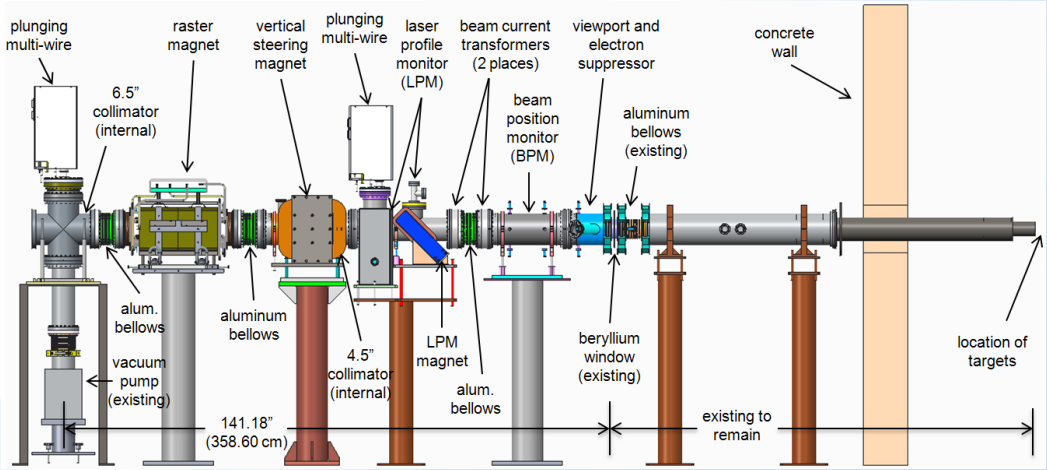
BLIP beam raster system

- 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

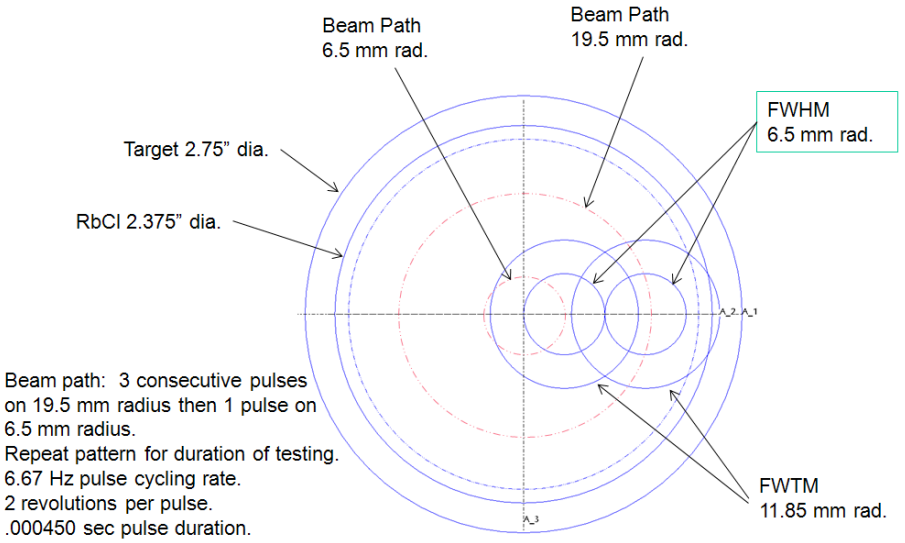


Linac intensity upgrade

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

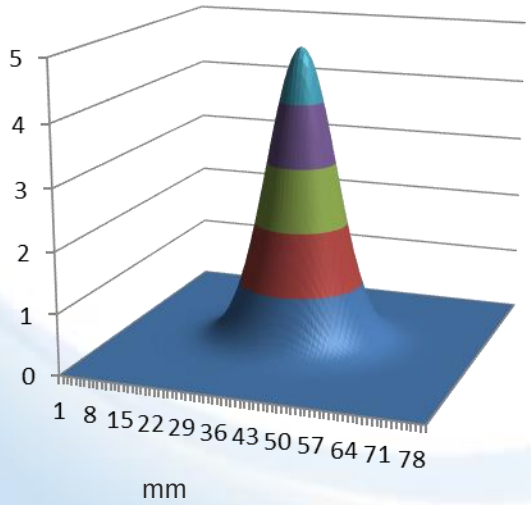


Raster motion and distribution on target (simulation)

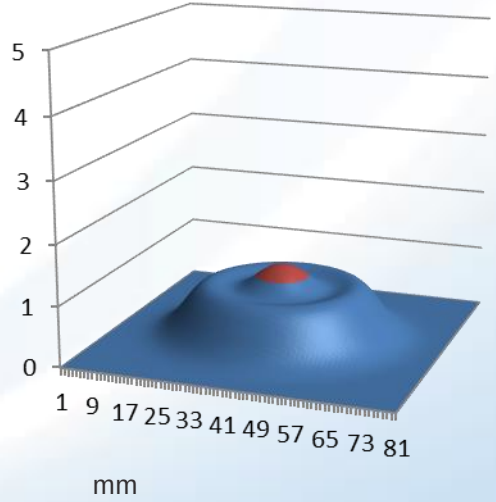


Beam path: 3 consecutive pulses on 19.5 mm radius then 1 pulse on 6.5 mm radius.
Repeat pattern for duration of testing.
6.67 Hz pulse cycling rate.
2 revolutions per pulse.
.000450 sec pulse duration.

Total number of protons is the same for both plots



Beam distribution without raster

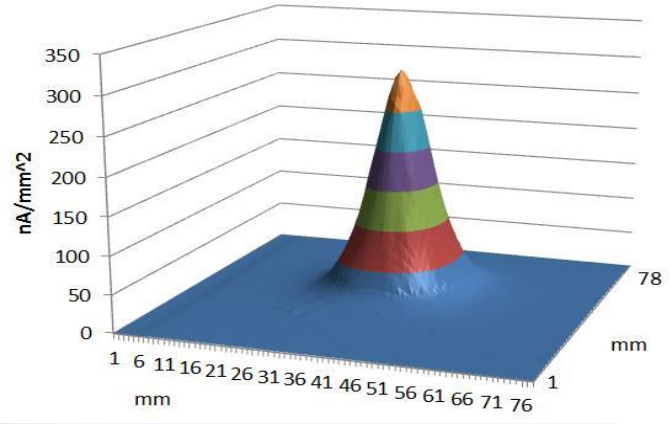


More uniform beam distribution with raster is expected

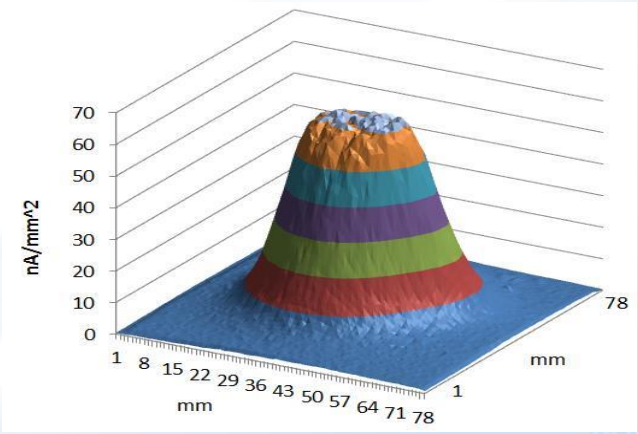
Raster Project Status

- The system was available for operations earlier than planned
- System commissioning with beam began December 16, 2015
- Isotope production with the raster began January 4, 2016
  - Increased yields are higher than expected
- All required performance parameters have been achieved

Beam profile without raster: FWHM 13mm, FWTM 40mm



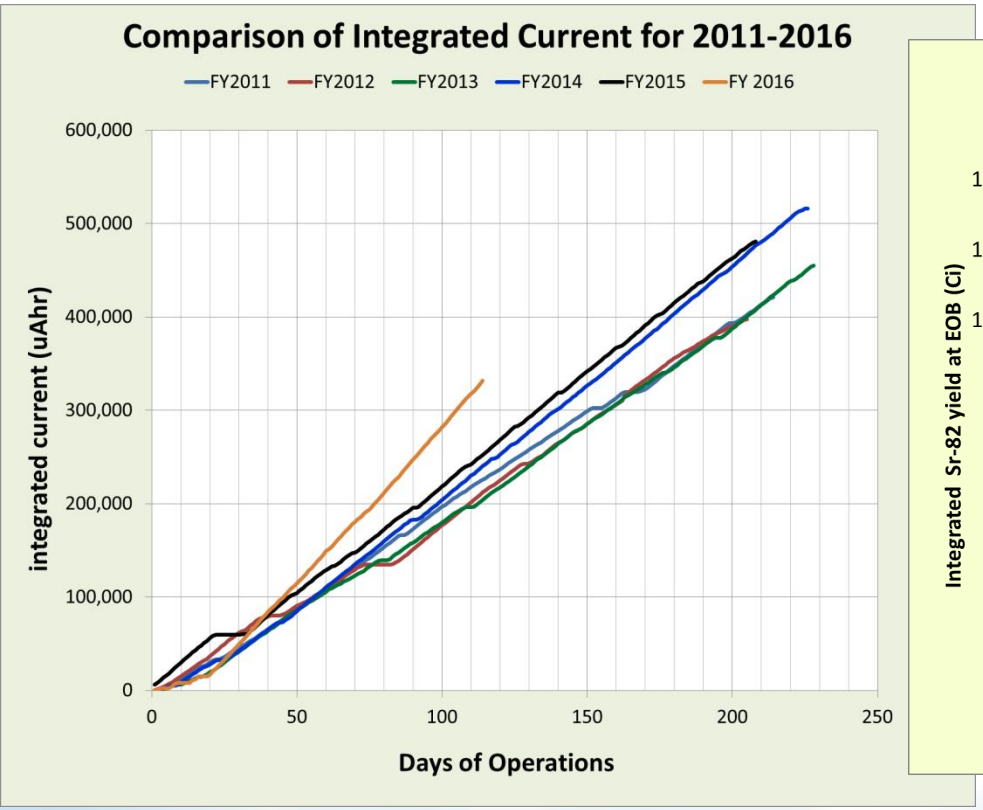
Beam profile with raster: FWHM 32mm, FWTM 60mm, power density reduced ~5 fold

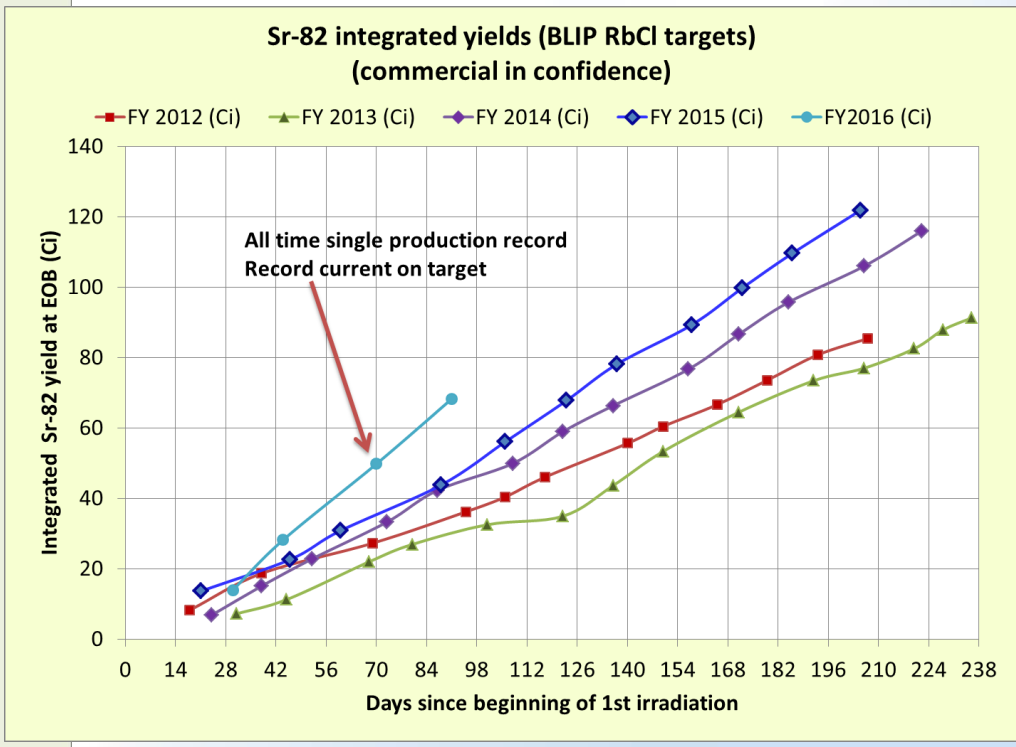


BLIP/TPL Performance

FY 2016 performance is with AGS operational for pp running for RHIC

- The Linac Intensity Upgrade project was partially completed during the last shutdown, ***165 μA available to the programs***
- Present BLIP current is limited to 165 μA with raster



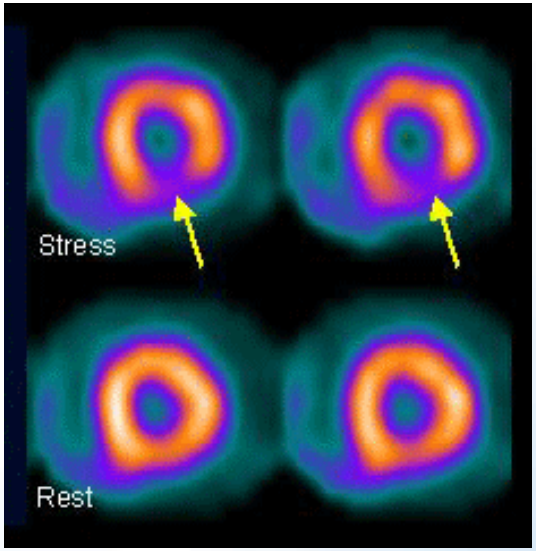


Sr-82 Application

$^{82}Sr/^{82}Rb$ generator

- Rb is a potassium mimic taken up in viable cardiac muscle tissue
- ^{82}Rb generator can be used at facilities without a cyclotron
- $^{82}Sr/^{82}Rb$ generator can be used for at least a month
- ^{82}Sr can only be made with high energy protons
- The generator is typically loaded with 100 mCi (3.7GBq) of ^{82}Sr
- Patient Dose: 30-60 mCi of $^{82}RbCl$

Hundreds of thousands of patients are now imaged annually in the US and the demand is growing



Coronary Artery Disease

$^{82}RbCl$ used under rest and hyperemic (pharmacological) stress conditions

cGMP – current Good Manufacturing Practice

- Doing It Right and
- Documenting It!

Good Manufacturing Practices ensure:

- safety
- consistent ***quality*** of drug/drug component characteristics:
  - identity
  - strength
  - purity
- freedom from contamination

Elements of cGMP Control

- Organization
- Personnel
- Training
- Documentation
- Building and Facilities
- Equipment
- Preventive maintenance
- Purchase, receipt and control of raw materials
- Work-in-Progress (WIP) and Finished-Goods (FG) control
- Warehousing
- Distribution
- Quality Assurance/Quality Control labs
- Methods validation
- Qualification

FY2016 Audits

- Internal Audit Jan. 12-13th
  - 4 findings
- FDA Audit Jan. 26-29th
  - One observations – Voluntary Action Indicated (VAI) - corrective action was completed
  - Establishment Inspection Report indicating close out of the audit has been received
  - Overall, MIRP did very well for our 1st official FDA audit
- Bracco (external customer) audit Mar. 29 – Mar. 30
  - 3 findings

Alpha Therapy in Practice: ^{223}Ra

Xofigo (radium-223 dichloride, Bayer)- First FDA Approved Alpha Therapy Agent in 2013

Ra-223 ($t_{1/2}$ = 11.43 d; multiple α particles between 5-6 MeV)

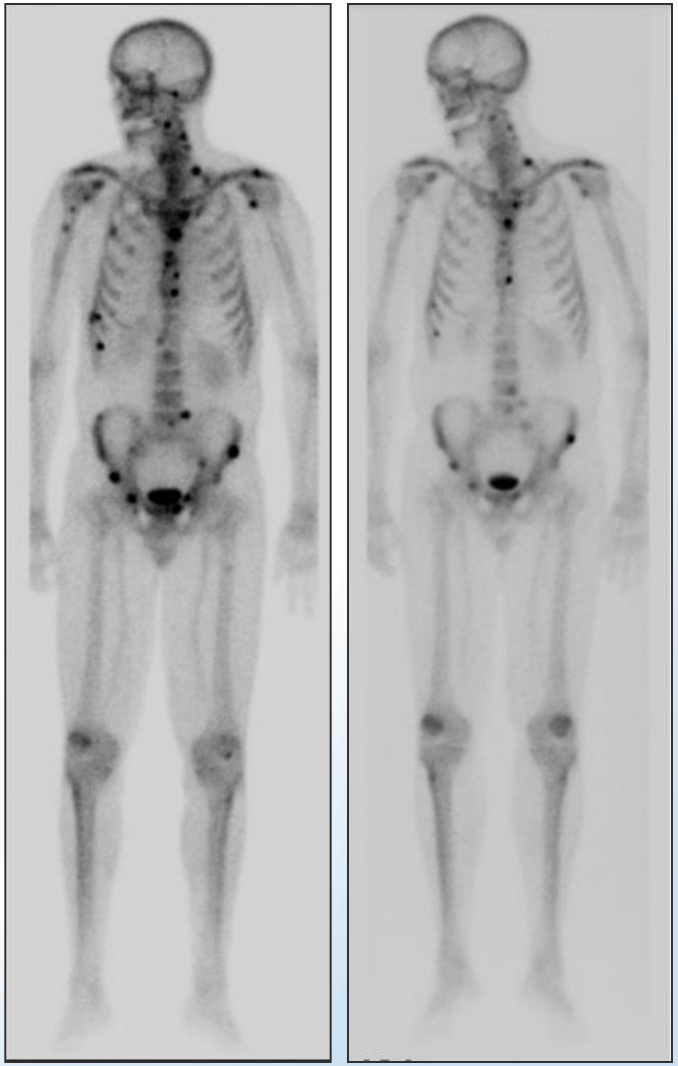
Used to treat bone metastases in end-stage prostate cancer

-Radium is preferentially absorbed by bone by virtue of its chemical similarity to calcium

-Naturally targets new bone growth in and around bone metastases

Therapeutic effect is largely palliative, it is not targeted

Paves the way for other alpha therapy agents!

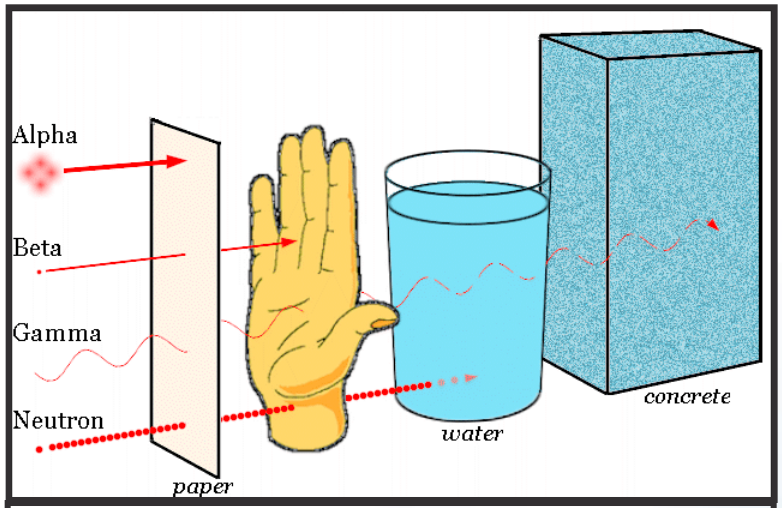


Targeted Alpha Therapy in Theory

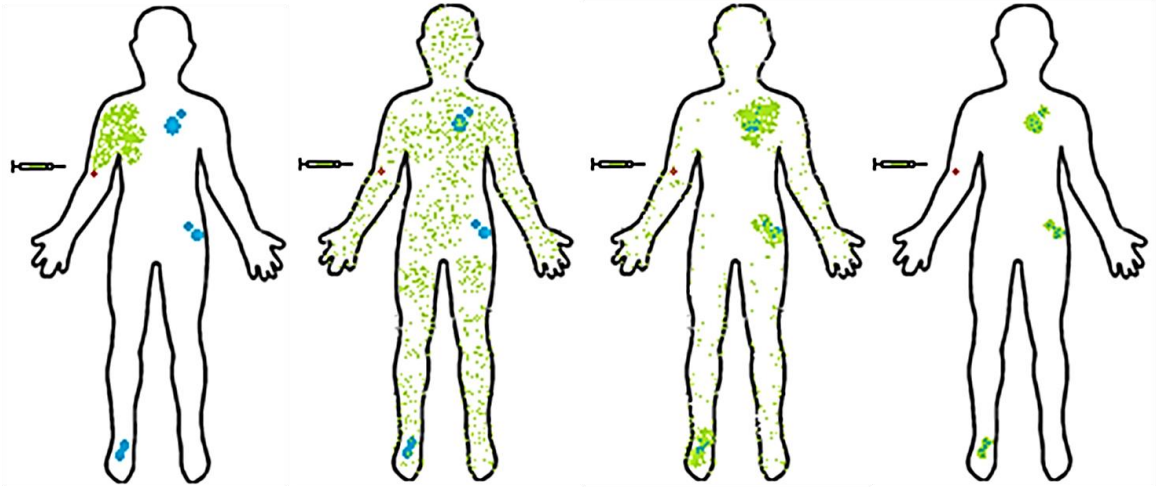
"High-linear-energy α-particle emissions create dense ionization paths in tissue that render high target-to-nontarget dose ratios that are highly effective at cell killing"

George Sgouros, SNNMI-MIRD, 2015

The properties of α-emitting isotopes make them well suited for treatment of cancer



Range and effects of alpha, beta, gamma and neutron radiation



1.The targeted radioligand is administered systemically to the patient.

2.The radioligand distributes throughout the patient.

3.The radioligand localizes and concentrates in target tissues (e.g. tumors) reducing radiation dose to non-target normal tissues.

4.The radioligand is retained within the target tissues (tumors) to selectively deliver cytotoxic doses of radiation.

Ac-225 Application

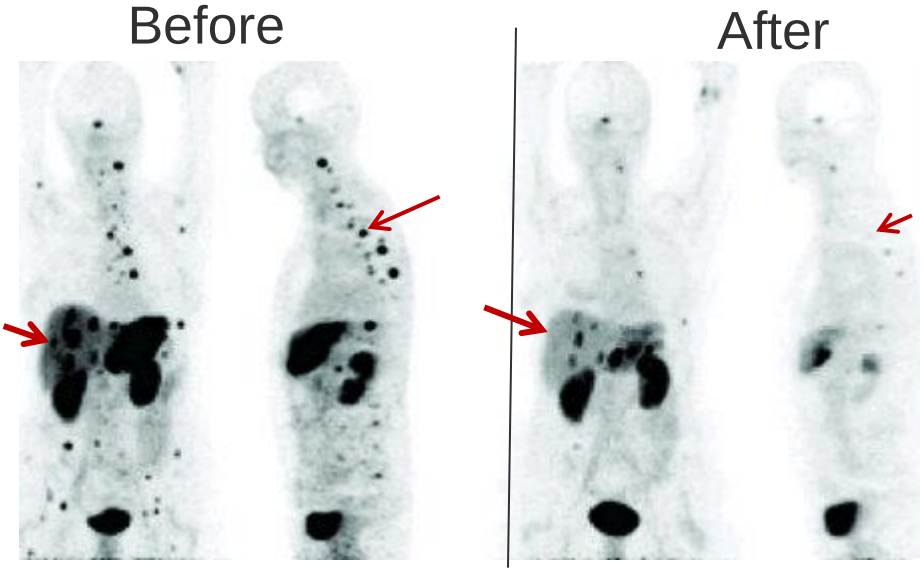
- Ac-225 is recognized as the highest priority α-emitter
- Ac-225 production is recognized as top research priority

Radiopharmaceutical Source	Mechanism	Patient Dose
^{225}Ac	Four alpha emissions when ^{225}Ac decays to ^{209}Bi and is retained by the target	~25-400 µCi / patient for therapy
^{213}Bi from $^{225}Ac/^{213}Bi$ generator	One alpha emission when ^{213}Bi decays to ^{209}Bi and is retained by the target	Each ^{225}Ac generator: 100-150 mCi could treat dozens of patients ^{213}Bi: ~75 mCi / patient for therapy

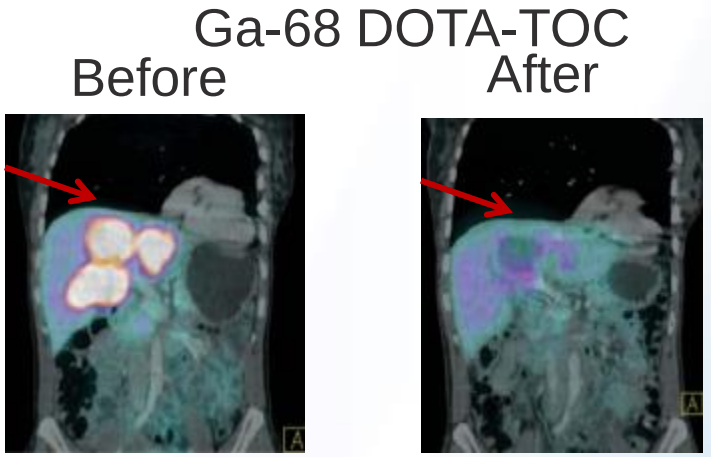
  - Treated a patient with prostate cancer
- BNL has potential to fill 99% gap in Ac-225 availability

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

SNMMI press release June 11, 2012
(alpha therapy worked when beta therapy failed)



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



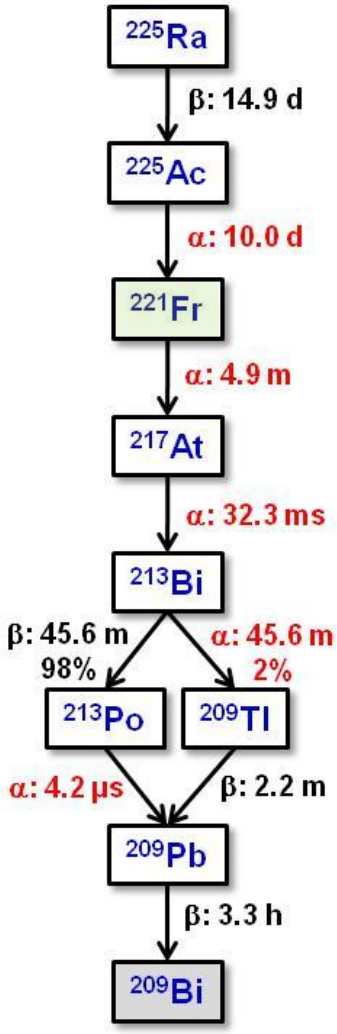
Case II: Response of multiple liver lesions after i.a. therapy with 14 GBq ^{213}Bi DOTA-TOC

- 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

Accelerator-Produced Ac-225 for Targeted Therapy



- Clinical data suggests both α-emitting Ac-225 ($t_{1/2}$ 10 d) and its daughter, Bi-213 ($t_{1/2}$ 45.6 min) will be powerful isotopes for targeted alpha therapy for cancer
- Current world-wide, annual supply is 1.7 Ci/yr
  - 50+ Ci/yr required to support expanded clinical trials and drug development
- Developing novel accelerator-production method to address demand
  - Working with clinical sites to evaluate material

ORNL Final Ac-225 Product

BROOKHAVEN NATIONAL LABORATORY | OAK RIDGE National Laboratory | Los Alamos NATIONAL LABORATORY EST. 1943

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Ac-225 Progress

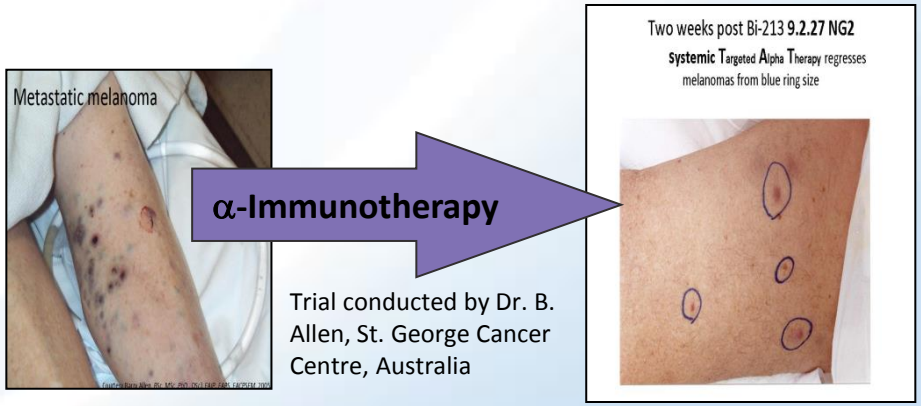
Stage 1 – Feasibility of Production/Use

- ITG tested accelerator-produced Ac-225 on generator
  - Treated a patient with prostate cancer
- Subcontractor to test toxicity and dosimetry
  - Assess impact of Ac-227 ($t_{1/2}$ = 22 yrs) impurity on direct use
- BNL will supply the material
  - Feb-July 2016

Stage 2 – Scale-Up

Stage 3 – Clinical Trials

- Generator use will require QC that is less or similar to Sr-82
- Need to implement rigorous QC for direct human use



Trial conducted by Dr. B. Allen, St. George Cancer Centre, Australia

Accelerator Production of ^{225}Ac: Initial R&D Promised Significant Impact

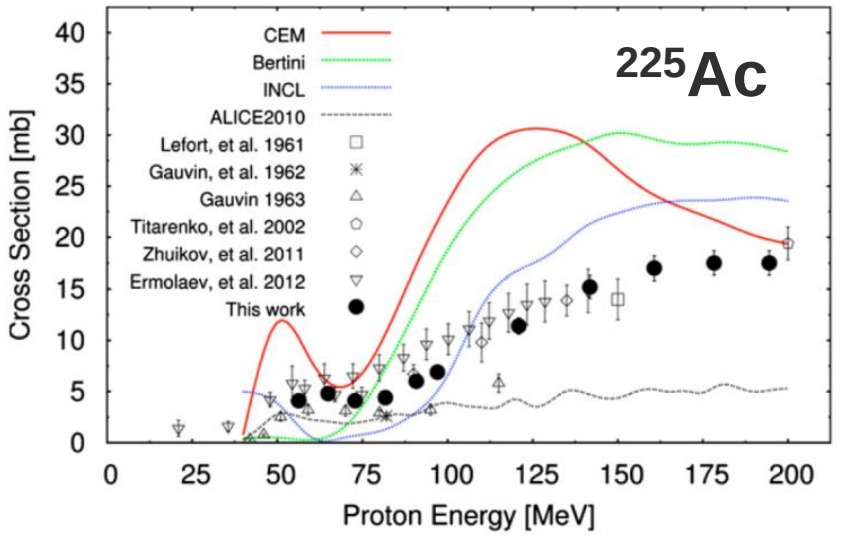


Fig. 1. Experimental and theoretical cumulative cross sections for the formation of ^{225}Ac by the proton bombardment of thorium.

Anticipated Thick Target Yields	5 g/cm^2 target yield for a 10 day irradiation
	Ac-225 (Ci)
IPF (250 μA)	1.4
BNL (100 μA)	2.0

J.W. Weidner et al. Appl. Radiat. Isot. 70 (2012) 2590
J.W. Weidner et al. Appl. Radiat. Isot. 70 (2012) 2602
J.W. Engle et. al. Phys. Rev. C. 88 (2013) 014604
J.W. Engle et. al. Radiochim. Acta 102 (2014) 569

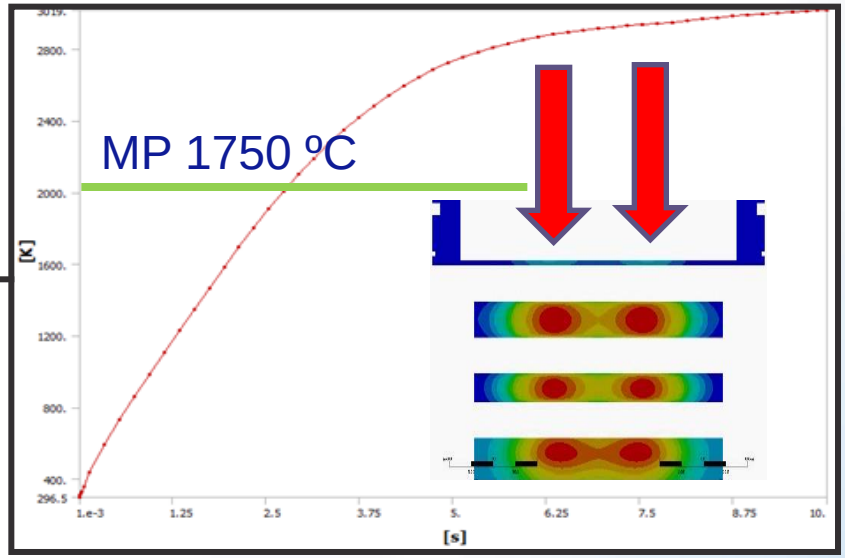
^{225}Ac yield curve based on measured cross sections show that Ci-scale production is feasible at LANL and BNL

Initial Focus on R&D to Define Technical Risks Unique to Accelerator Production: Production Targetry

In order to realize the production potential defined by our cross section measurements, we must design targets capable of withstanding the proton beams delivered at IPF and BLIP.

Approximately 5-7 kW of power deposited in each target. Power densities are capable of melting Th-metal (m.p. = 1750.0 ° C)

Focus on optimization of thermal contact between Th target material and target cladding.



Ac-225 Progress at BNL

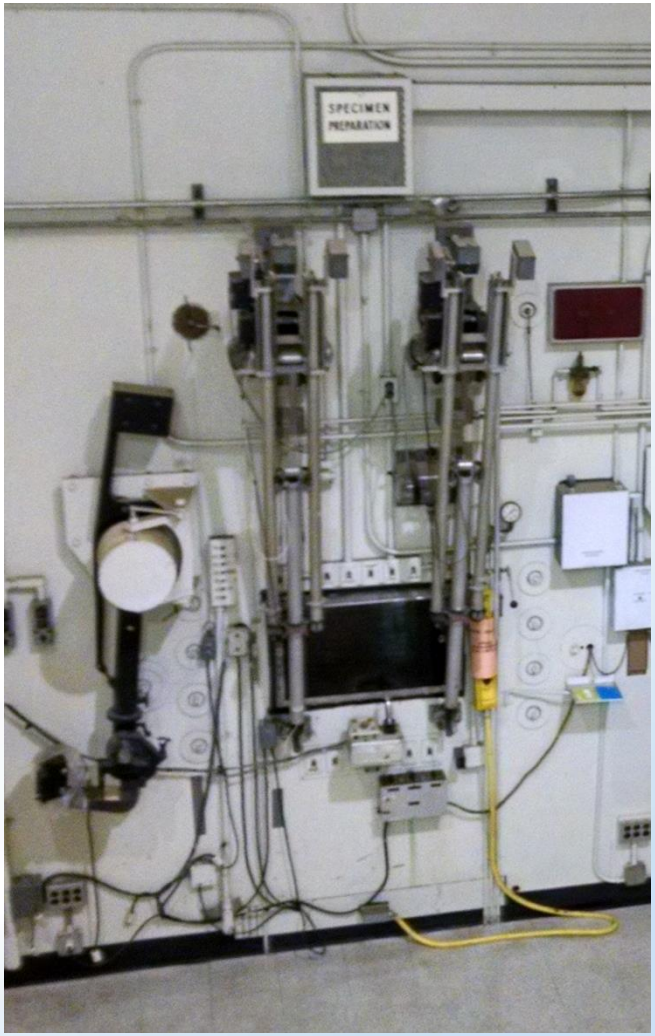
- Part of tri-lab effort to utilize 200 MeV accelerator to irradiate Th to produce Ac-225
- Currently not approved to process an irradiated Th foil or Th target at BNL
  - Targets are processed at ORNL
  - BNL approved work is with less than 1 mCi of Ac-225 in a HEPA/Charcoal vented glove box

What is needed for processing a proton irradiated Th target at BNL for Ac-225 production

- Safety approval
- Waste management considerations
- Potential facility upgrades
  - Dedicated hot cells with charcoal filtration
  - Dispensing hood or glove box to handle final product
  - Ac-225 target opener
  - ***General Infrastructure funding***

GPP Funding for Facility Upgrades

- Sent proposal to DOE on Apr. 1
- $8.4M for MEL hot cell upgrades for Ac-225 production
  - Deconning and refurbishing MEL hot cell interior
  - Retrofitting ventilation
  - Upgrading air quality
  - Refurbishing manipulators and lead glass windows
  - Installing new electrical wiring
  - Purchasing and installing radiation-resistant cameras



Summary

- Completed all FY2015 ATS
- We are progressing well towards full cGMP compliance
  - Validations
  - Stability Study program
  - Dedicated facilities for Sr-82 production
- We are developing long term plans that integrate thorium processing in with a fully cGMP compliant Sr-82 production
- Evaluating new and improved product lines for MIRP

Future Plans

cGMP compliance

- Continue to upgrade facilities
- Work closely with Isotope program
- Risk Analysis

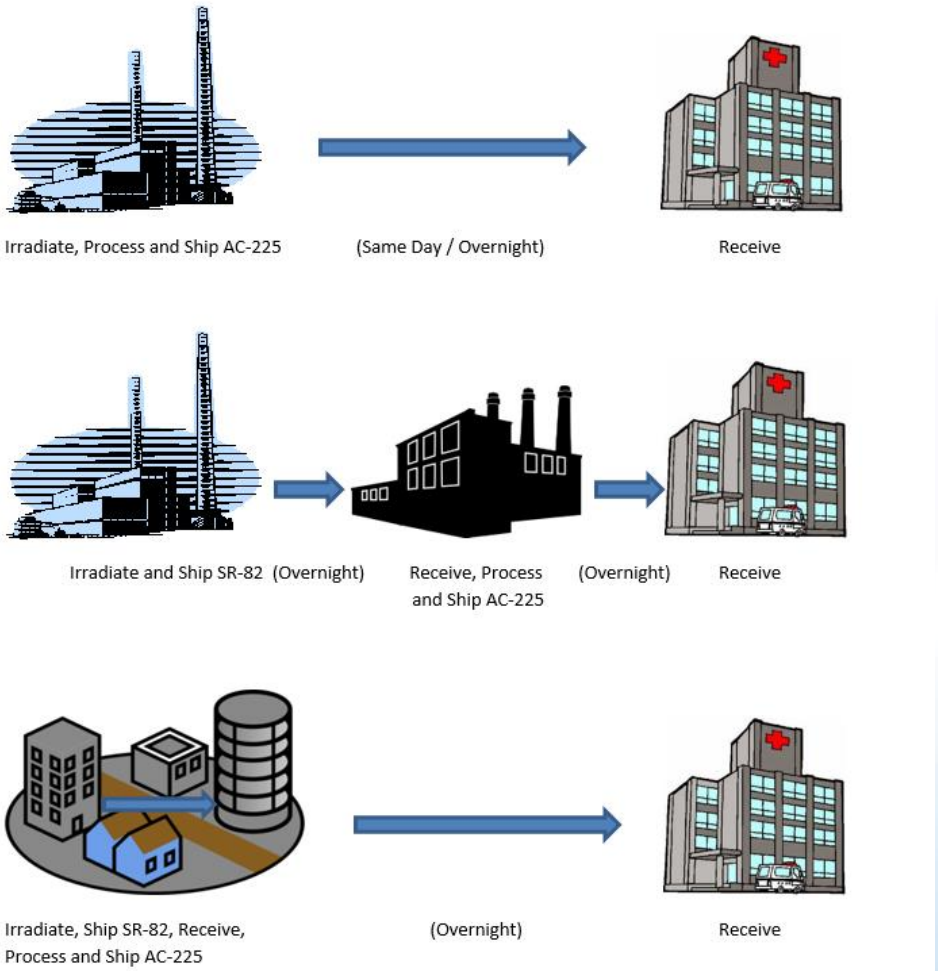
Future Processing

- Processing of Thorium Targets
- Increase beam Intensity
- Setup second beamline
- Evaluate new targets for C and N slot

Research

- Increase R&D on production and separations
- Establish more external collaborations
  - Hunter College, Lehman College
  - Sloan Kettering, Stony Brook
- Work Development NRT, DOE IGERT

Why BNL


Irradiate, Process and Ship AC-225
(Same Day / Overnight)
Receive
Irradiate and Ship SR-82
(Overnight)
Receive, Process and Ship AC-225
(Overnight)
Receive
Irradiate, Ship SR-82, Receive, Process and Ship AC-225
(Overnight)
Receive

BNL Thorium Processing

- cGMP
- Transportation onsite
- Accelerator Production Facility
- Cost effective
- Cross section higher at 200 MeV
- Minimal Ac-227 impurity
- Shipping containers available for purified material
- Less decay lost
- Load multiple targets
- Lower impact on Sr-82 production