Production of Medical Radioisotopes for Medical Applications

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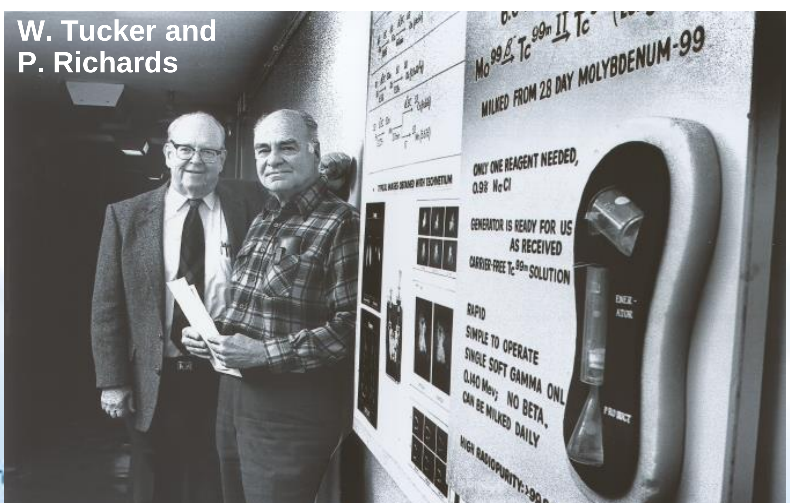
BROOKHAVEN NATIONAL LABORATORY

a passion for discovery

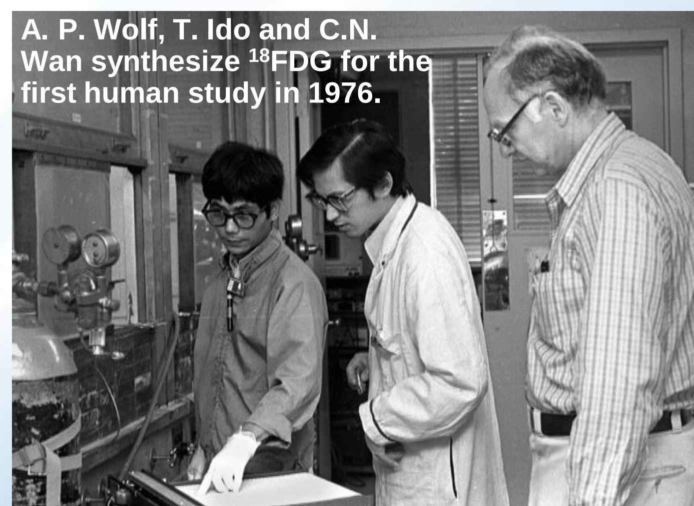
Office of Science

BNL is the Birthplace of Nuclear Medicine

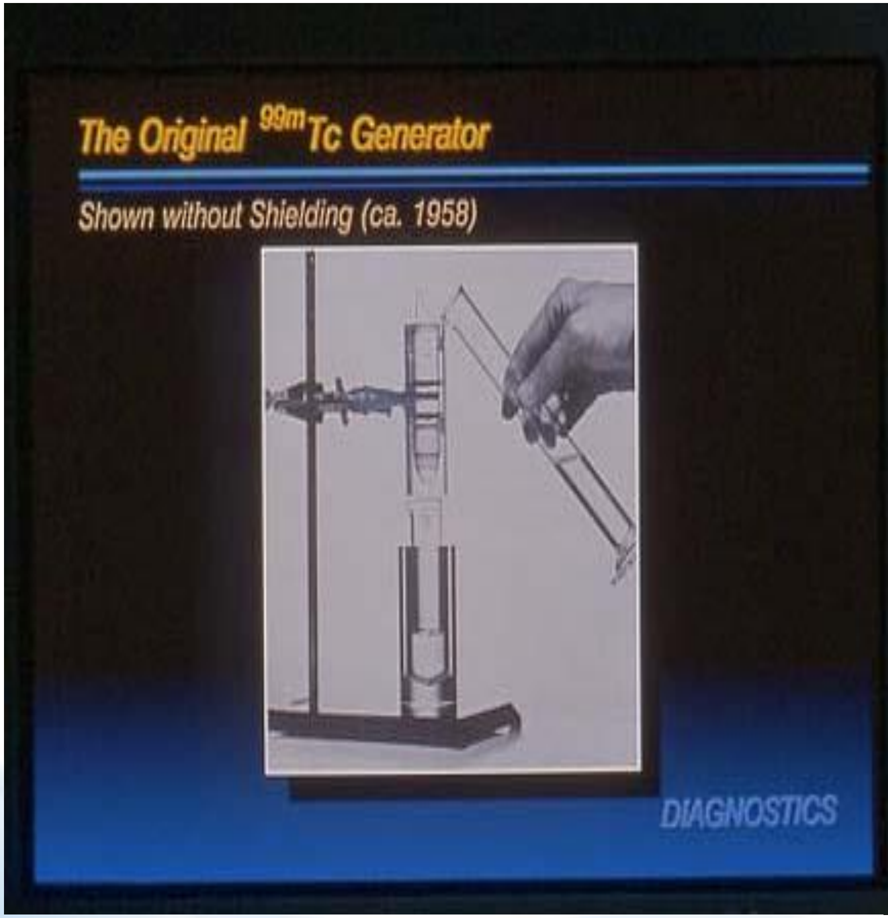
- In the late 1950’s, BNL scientists Walter Tucker and Powell Richards developed a generator system for producing Tc-99m and suggested its use for medical imaging. Tc-99m is now used in over 10 million patients/year in the U. S. alone.
- In the 1970's, scientists at BNL, U. Penn and NIH, combined chemistry, 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)

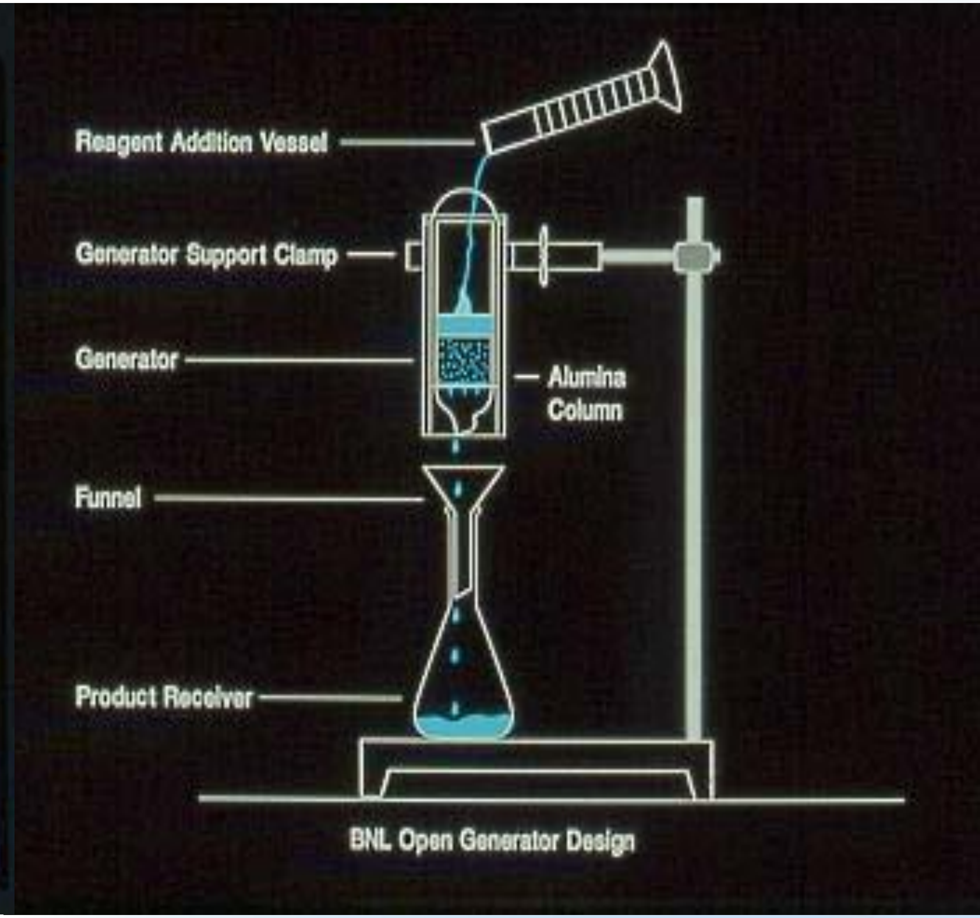


W. Tucker and P. Richards

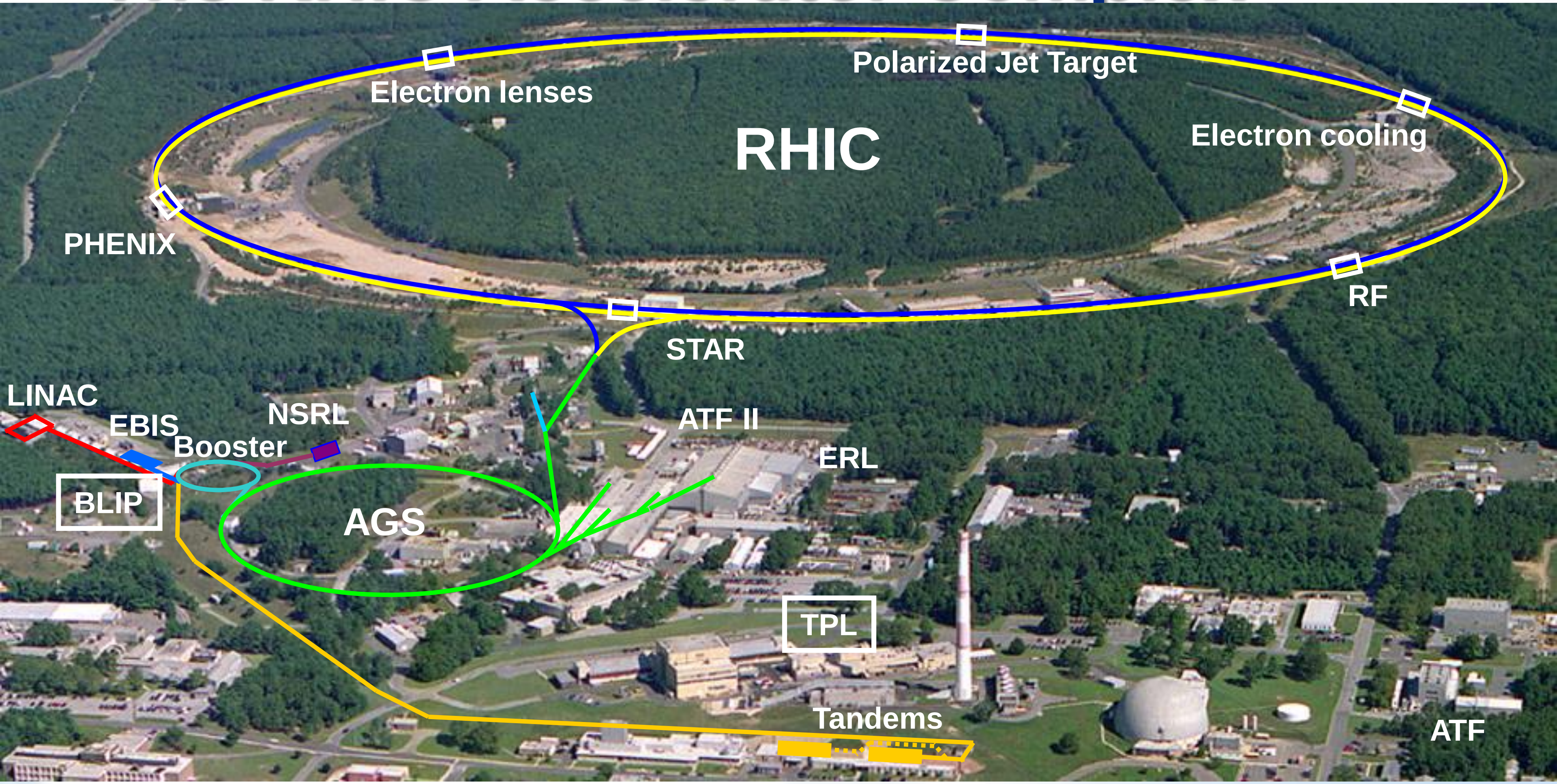

A. P. Wolf, T. Ido and C.N. Wan synthesize ^{18}FDG for the first human study in 1976.

Brookhaven National Lab
Open Generator Design: Column Chromatography



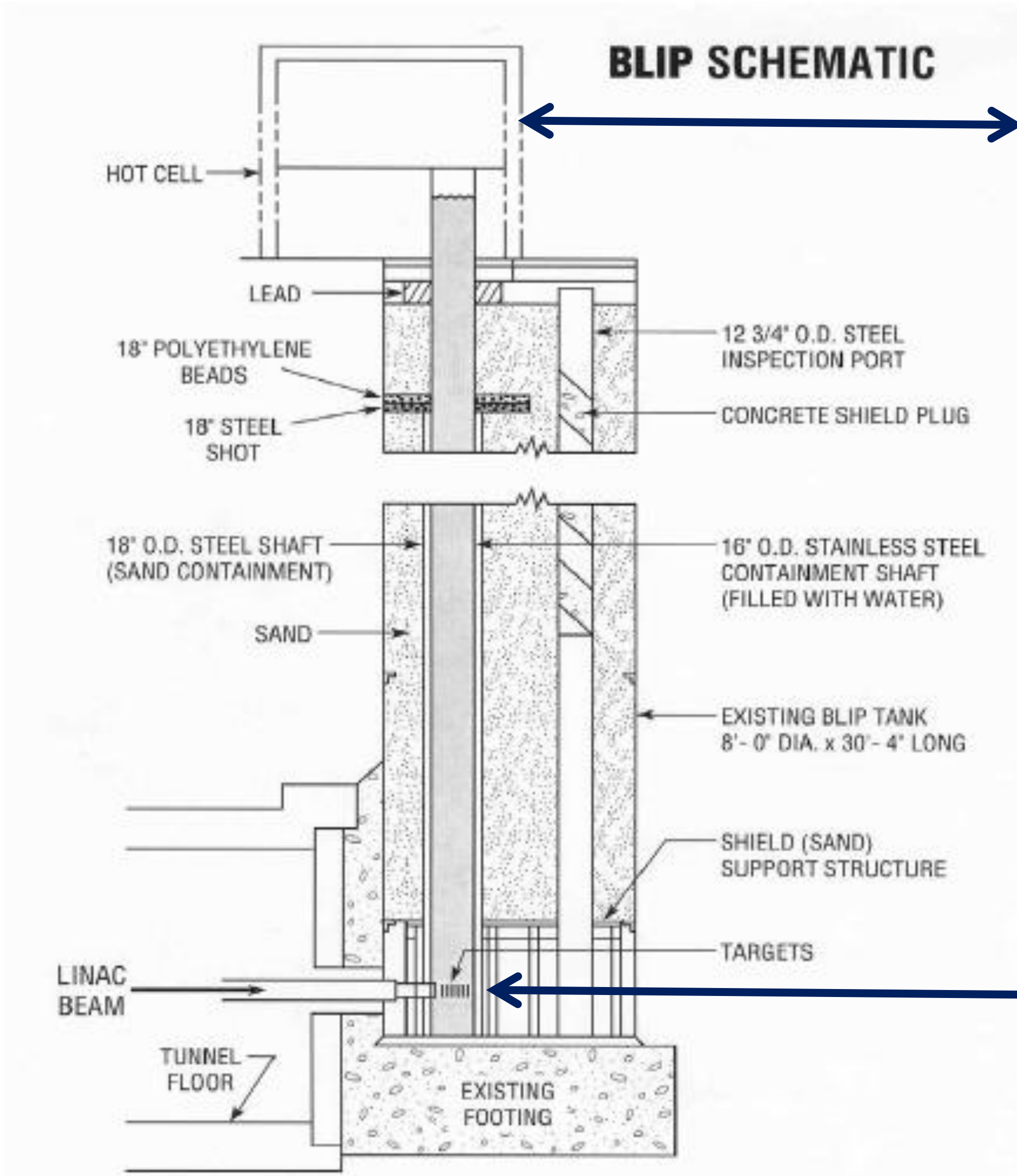


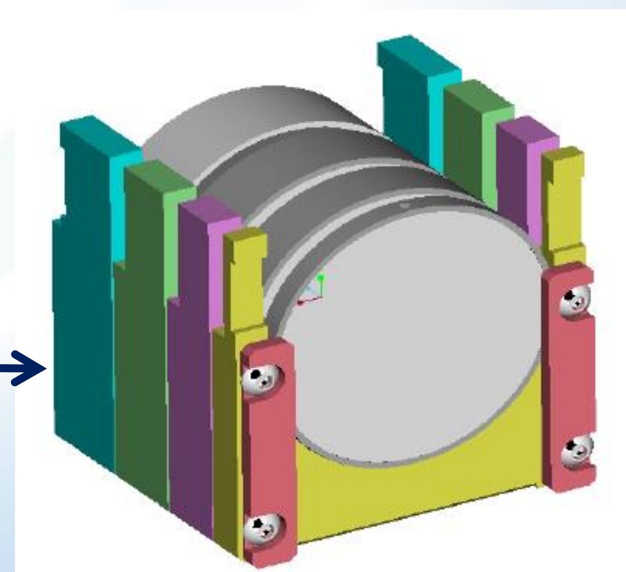
The RHIC Accelerator Complex



- Highly flexible and only US Hadron Collider exploring the QCD phase diagram and the spin of the proton
- Injectors also provide beams for unique applications: Isotope production (BLIP/TPL); Cosmic radiation simulation (NSRL); Commercial applications (Tandem)
- R&D for future facilities and accelerator applications (ERL, ATF/ATFII)

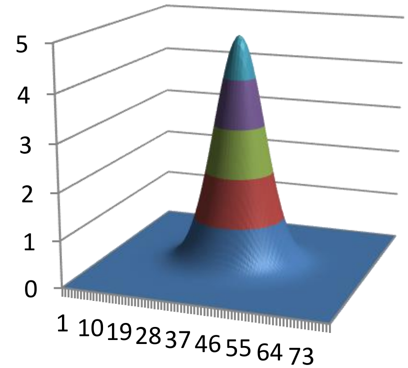
Brookhaven Linear Isotope Producer (BLIP)

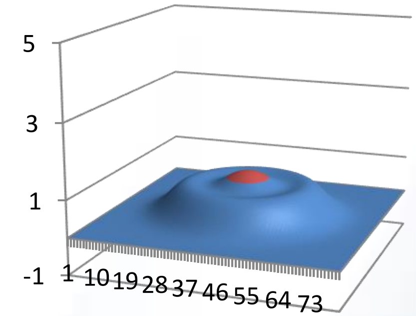


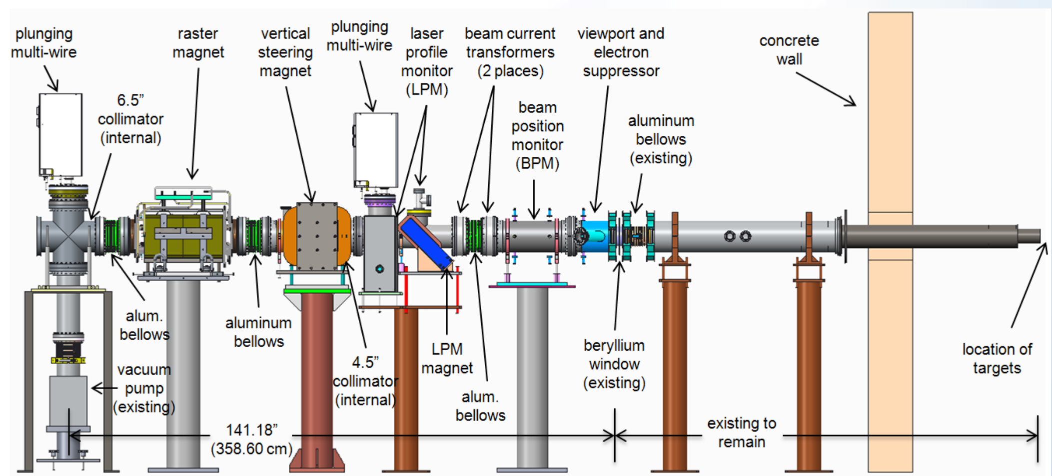


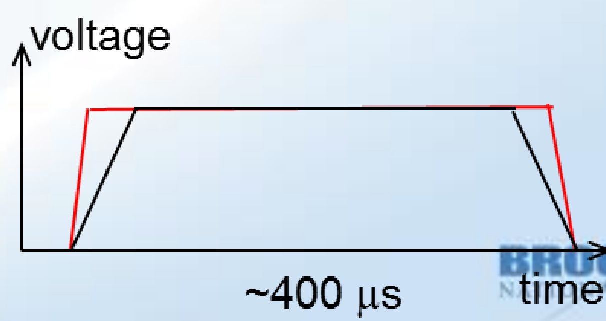
BLIP Beam Enhancements

- BLIP beam raster system development
  - **Reduction in localized target heating**
    - **Enables increase in beam current from 100 µA to 125 µA (greater isotope yields)**
    - **Greatly lowers possibility of target failures**
- BNL linac intensity upgrade
  - **Phase 1 (in progress)**
    Changes pulse shape to effectively increase current from 125 µA to 140 µA
  - **Phase 2**
    Increases current to 250 µA by increasing pulse length

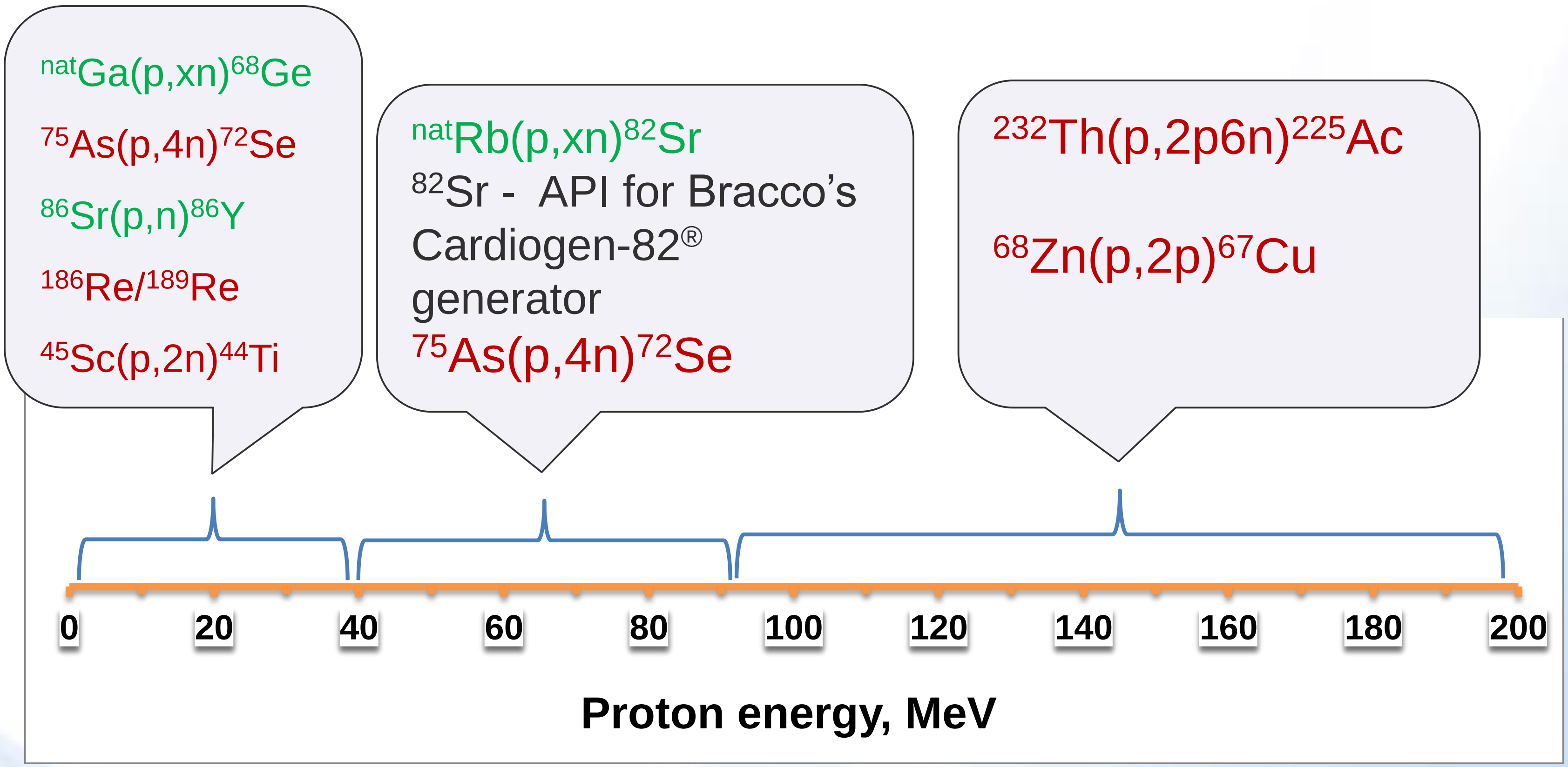








Opportunities for isotope production and R&D at BLIP



Theranostics

- 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 therapy.

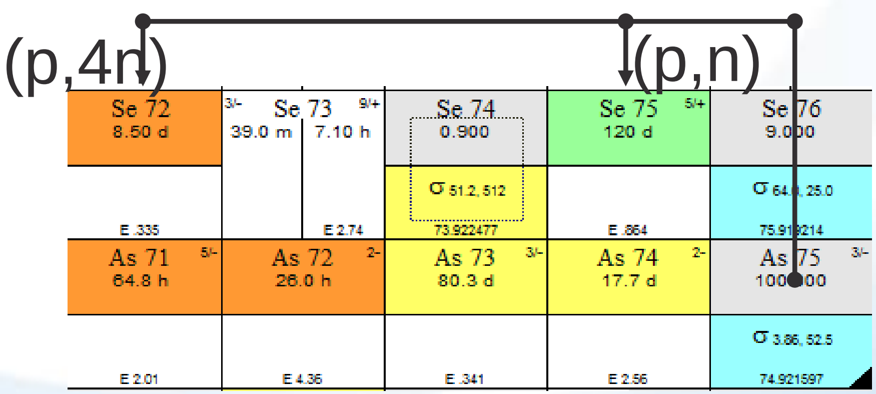
High Specific Activity ^{72}As – theranostic pair to ^{77}As

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

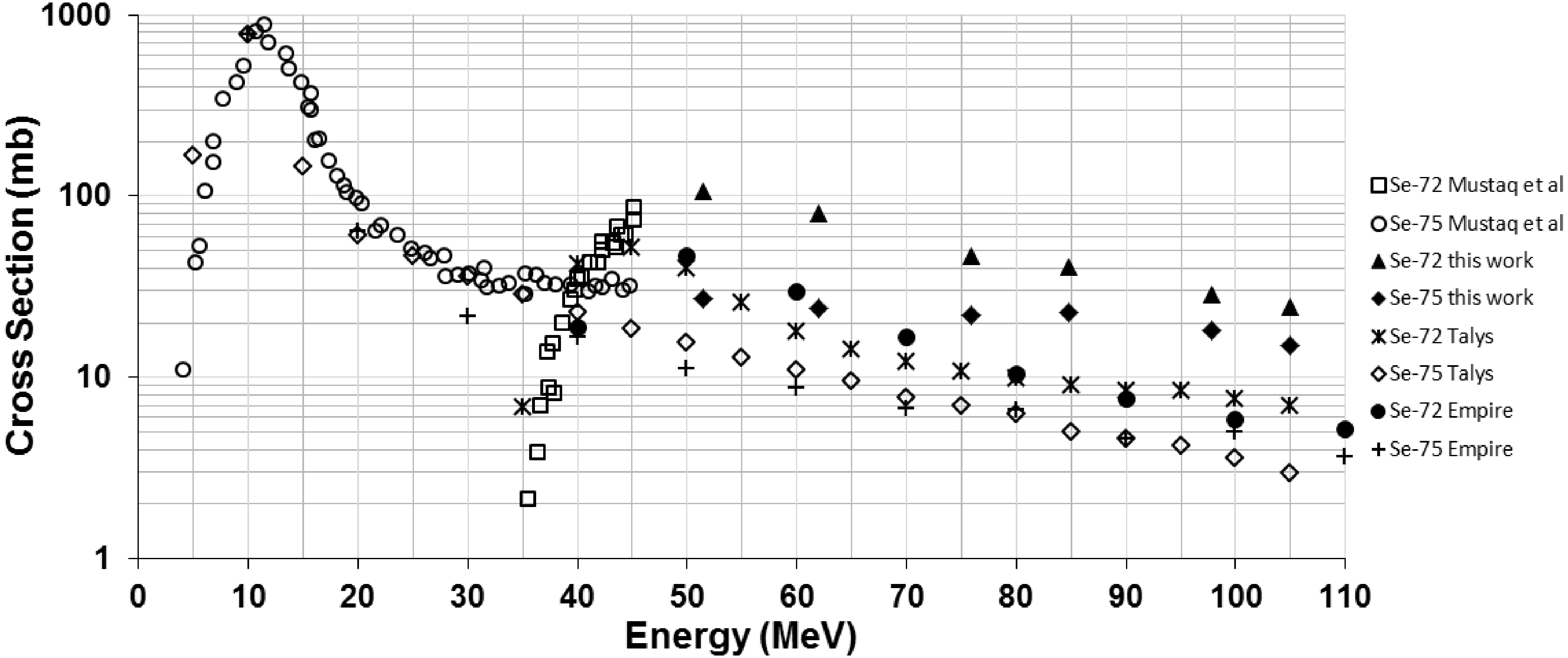
- Positron energy comparison

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 ^{72}As 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

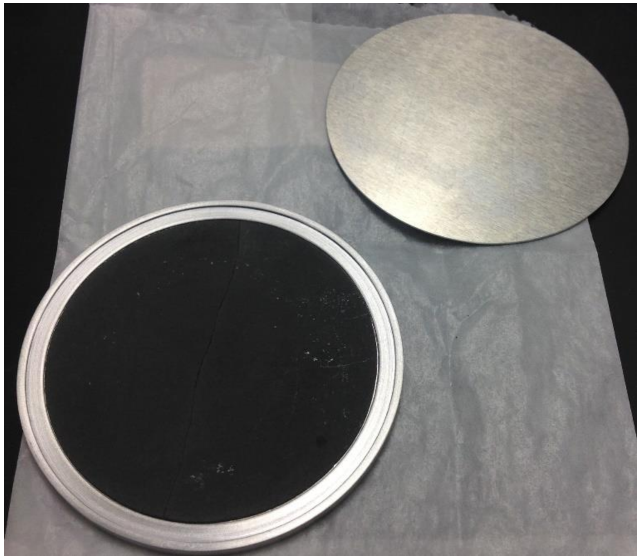


Excitation functions for ^{75}Se and ^{72}Se production from As



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

BNL ID	Design	Target Material	Time Period	Beam time, d	Beam Current, μA	Activity Produced (mCi)
BXA	Welded Al	GaAs	6/8/16 to 6/13/16	4.85	136.4, rastered	101.6
BXI	Welded Al	As	7/29/16 to 8/1/16	2.87	163.2, rastered	373.4



Irradiation parameters:

- Target size: d × h=2.375 × 0.020 inches
- Synergistic with RbCl targets, positioned upstream
- E on target = 105 MeV
- Theoretical yield 9.9 mCi/μA based on cross section data

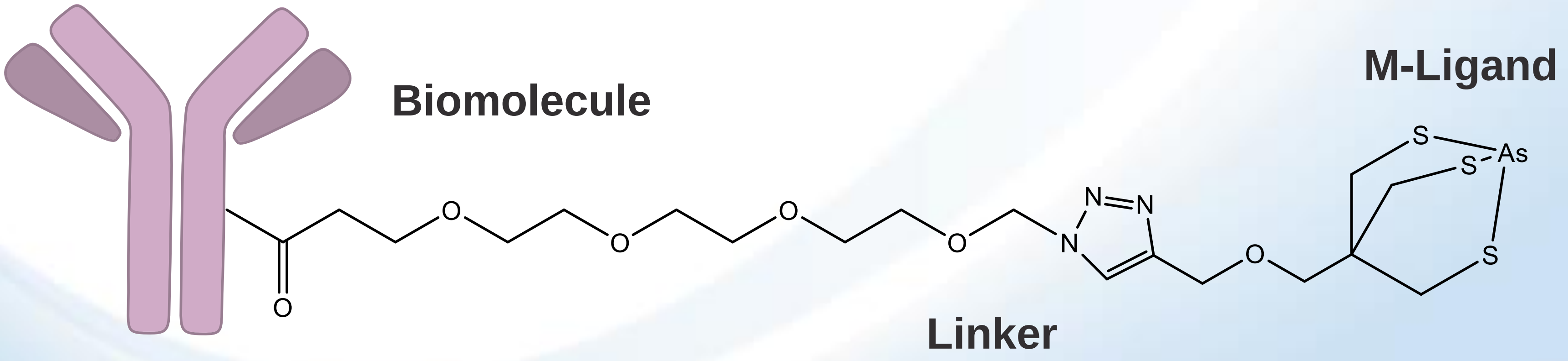
$^{72}Se/^{72}As$ Generator

- 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

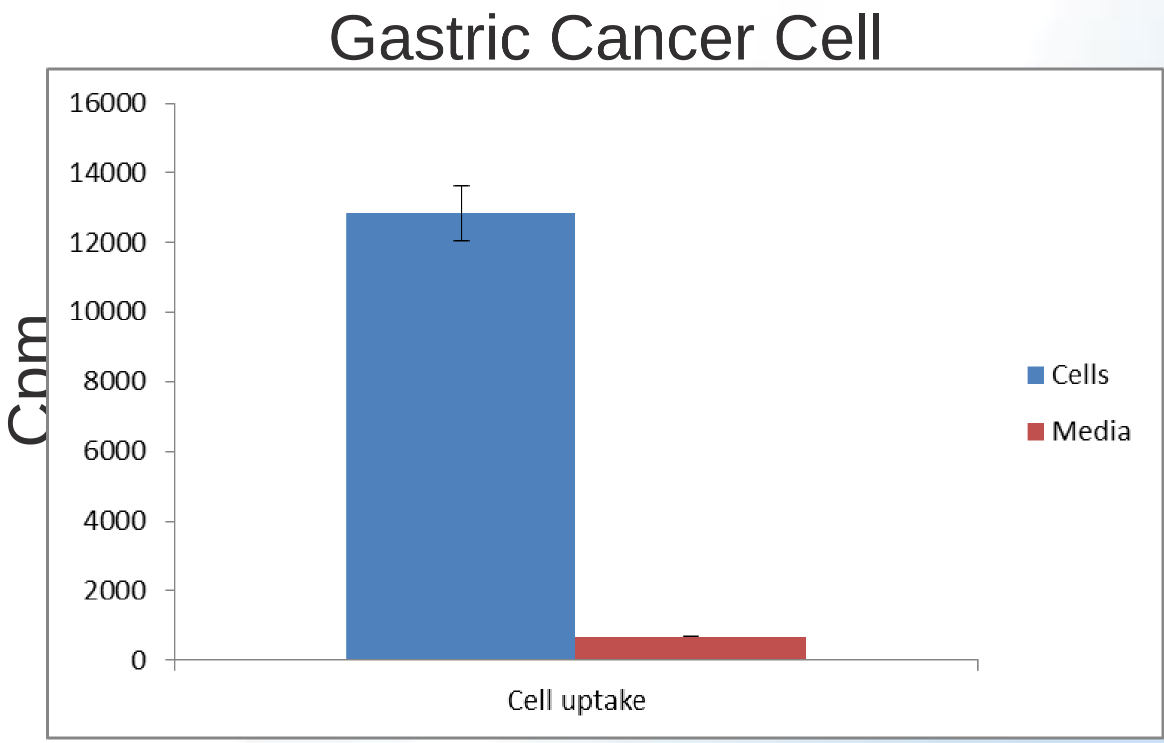
- Trastuzumab (Herceptin)
  - 2mg/mL/rxn
- Daratumumab
  - 1mg/mL/rxn
  - control

- 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

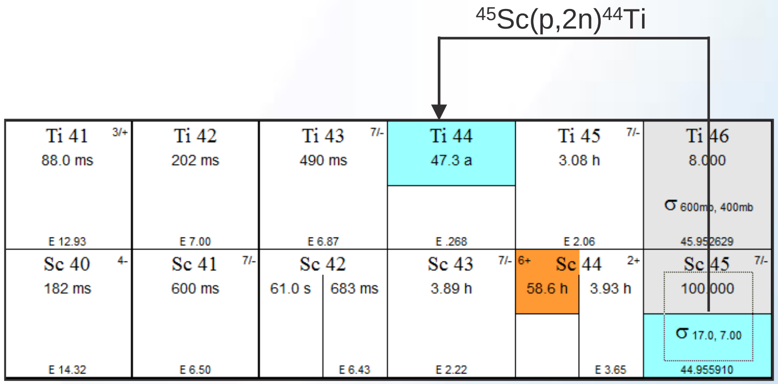


18.5 times uptake in cells!!!

Completed at Stony Brook University

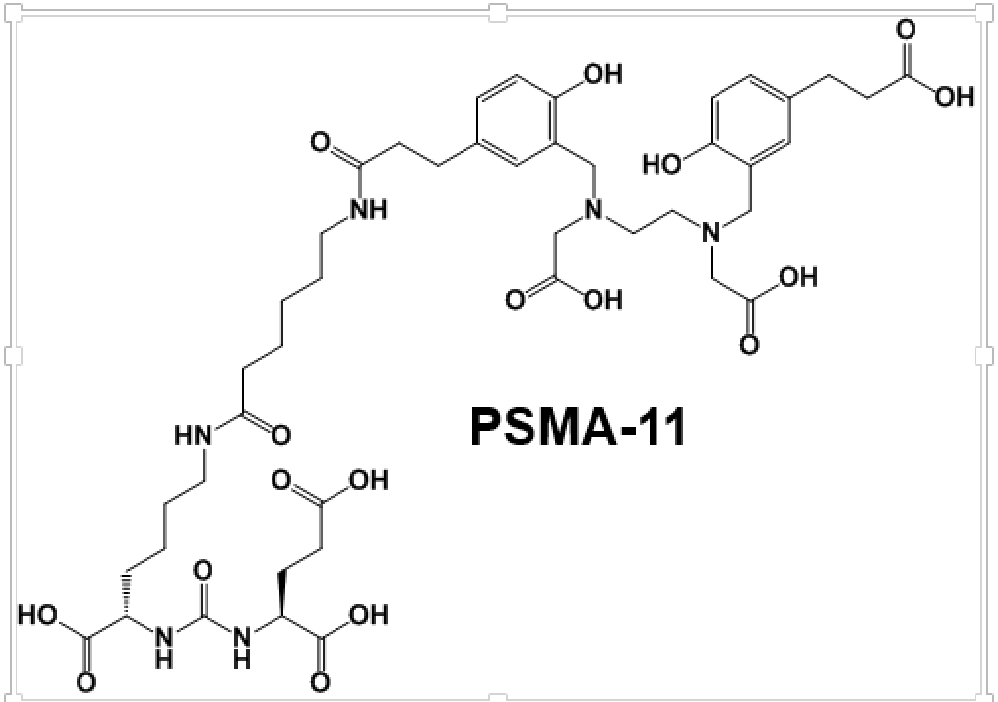
Production at < 30 MeV: ^{44}Ti (59.1y) parent of ^{44}Sc (3.97 h)

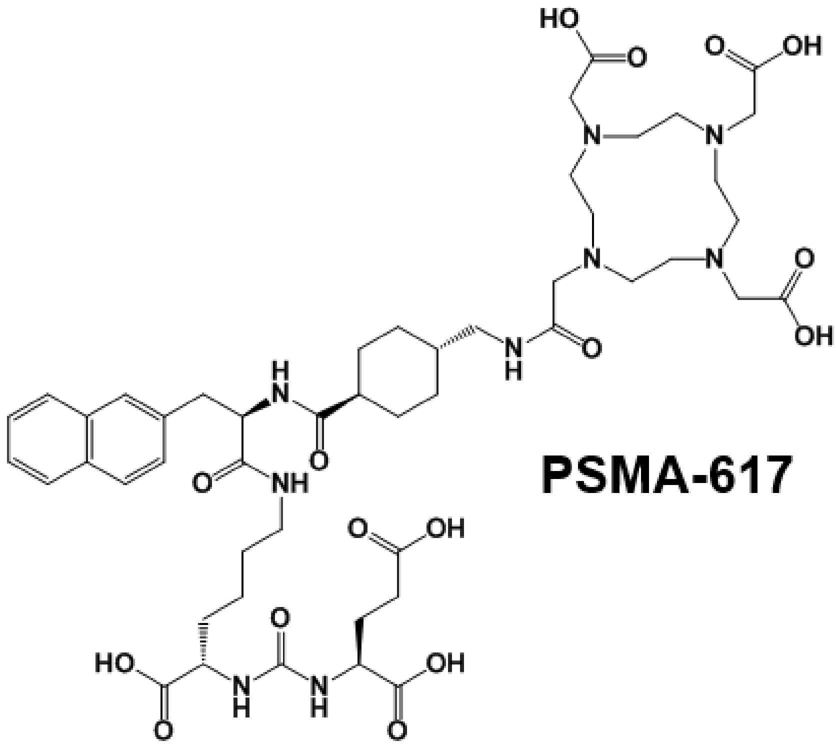
- Scandium-44
  - Decays by electron capture to Ca-44 (stable), mean $E_{\beta+}$=632 keV, Eγ=1157.02 keV (99.9%)
  - Metallic isotope that offers intermediate half-life of 3.97 h (Ga-68 – 67.7 min, Zr-89 – 78.41 h)
  - Offers theranostics opportunities
    - Pretherapeutic dosimetry evaluation for M^{3+}-radiopharmaceuticals
    - 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)
- ^{44}Ti production requires long irradiations: dedicated irradiations are not economically viable



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

PSMA Targeting: The Principle of Theragnostics



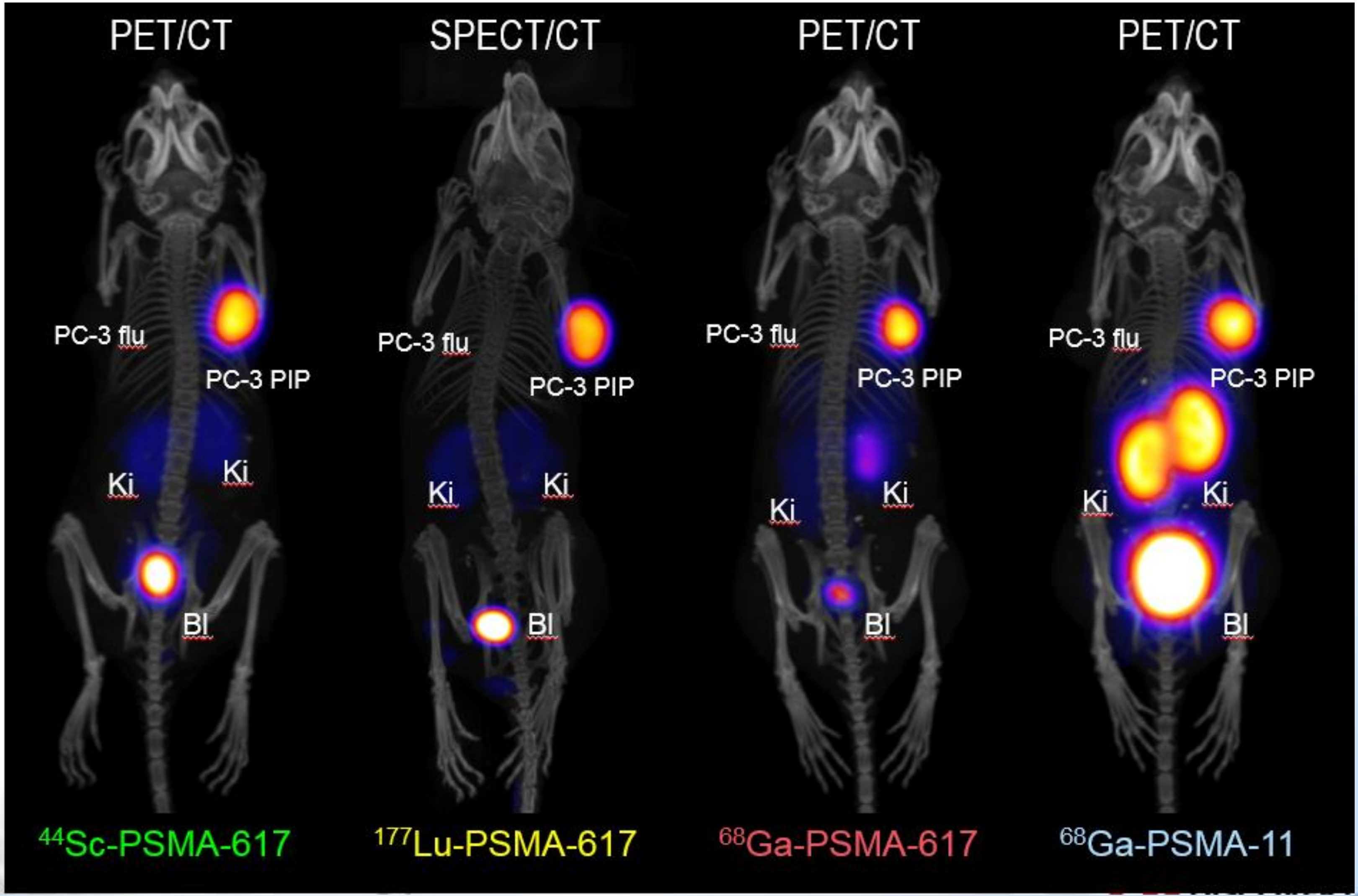


^{68}Ga

^{44}Sc ^{177}Lu ^{68}Ga

Courtesy of C. Mueller of PSI

Images Obtained with PSMA Ligands



PC-3 PIP = PSMA^{pos} tumor, PC-3 flu = PSMA^{neg} tumor; Ki = Kidney, Bl = bladder

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2017; 7(18): 4359-4369. doi: 10.7150/thno.20586

Research Paper

Clinical Translation and First In-Human Use of [^{44}Sc]Sc-PSMA-617 for PET Imaging of Metastasized Castrate-Resistant Prostate Cancer

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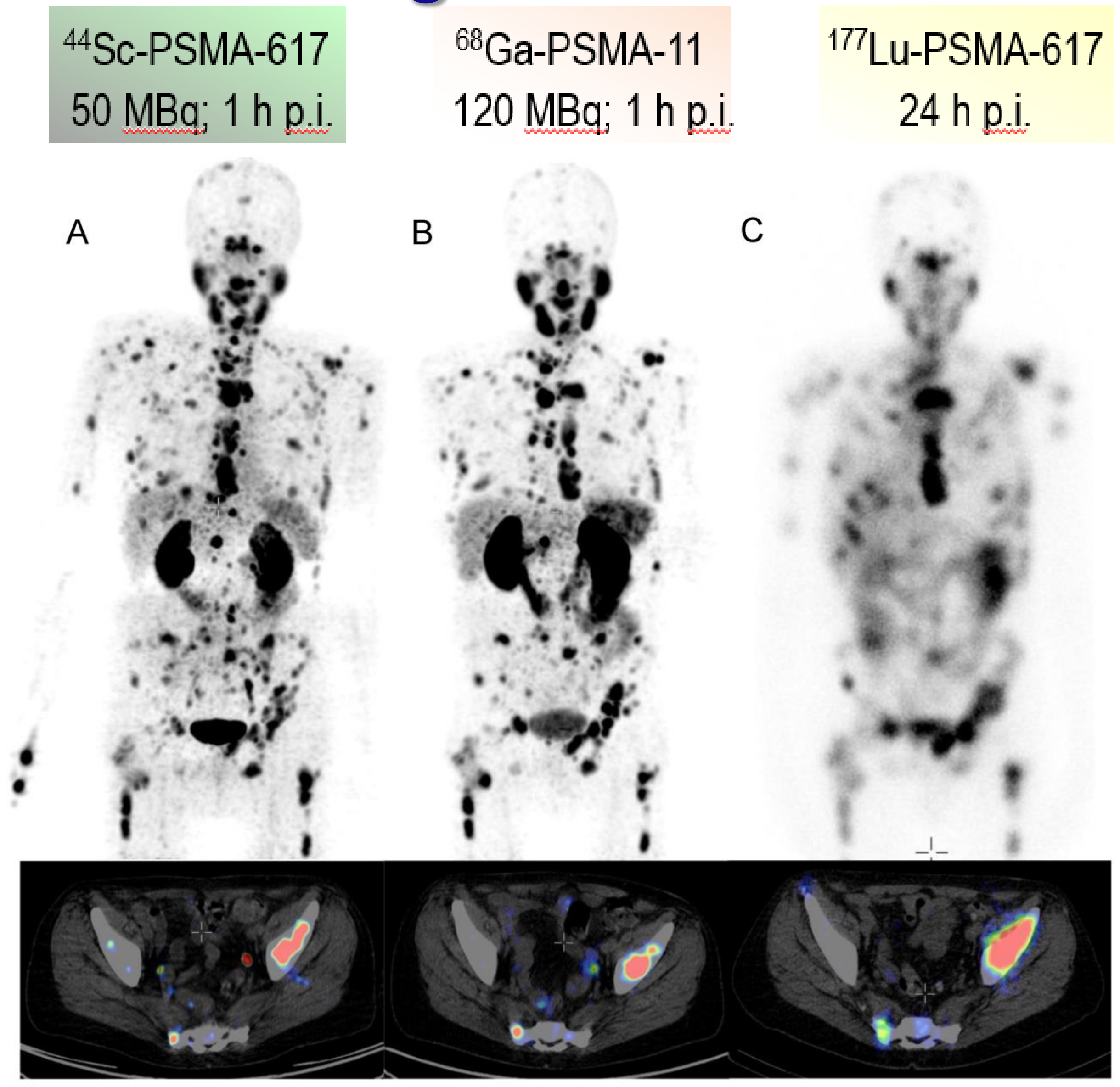
First-in-Man Using ^{44}Sc-PSMA-617



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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)

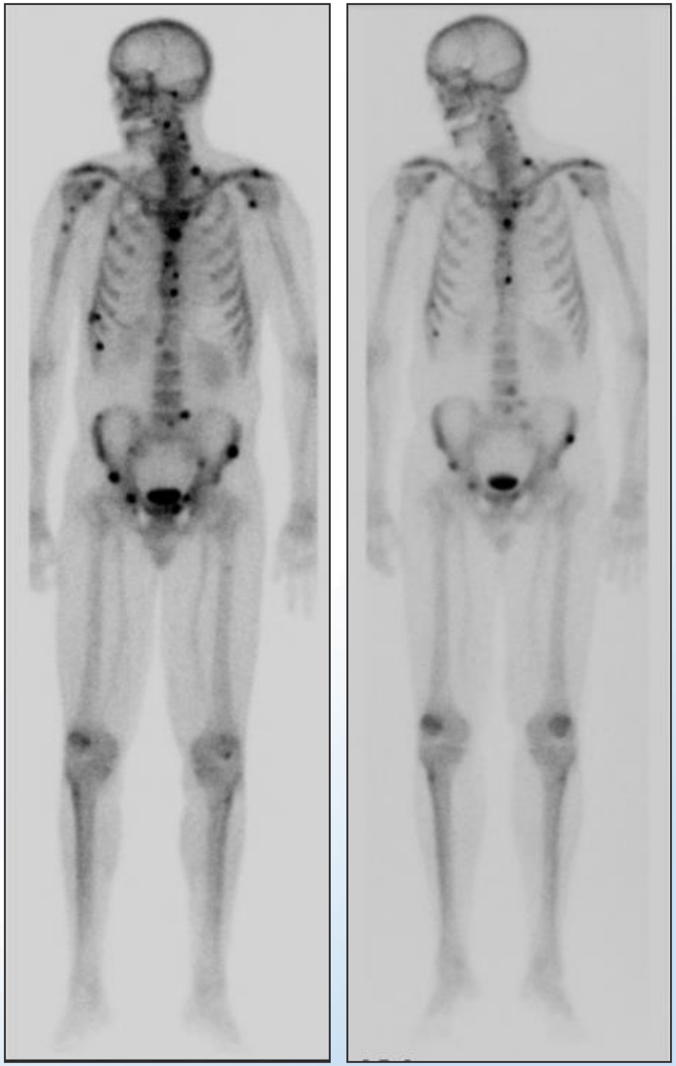
Used to treat bone metastases in end-stage prostate cancer

-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!



Physicochemical characteristics of β-emitters and α-emitters

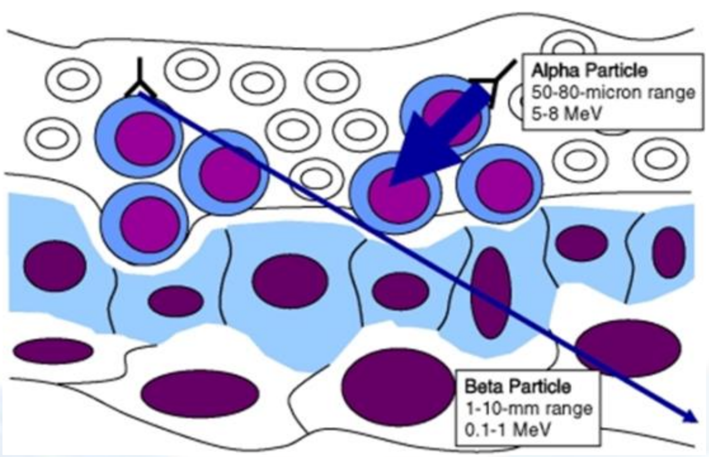
β-emitters

- Intermediate LET radiation (0.50–2.30 MeV) ; long range in tissues (1–12 mm of tissue penetration).
- ß-particles range: target clusters of cells (from 10 to 1,000 cells)

α-emitters

- High-LET radiation (60–230 keV/μm)
- Short to intermediate path length (^{212}Pb: 50–80 μm) in tissues
- Path length: target several cells (2–10 cells)
- High LET causes Irreversible damage of double stranded DNA

Nuclide	$T_{1/2}$	Emission	Mean path length
I-125	60.0d	auger	10nm
At-211	7.2h	alpha	65nm
Pb-212	10.6h	alpha	50-80 um (0.05-0.08mm)
Lu-177	6.7d	beta/gamma	0.7mm
Cu-67	2.58d	beta/gamma	0.7mm
I-131	8.04d	beta/gamma	0.9mm
Sm-153	1.95d	beta/gamma	1.2mm
Re-186	3.8d	beta/gamma	1.8mm
P-32	14.3d	beta	2.9mm
Re-188	17h	beta/gamma	3.5mm
In-114m	50d	beta/gamma	3.6mm
Y-90	2.67d	beta	3.9mm



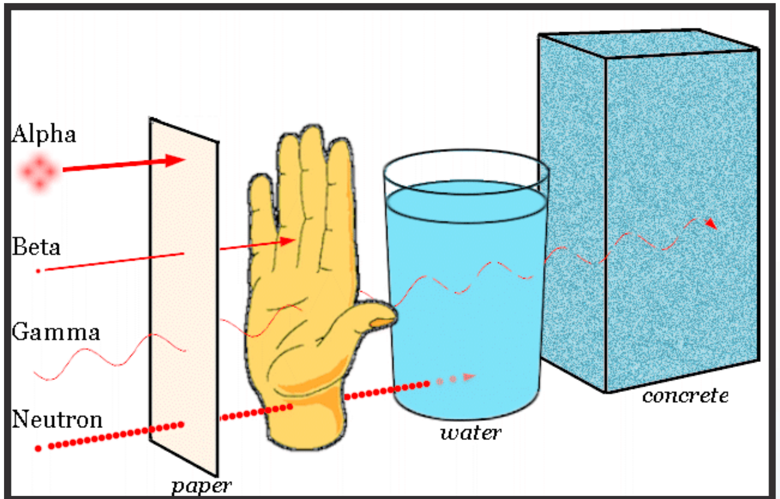
Slide courtesy of Dr. M. McDevitt, Memorial Sloan Kettering

Targeted Alpha Therapy in Theory

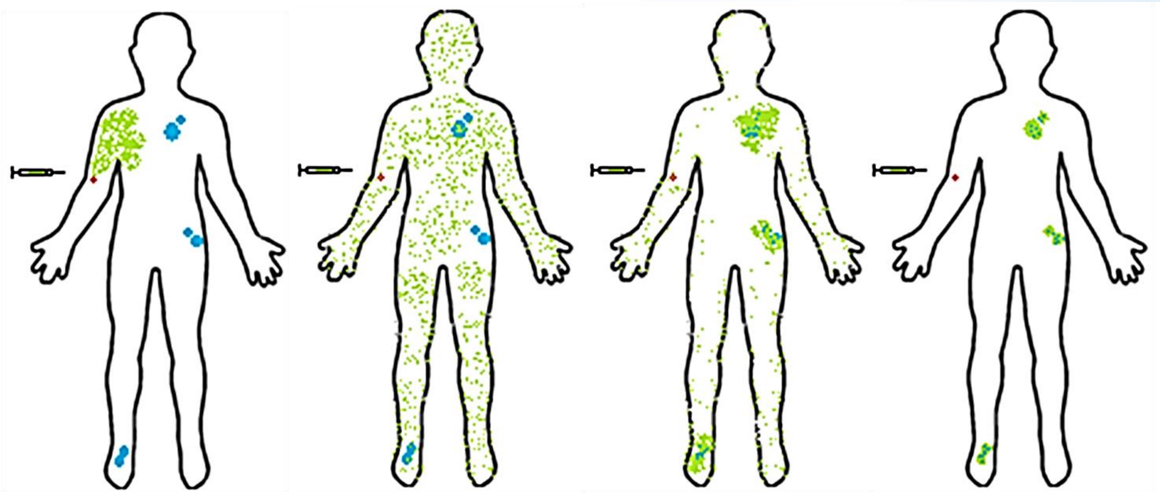
"High-linear-energy α-particle emissions create dense ionization paths in tissue that render high target-to-nontarget dose ratios that are highly effective at cell killing"

George Sgouros, SNNMI-MIRD, 2015

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

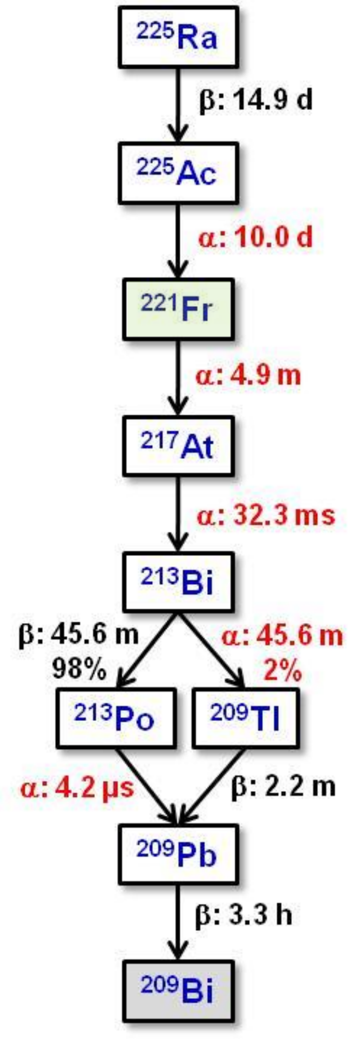


Range and effects of alpha, beta, gamma and neutron radiation



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.

Accelerator-Produced ^{225}Ac 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

Relative Dose

		Dose (rem/mCi)	
Organ	**^{131}I**	**^{211}At**	**^{225}Ac**
Heart Wall	0.315	6.01	31.4
Kidneys	23.9	350	3250
Liver	0.645	9.99	53.2
Lungs	0.101	0.922	4.91
Spleen	0.54	3.31	17.8
Tumor	175	547	26900
Urinary Bladder Wall	0.265	0.00428	0.0243
Uterus	0.108	0.00453	0.0166
Total Body	0.361	2.31	31.7

Courtesy of David Schlyer

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

Facility	Nuclear Reaction
Reactor (thermal neutrons)	$^{226}Ra(3n,\gamma)^{229}Ra \rightarrow ^{229}Ac \rightarrow ^{229}Th$
Accelerator (electrons)	$^{226}Ra(\gamma,n)^{225}Ra \rightarrow ^{225}Ac$
Accelerator (low energy particles)	$^{226}Ra(p,2n)^{225}Ac$ $^{226}Ra(\alpha,n)\ ^{229}Th$ $^{232}Th(p,x)\ ^{229}Th$
Accelerator (high energy protons)	**$^{232}Th(p,x)^{225}Ac$** $^{232}Th(p,x)^{225}Ra \rightarrow ^{225}Ac$

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

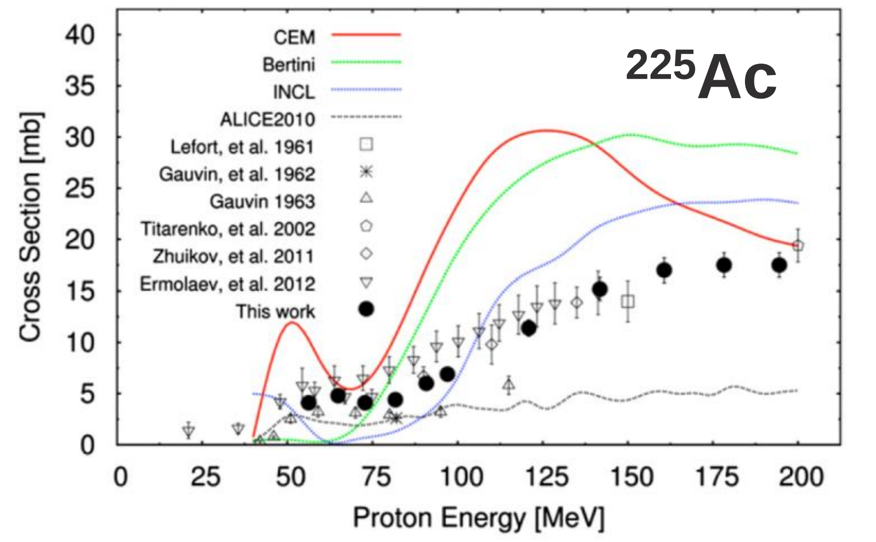


Fig. 1. Experimental and theoretical cumulative cross sections for the formation of ^{225}Ac by the proton bombardment of thorium.

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

Basis of the Tri-Lab Effort: Leveraging Unique DOE Isotope Program Facilities, Capabilities and Expertise to Address ^{225}Ac Supply

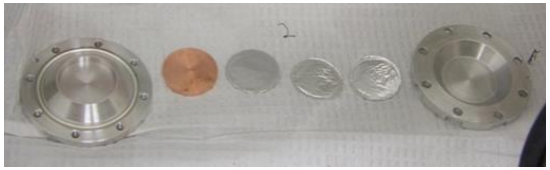
LANL Isotope Production Facility (IPF) at LANSCE; 100 MeV incident energy up to 250 μA for routine production

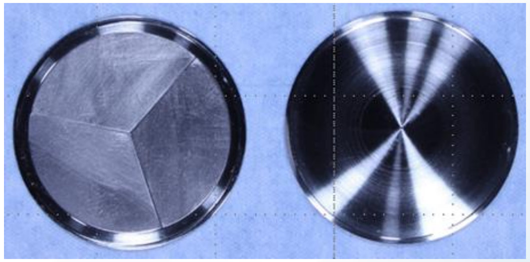
ORNL - Approximately 20 years of experience in the isolation of ^{225}Ac from fissile ^{233}U via ^{229}Th

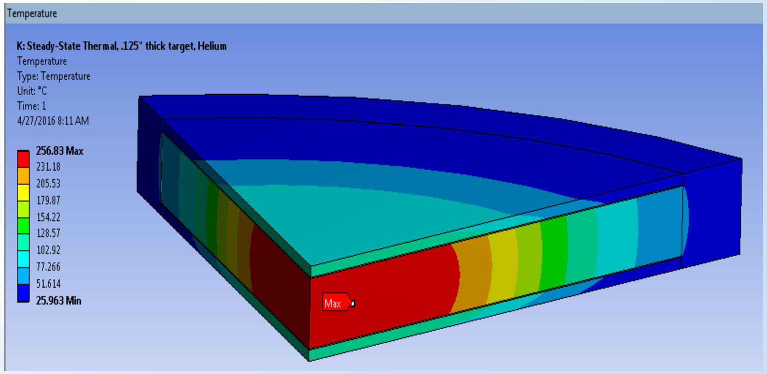
BNL Linac at the Brookhaven Linac Isotope Producer (BLIP) 160 μA intensity to targets at incident energies ranging from 66-202 MeV

Target Challenge: develop thick Th targets to withstand high beam current to support clinical scale production

- Initial targets were thin Th foils (0.127mm, 0.9g) encapsulated in Al. Used to support small scale production for chemistry development and for ^{225}Ac cross section determinations.
- Recent larger diameter (0.38mm thick,13g)BNL targets to support new rastered beam at BLIP were sealed in inconel by electron beam welding.
- 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 assuming ideal thermal contact for a 3 mm thick target (105g) predicts low peak temperature but actual thermal contact conductance will be lower.







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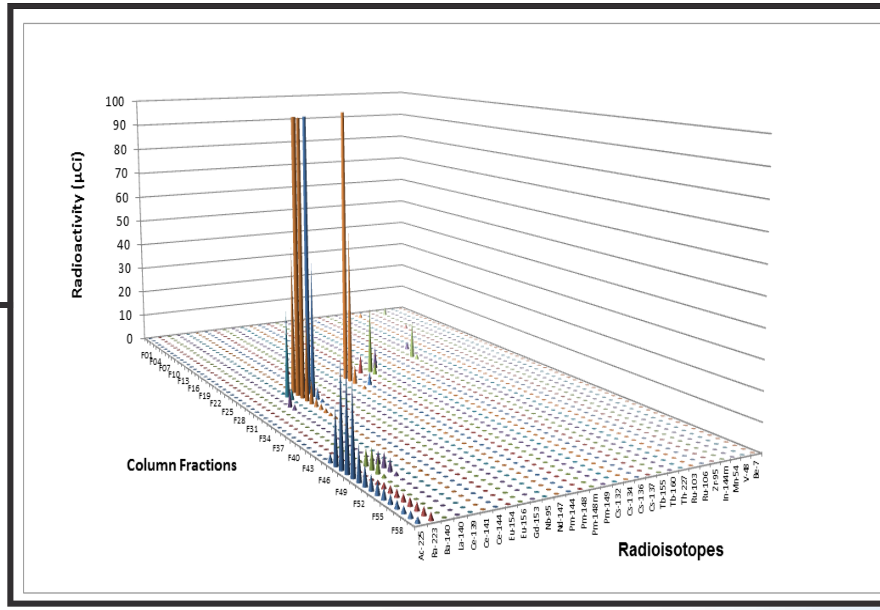
Technical Risks Unique to Accelerator Production: Process Chemistry



Accelerator production introduces complex chemistry challenges like separation of ^{225}Ac from Th target mass, radiolanthanide byproducts and other nca radionuclides

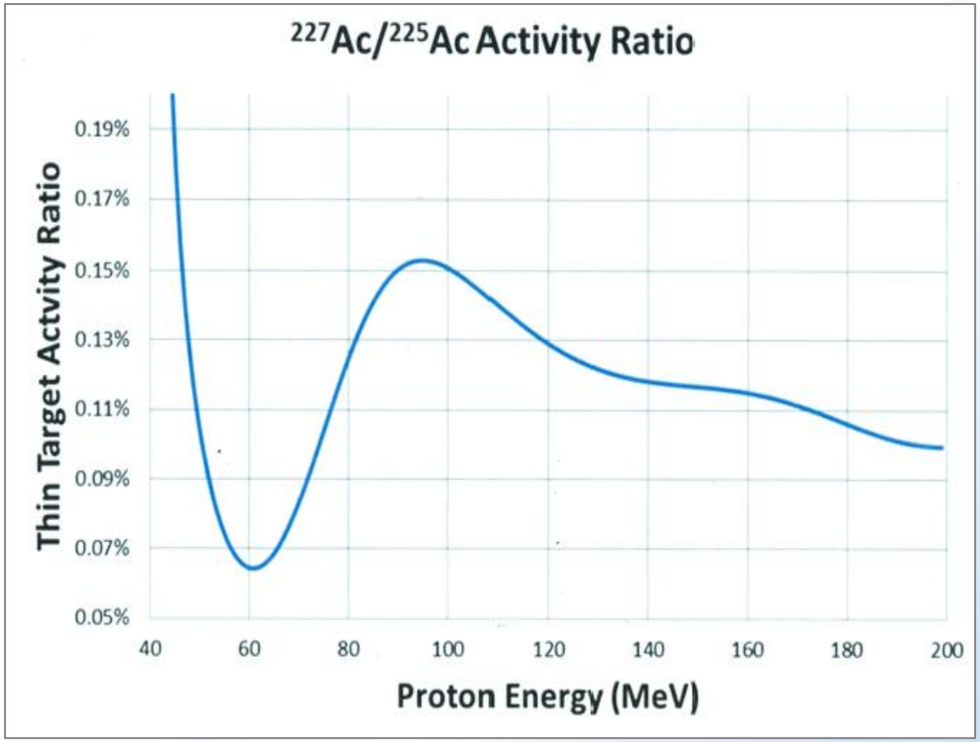
Exploring the application of HPIC to separate ^{225}Ac from radiolanthanides

Developing conventional, in-hot-cell process flow sheet using column chromatography approaches

Challenges Associated with Accelerator Produced ^{225}Ac and Direct Application: The ^{227}Ac Content

- **Production of ^{225}Ac also results in the co-production of ^{227}Ac ($t_{1/2}$ = 21.8 y). Ratio improves at higher proton energy, but degrades with longer irradiations.**

- **Concern regarding impact of ^{227}Ac on dosimetry, toxicity and waste disposal**



Instantaneous activity ratio of ^{227}Ac to ^{225}Ac for a thin Th target as a function of proton beam energy. Note that beam energy range captures current capabilities at BNL's BLIP and LANL's IPF facilities.

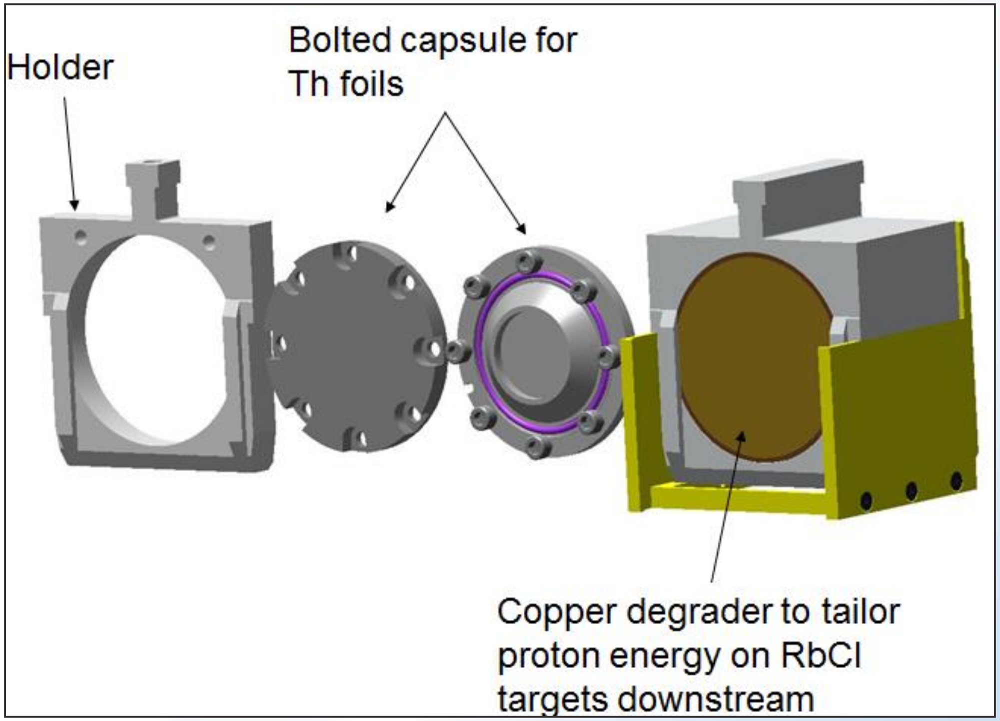
Quality of Product: “Proto-Production” for Materials Evaluation

22 thorium targets have been irradiated at LANL and BNL in support of initial target R&D, chemistry development and product evaluation.

Approximately 150 mCi of accelerator-produced Ac-225 has been isolated and distributed from ORNL for independent evaluation by end users.

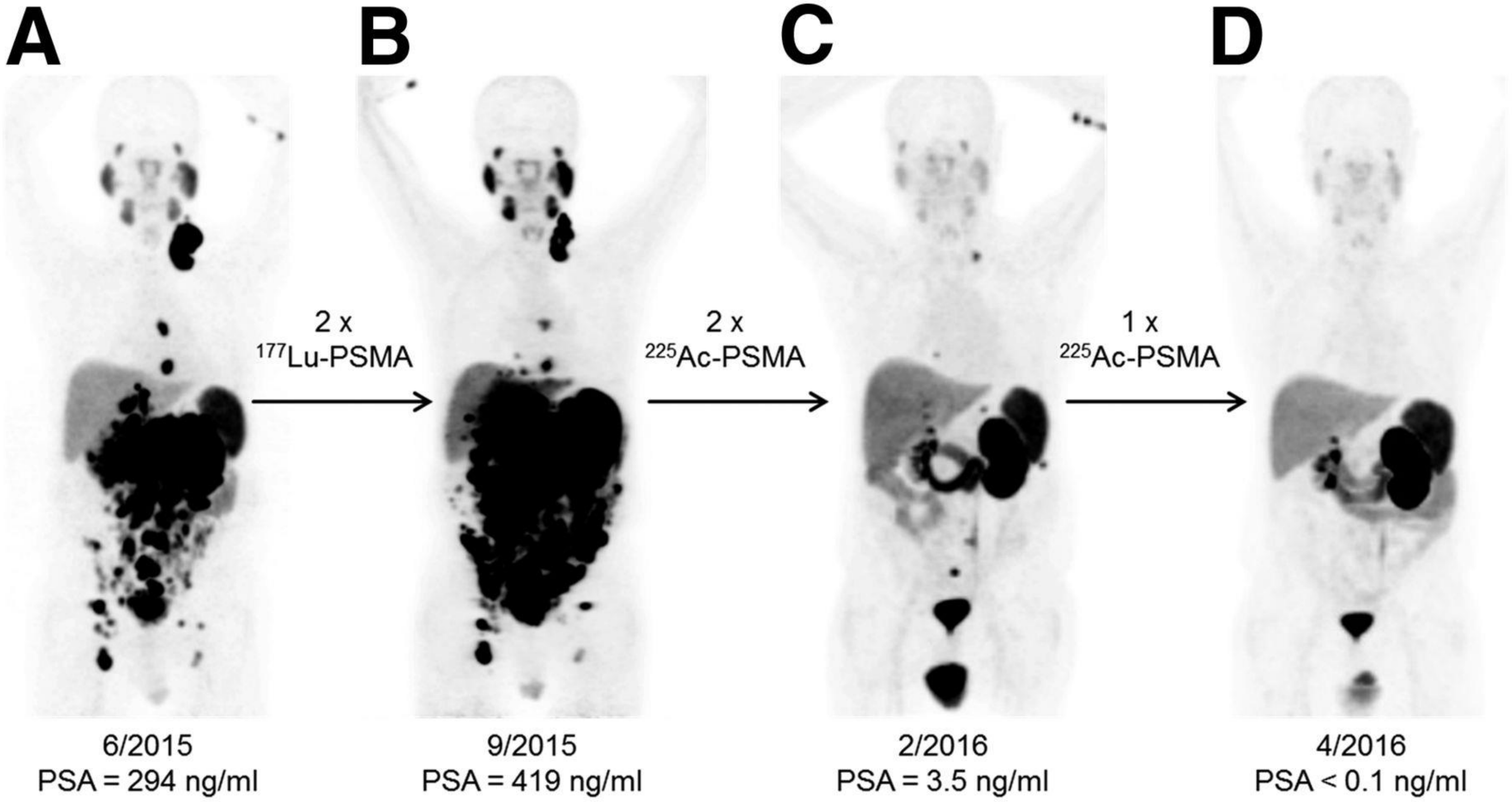
^{225}Ac/^{213}Bi generator performance is equivalent to generators derived from ^{229}Th-derived ^{225}Ac.

Preliminary direct labeling studies of the accelerator-derived ^{225}Ac product are promising



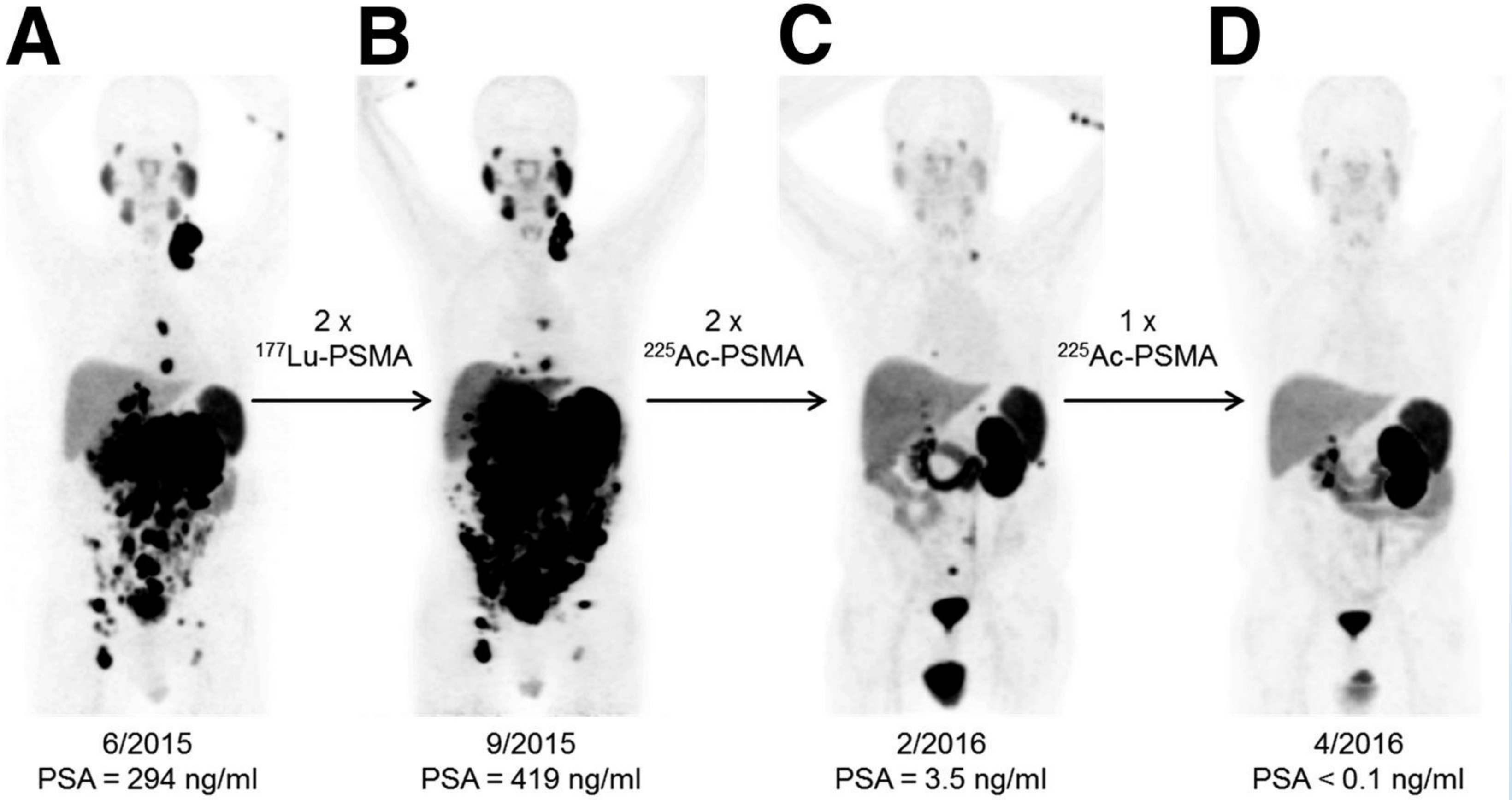
Recent Target Developments: Rendering of front basket of 200 MeV Th target array at BLIP

Prostate Cancer Therapy



68Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting 177Lu-PSMA-617 presented progression (B). Clemens Kratochwil et al. J Nucl Med 2016;57:1941-1944

Prostate Cancer Therapy



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Summary

- BLIP routinely receives proton beam from LINAC at 117 MeV and average current 165 µA
- A total of 160 mm of target space is available both for research and production
- 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 RbCl targets and used for production of ^{72}Se, ^{44}Ti, ^{225}Ac and other radionuclides.
- Targetry has been developed allowing for long irradiations, further chemistry has been developed to allow for processing.

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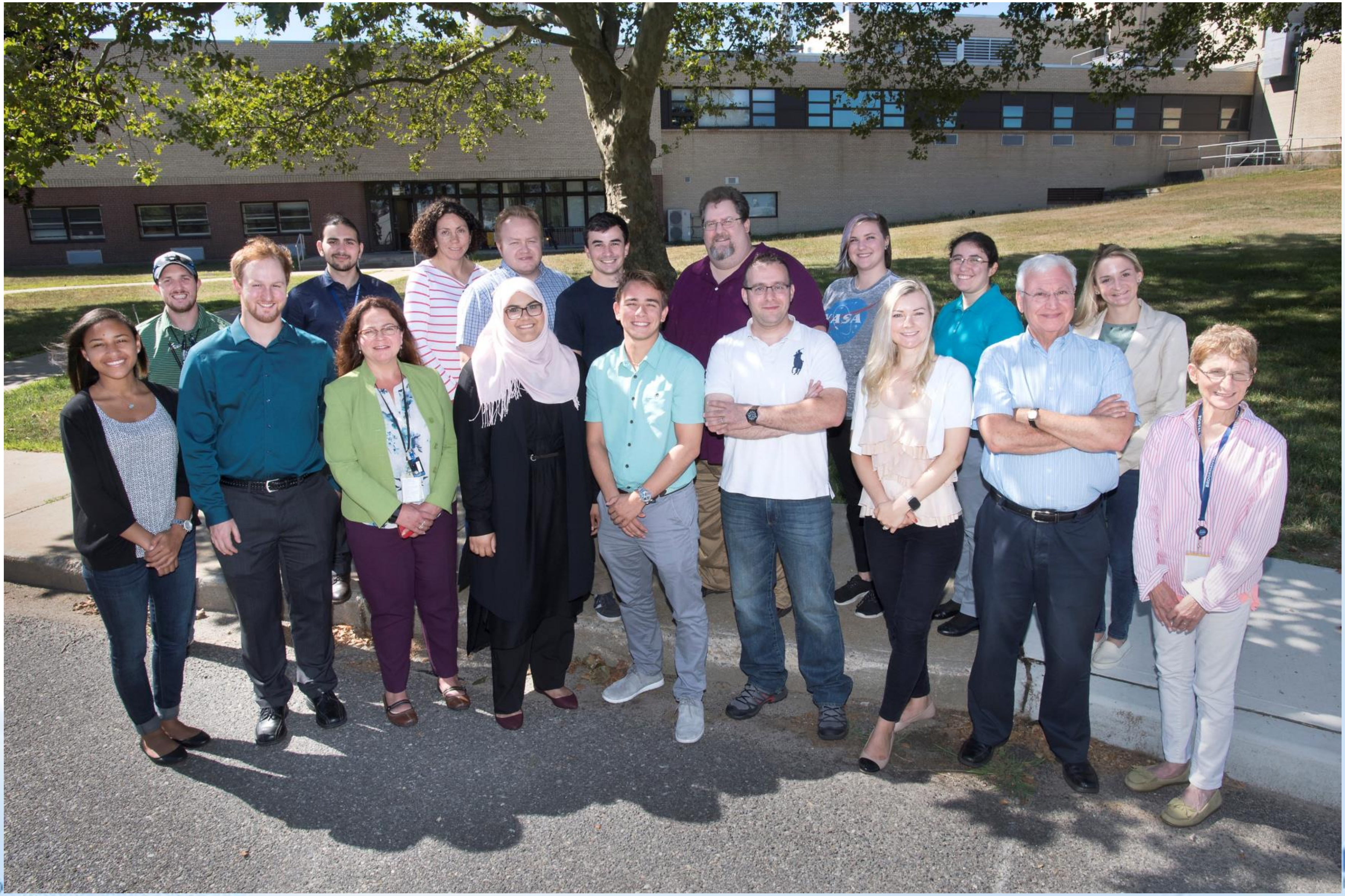

Questions