BNL Medical Isotope Research and Production Program

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70 YEARS OF DISCOVERY

A CENTURY OF SERVICE

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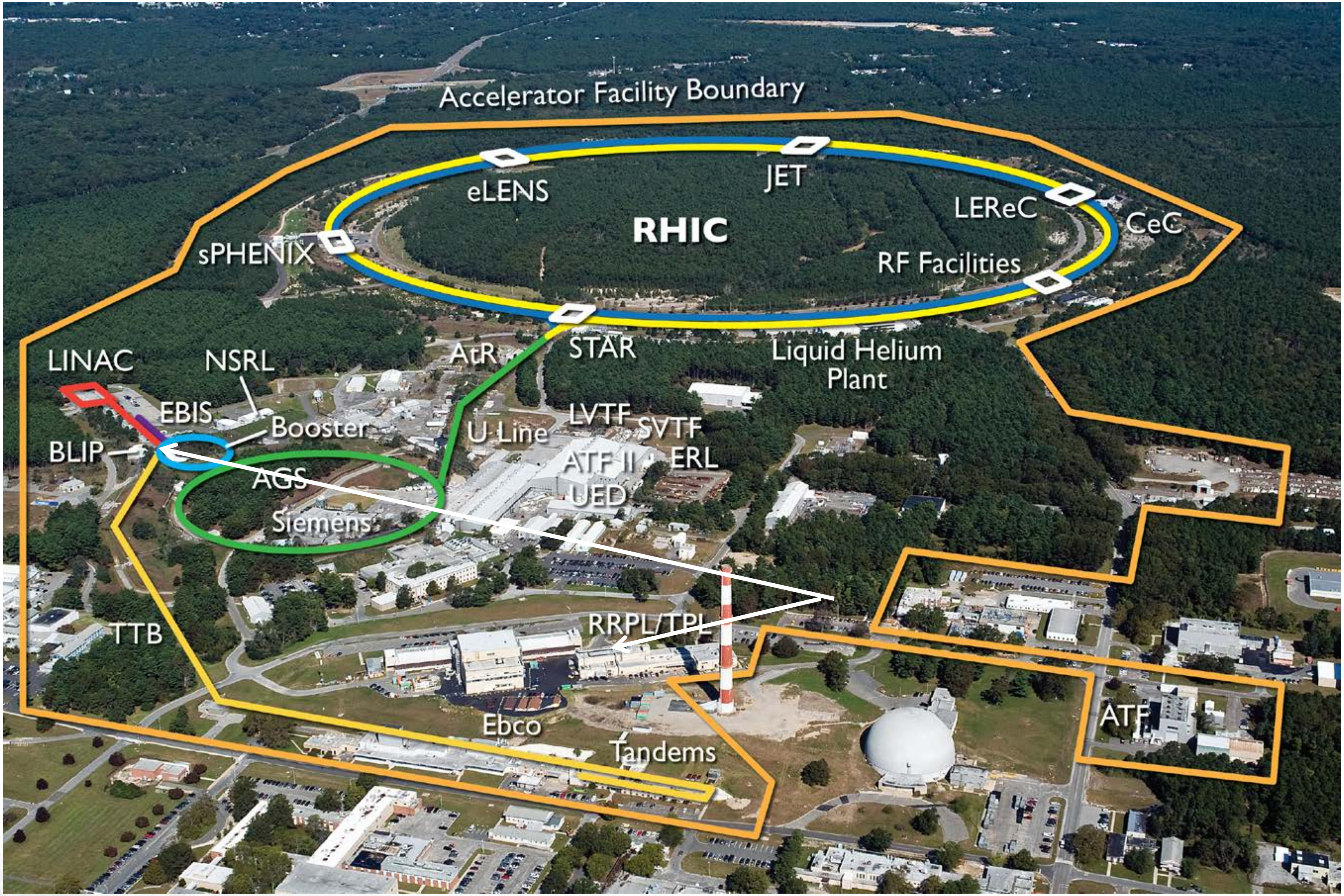
Isotope Program Missions

- 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

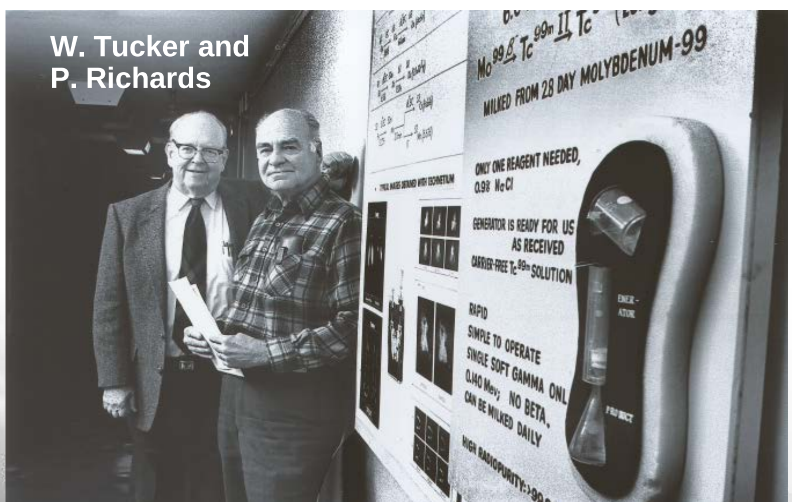
Attributes:

- 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

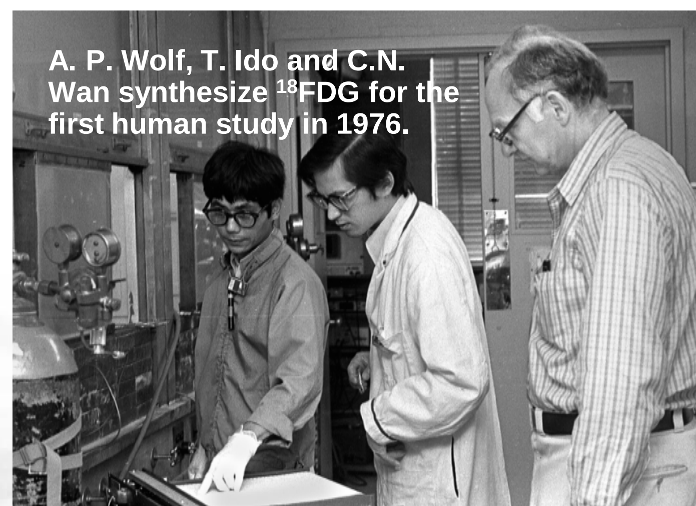

Accelerator Facility Boundary
eLENS
JET
RHIC
LEReC
CeC
sPHENIX
RF Facilities
STAR
LINAC
NSRL
AtR
Liquid Helium
Plant
EBIS
Booster
LVTF
SVTF
U Line
BLIP
ATF II
ERL
AGS
UED
Siemens
TTB
RRPL/TPL
ATF
Ebco
Tandems

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

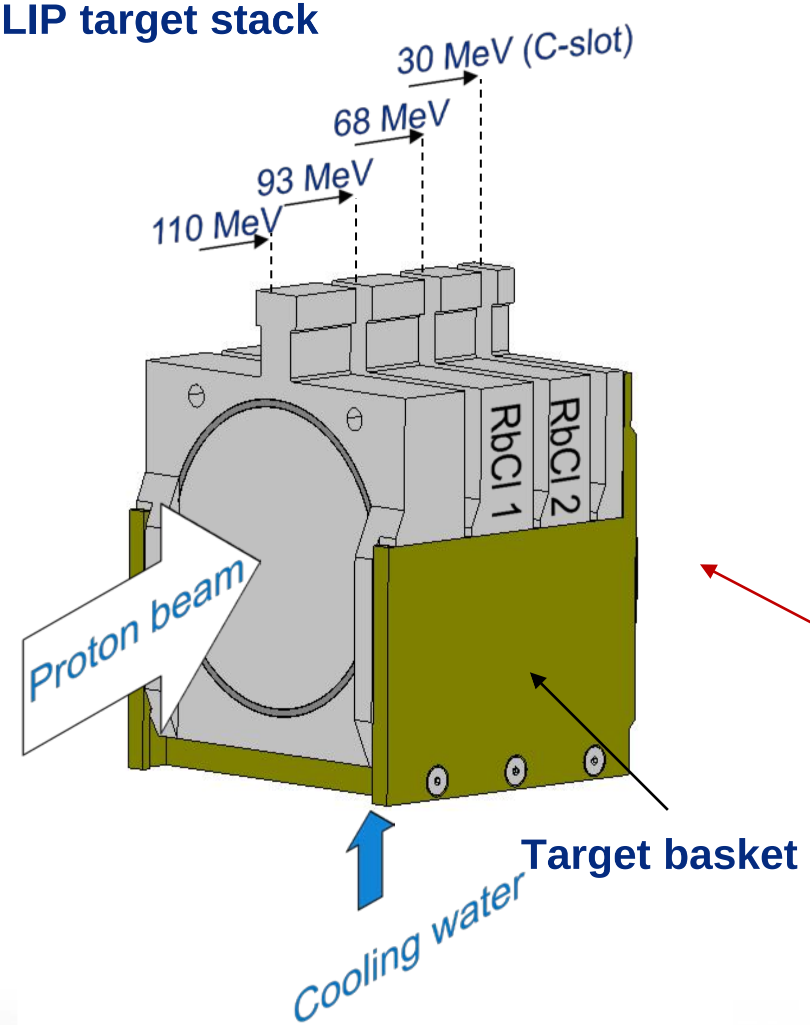

A. P. Wolf, T. Ido and C.N. Wan synthesize ^{18}FDG for the first human study in 1976.

Brookhaven Linac Isotope Producer (BLIP)

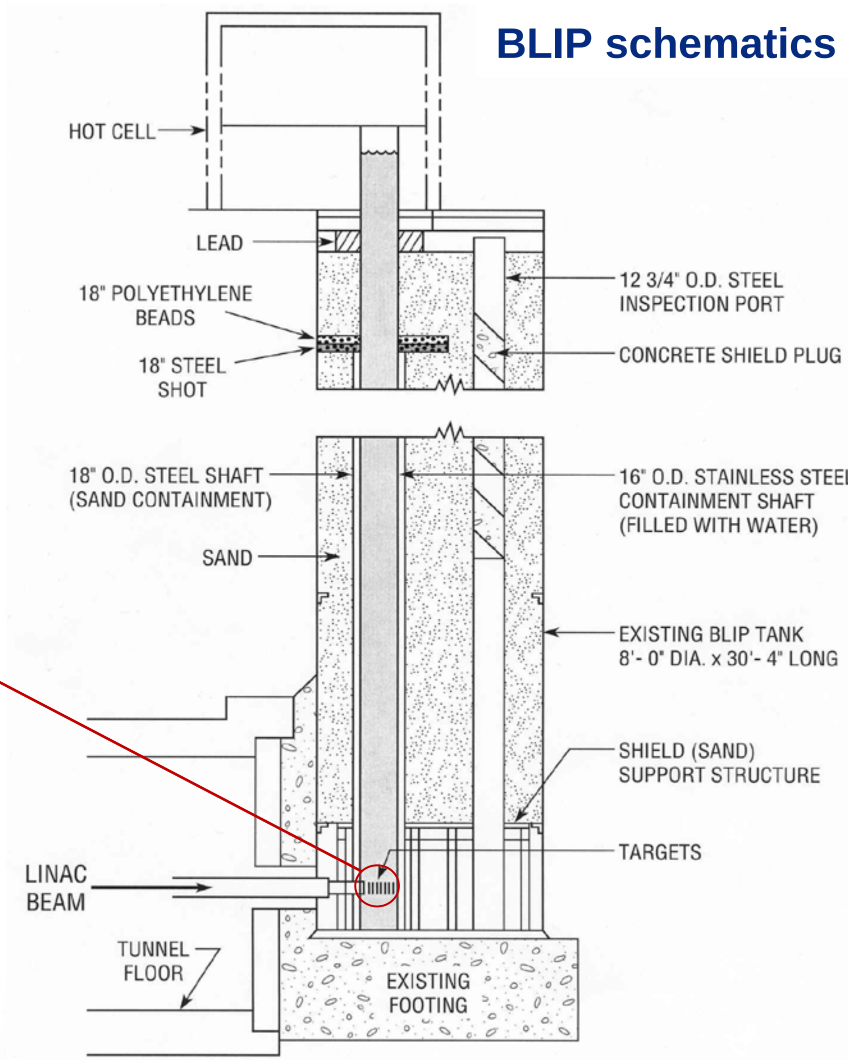
- First to use a high energy proton accelerator to produce isotopes (1972)
- BLIP utilizes the beam from the 200-MeV Linac that injects the Booster, which leads to AGS and RHIC accelerators (nuclear physics)
- Excess Booster pulses (~90%) are diverted to BLIP. Energy is incrementally variable from 66-202 MeV
- The BLIP beam line is a synergistic 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

Irradiate Stacked Targets

BLIP target stack



BLIP schematics



TPL Hot cells and Radiochemistry Labs

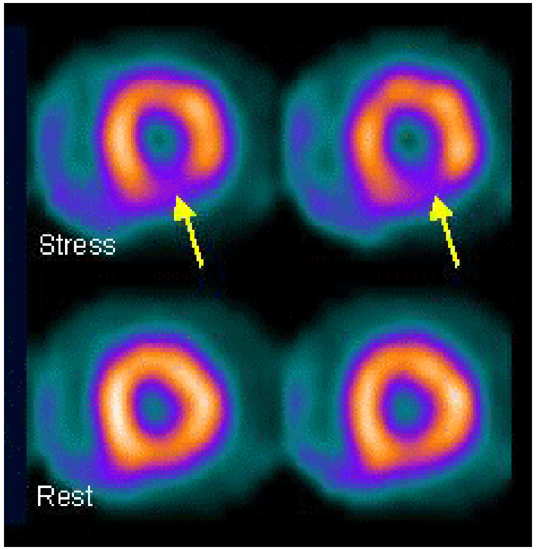
- Hot cells outfitted with manipulators and equipment for high level radioactivity work
- Radiochemistry labs outfitted with analytical equipment for characterization of final product

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 <u>only</u> 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 $^{82}RbCl$

<u>Hundreds of thousands of patients are now imaged annually in the US</u> and the <u>demand is growing</u>



Coronary Artery Disease

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

NSAC-I Recommendations 2015

- Significant increase of funding for research and development and support of facilities
  - Production of alpha-emitting isotopes (^{225}Ac, ^{211}At, ^{212}Pb)
  - High specific activity theranostic isotopes ($^{44,43,47}Sc$, $^{186,189}Re$, $^{64,67}Cu$, $^{72,76}As$)
  - Development of targetry to survive harsh conditions
  - Increase opportunities for basic R&D
  - Upgrade the Linac intensity and install beam raster system
  - Establish second target station enabling increased production and different beam energies delivered

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)

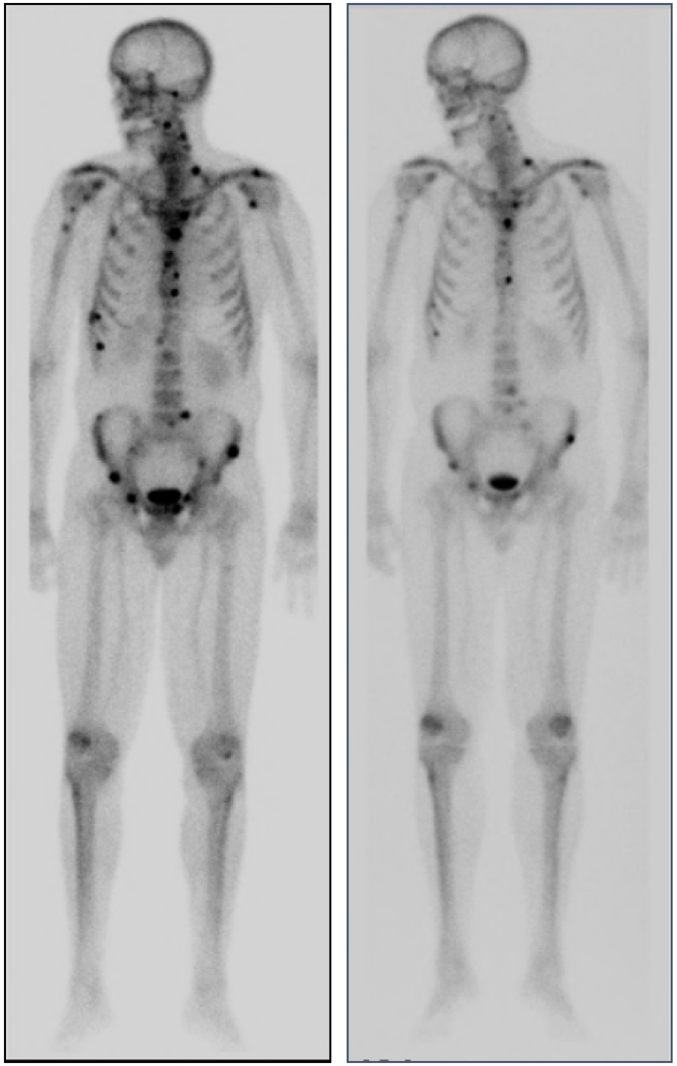
Used to treat bone metastases in end-stage prostate cancer

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

-Naturally targets new bone growth in and around bone metastases

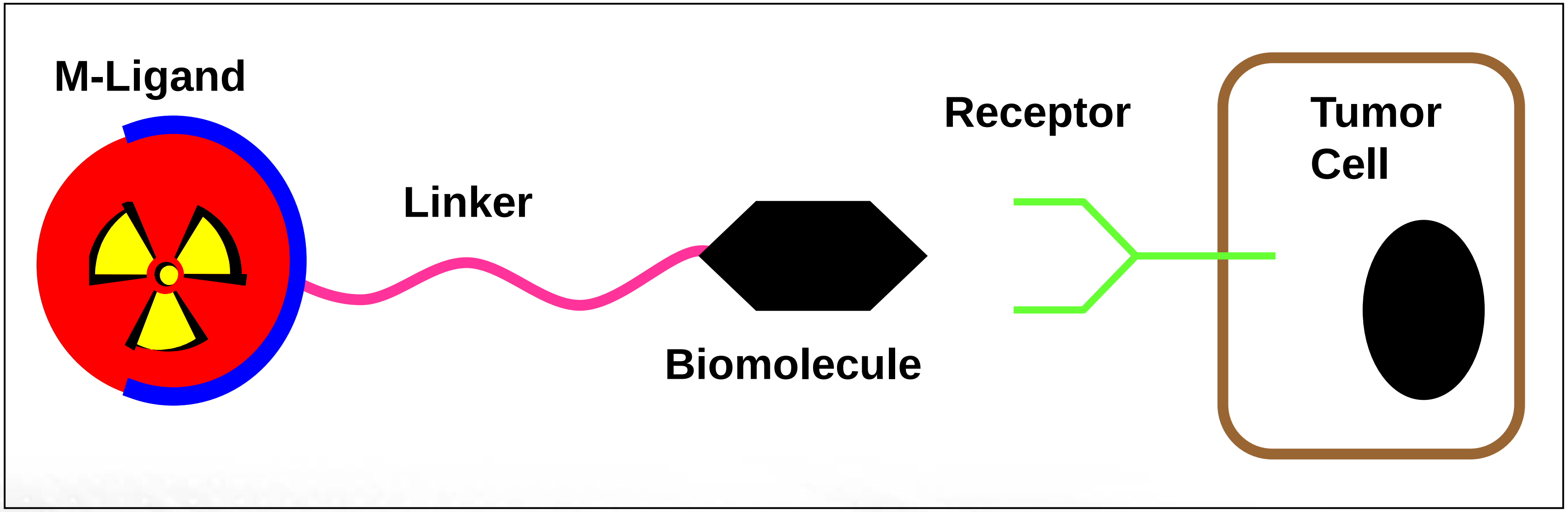
Therapeutic effect is largely palliative, it is not targeted

Paves the way for other alpha therapy agents!

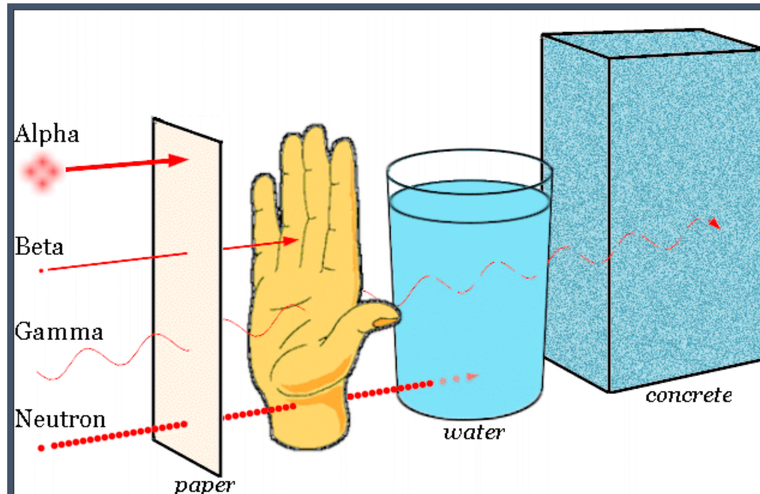


Targeted Approaches

- Bifunctional Chelating Agent
- Requires high specific activity



Targeted Alpha Therapy in Theory

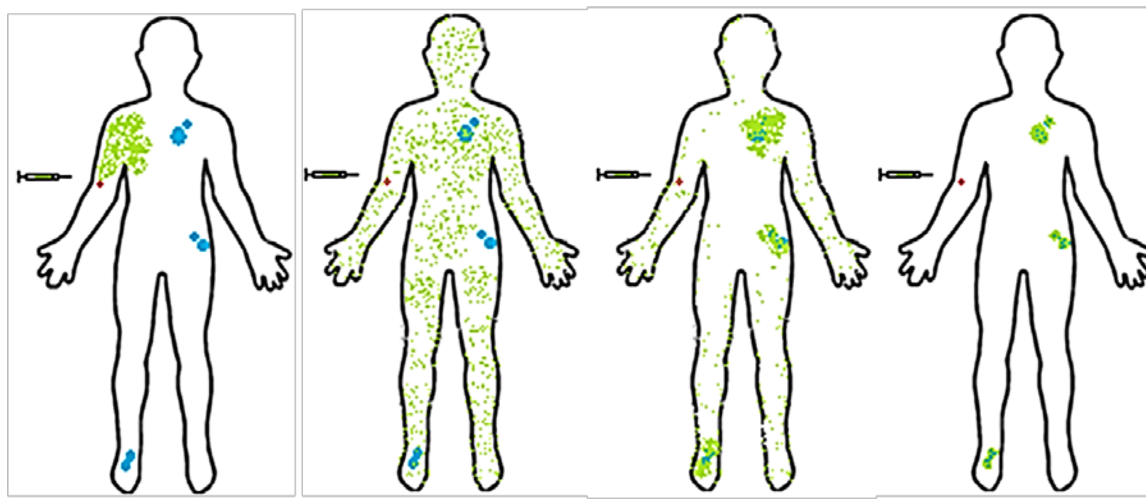


Range and effects of alpha, beta, gamma and neutron radiation

“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



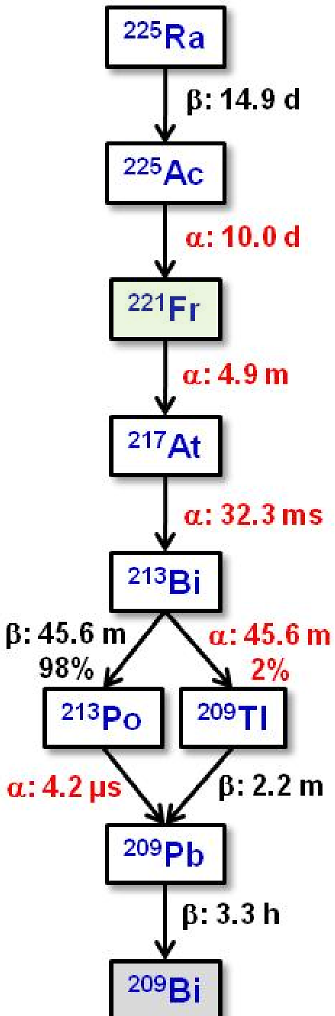
1.The targeted radioligand is administered systemically to the patient.

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.

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

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OAK RIDGE National Laboratory

Los Alamos NATIONAL LABORATORY EST. 1943

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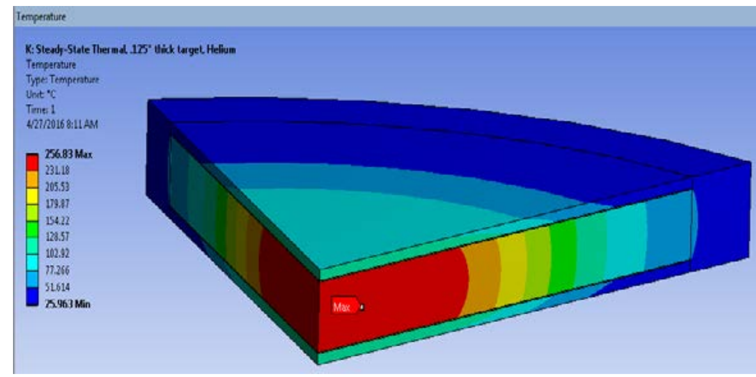
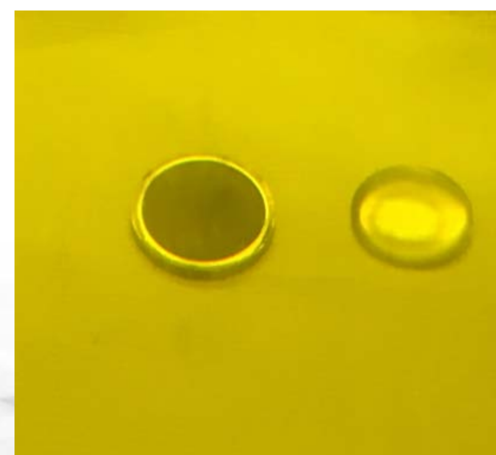
Target Challenge: develop thick Th targets to support clinical scale production

- Initial targets were thin Th foils (0.127mm, 0.9g) encapsulated in Al.

- Primary risk associated with Ci-Scale targets (~100g) is overheating. Capsule MP (1290°C) is lower than thorium MP (1755°C).



- Thermal behavior at Th/capsule interface is key.
- Thermal calculation for 165μA at 191 MeV incident energy predicts low peak temperature assuming ideal contact.
- Cook & look on 100 g target
- A 10d irradiation of this target type at 192 MeV, 160μA, would create 2.7Ci at EOB



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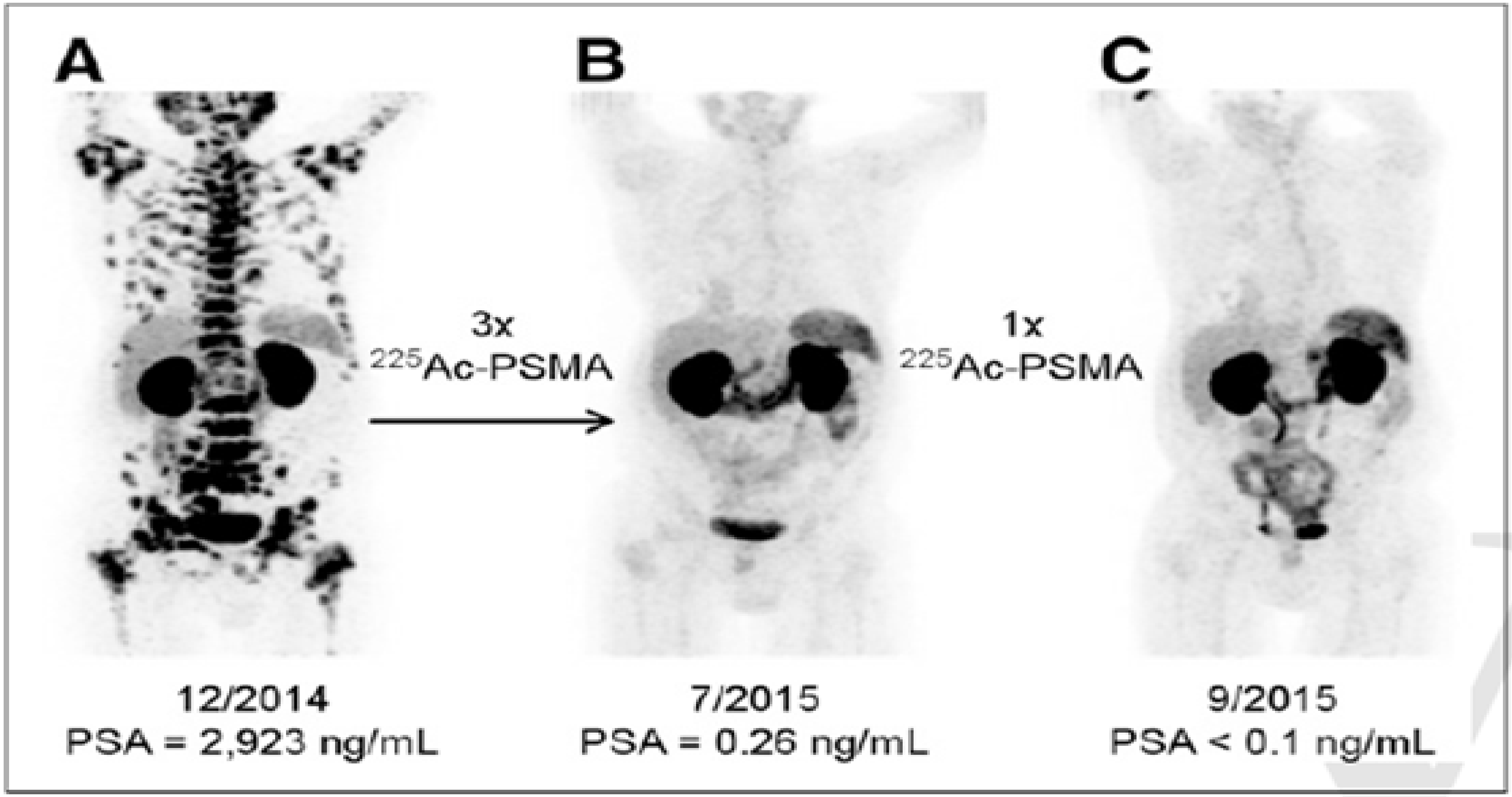
Prostate Cancer Therapy



J. Nucl. Med., 2016; 57 (12); 1941 DOI: 10.2967/jnumed.116.178673 C. Kratochwil

Work for Others

- ***Collaboration with N. Simos*** *for radiation damage studies (began 2000)*
  - **2014:** DOE-HEP, 200 MeV LARP collimator materials, 3 weeks (impact to Sr-82); 117 MeV parasitic (spallation neutrons) DOE-NEET,DOE-HEP LBNE, LARP HiLUMI, 9 weeks
  - **2015:** DOE-NE, 117 MeV parasitic (spallation neutrons), of nano-structured amorphous and ceramic coatings on nuclear steels
  - **2017:** DOE-HEP RaDIATE (Fermi, LHC, ESS, KEK, JPARC, FRIB) 8 weeks at 181 MeV: graphite/Mo composites, Be, Al alloys, Ir (~15% impact to Sr-82)
- ***Other Work:***
  - Nuclear Data

Future Plans

cGMP compliance

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

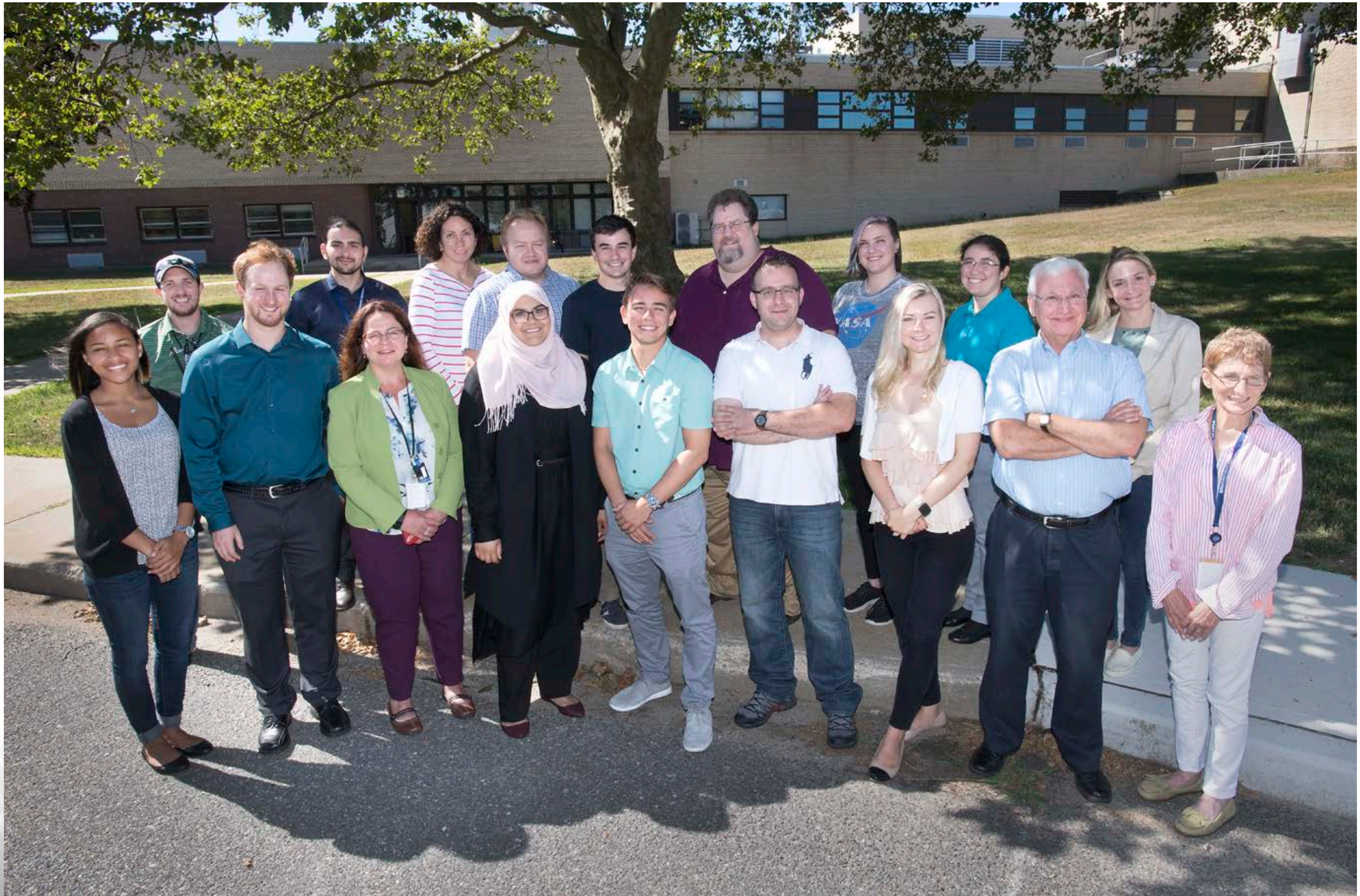
Future Processing

- 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

MIRP Group



Questions

Thank You

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