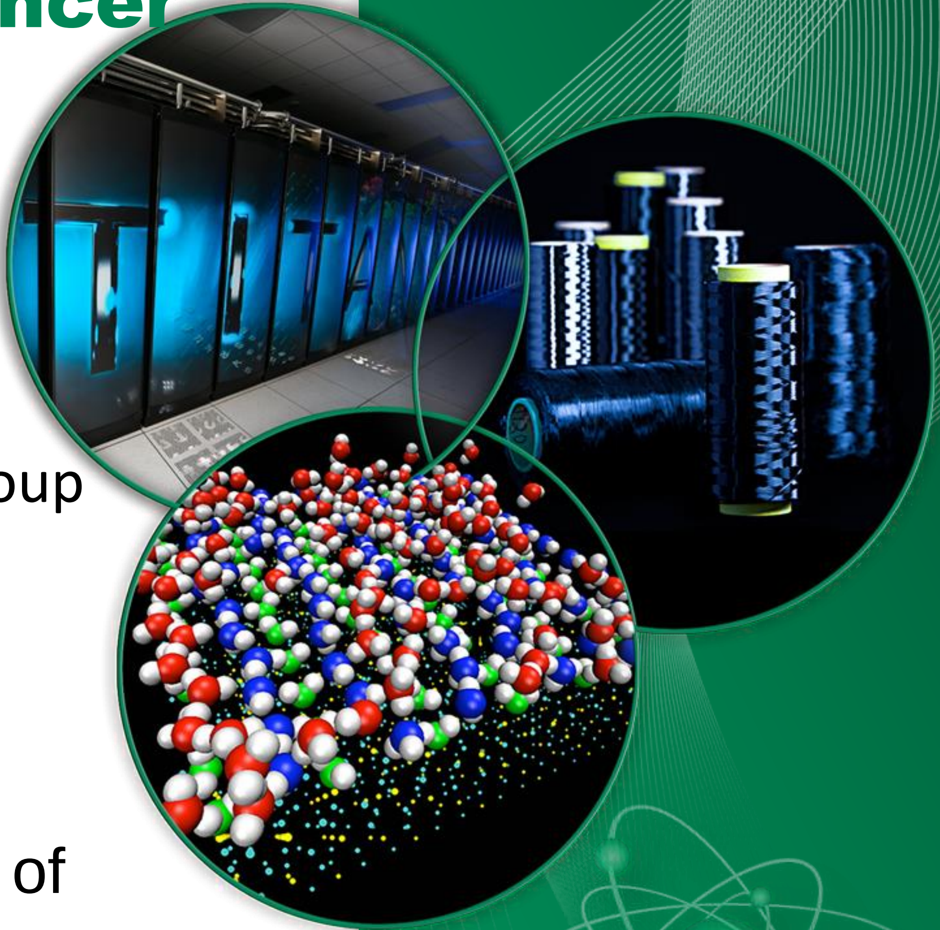
Production of Alpha-emitting Radionuclides for Cancer Therapy



Saed Mirzadeh

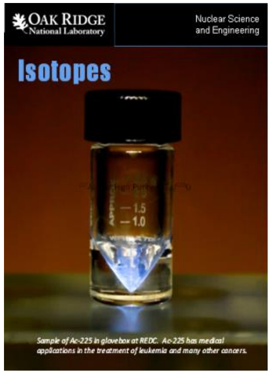
Medical Radioisotope Program
Nuclear Material Processing Group

Nuclear Security and Isotope Technology Division

Knoxville-Oak Ridge Section of the American Institute of Chemical Engineers,

Thursday, November 10, 2016

Outline



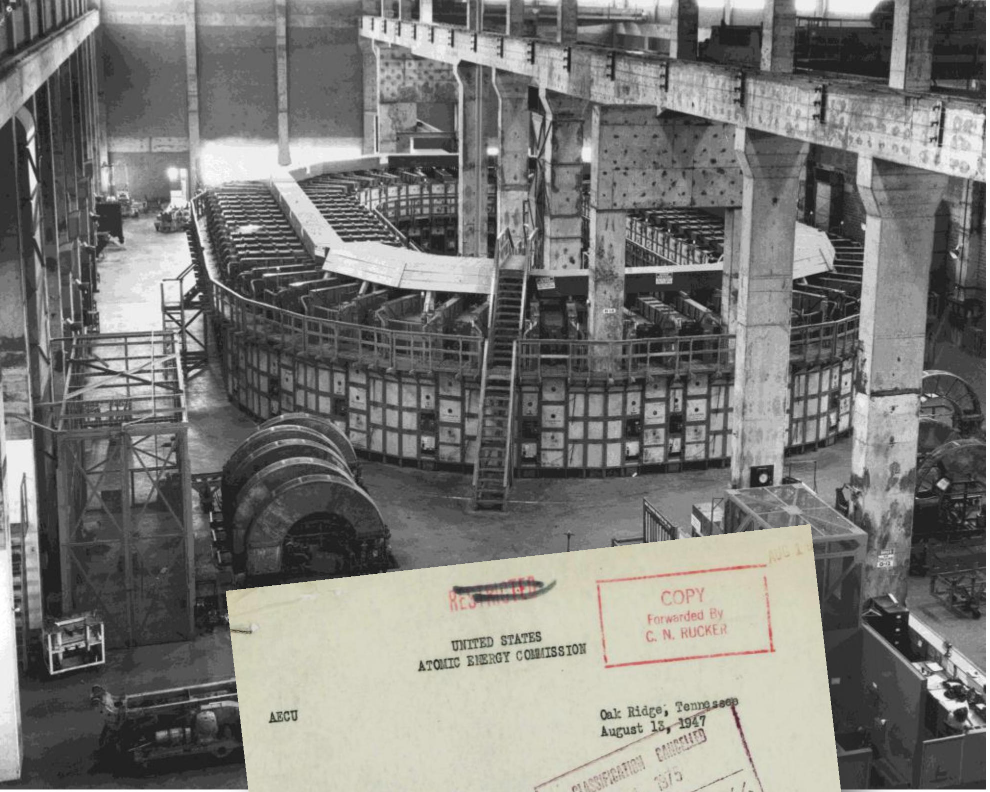
- **Background**
- **Availability of ^{225}Ac/^{213}Bi and ^{224}Ra/^{212}Pb generator systems through natural decay of ^{229}Th and ^{228}Th**
- **New Initiatives to Enhance Production of Ac-225**

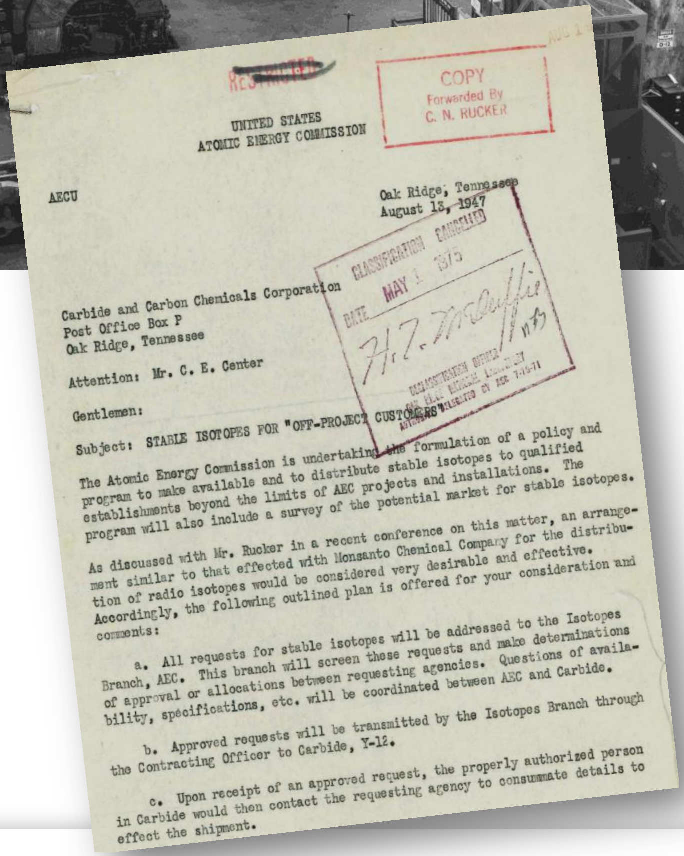
  a. Direct production of ^{225}Ac in a high energy proton accelerator
  b. Reactor Production of ^{229}Th at ORNL High Flux Isotope Reactor (Nuclear Data)
  c. Production of ^{229}Th via low energy protons (Nuclear Data)

- ***Xofigo*, *1st* approved "targeted" alpha therapy (TAT) for treatment of advanced prostate cancer**

- **^{227}Ac production: larger scale pilot demonstration**

Isotope production, enrichment and distribution began at Oak Ridge just after WWII





COPY
Forwarded By
C. N. RUCKER

UNITED STATES
ATOMIC ENERGY COMMISSION

AECU

Oak Ridge, Tennessee
August 13, 1947

Carbide and Carbon Chemicals Corporation
Post Office Box P
Oak Ridge, Tennessee

Attention: Mr. C. E. Center

Gentlemen:

Subject: STABLE ISOTOPES FOR "OFF-PROJECT CUSTOMERS"

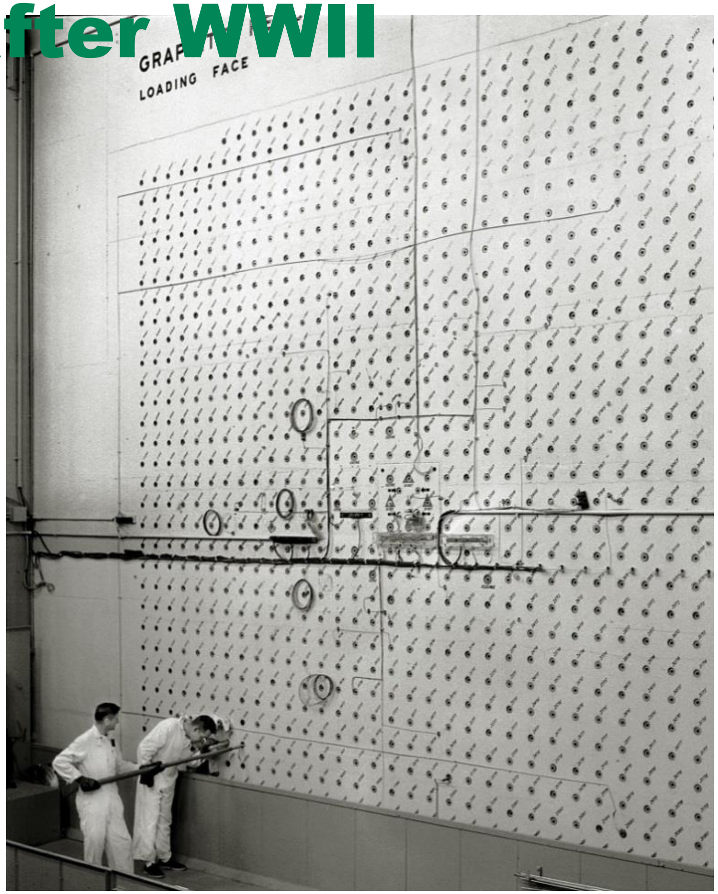
The Atomic Energy Commission is undertaking the formulation of a policy and program to make available and to distribute stable isotopes to qualified establishments beyond the limits of AEC projects and installations. The program will also include a survey of the potential market for stable isotopes.

As discussed with Mr. Rucker in a recent conference on this matter, an arrangement similar to that effected with Monsanto Chemical Company for the distribution of radio isotopes would be considered very desirable and effective. Accordingly, the following outlined plan is offered for your consideration and comments:

a. All requests for stable isotopes will be addressed to the Isotopes Branch, AEC. This branch will screen these requests and make determinations of approval or allocations between requesting agencies. Questions of availability, specifications, etc. will be coordinated between AEC and Carbide.

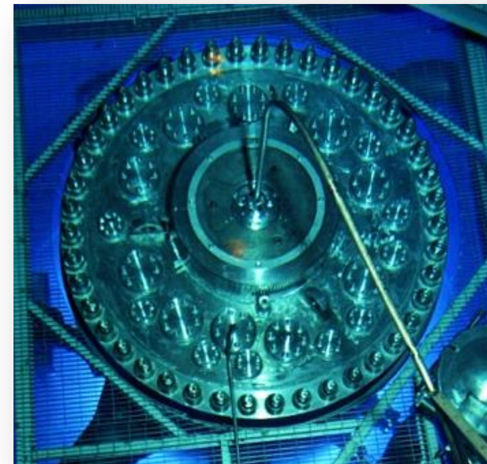
b. Approved requests will be transmitted by the Isotopes Branch through the Contracting Officer to Carbide, Y-12.

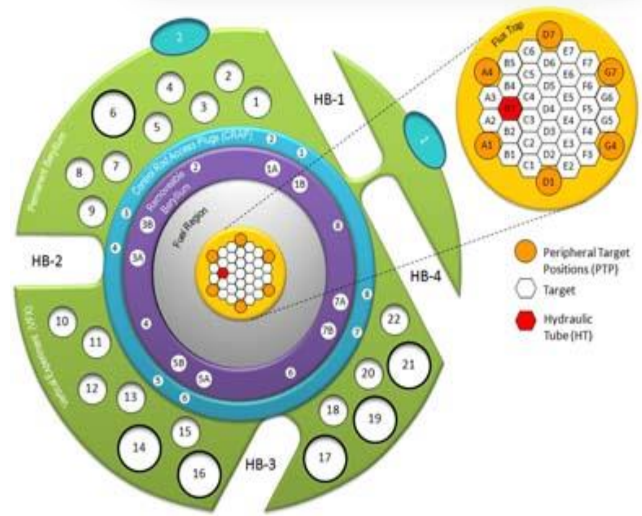
c. Upon receipt of an approved request, the properly authorized person in Carbide would then contact the requesting agency to consummate details to effect the shipment.



ORNL's unique combination of radioisotope research and production assets

- **High Flux Isotope Reactor (HFIR)**
  - LWR, flux trap; 85 MW full power; peak thermal neutron flux of 2.1×10^{15} $n.cm^{-2}.s^{-1}$
- **Hot Cell and Processing Facilities**
  - Five active nuclear facilities including REDC and one radiological facility
- **On path to reestablishing enrichment capabilities**





Alpha-Emitting and Other Novel Therapeutic Medical Radioisotopes Available from ORNL

Alpha emitters:

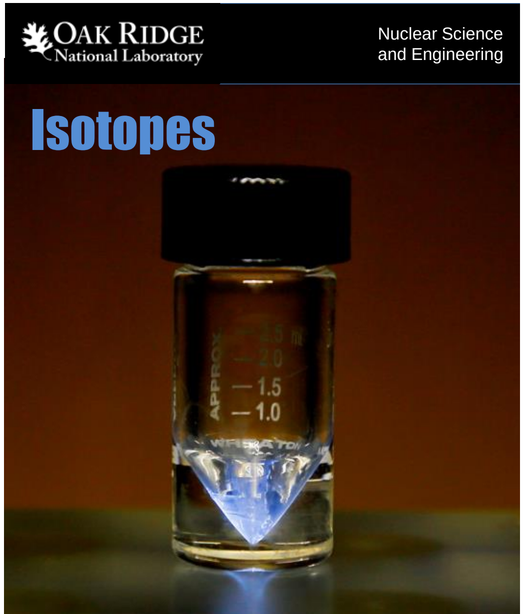
- Actinium-225/Bismuth-213
- Radium-224/Lead-212
- Actinium-227/Thorium-227/Radium-223

High-energy Beta emitter:

- Tungsten-188/Rhenium-188

Low-energy Beta emitter:

- Strontium-89



Sample of Ac-225 in glovebox at REDC. Ac-225 has medical applications in the treatment of leukemia and many other cancers.

Therapeutic Nuclear Medicine

- Targeted therapy
  - α, β, γ emitters delivered to diseased tissue
- Strategies
  - Molecular targeting: Monoclonal antibodies, peptides, etc; ^{90}Y, ^{177}Lu, ^{213}Bi
  - Natural targeting: Thyroid ($^{131}I^{-}$), Bone($^{89}SrCl_2$, $^{223}RaCl_2$, ^{153}Sm & ^{188}Re Phosphate complexes, ^{117m}Sn-DTPA), Liver (^{90}Y & ^{166}Ho particles)
  - Brachytherapy: Prostate cancer (^{103}Pd, ^{125}I, ^{131}Cs), others

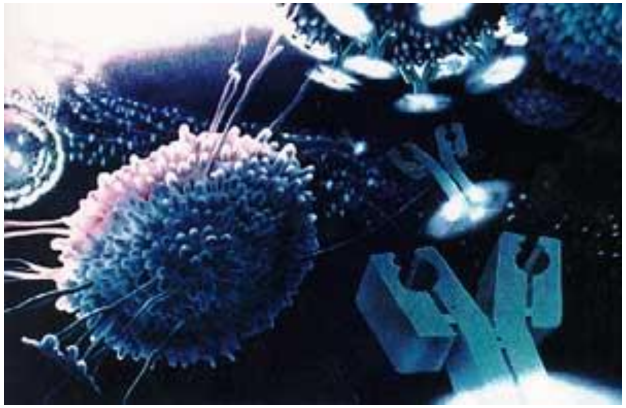
"Xofigo, 1st α-emitting radioisotope ($^{223}RaCl_2$), for treatment of bone cancer, received approval from FDA and European Commission in 2013"

"Zevalin", 1st β-emitting radioisotope (^{90}Y-Ibritumomab tiuxetan) for treatment B cell non-Hodgkin's lymphoma

Prostate Cancer Seed

Alpha-Emitters for Therapeutic Applications

- **Important attributes**
  - High linear energy transfer
  - Half-life compatible with therapy
  - Versatile Chemistry
  - Availability
- **Alpha-emitters of interest**
  - ^{212}Bi (60 m) and ^{213}Bi (46 m)
  - ^{212}Pb(10 h)/ ^{212}Bi
  - ^{225}Ac(10 d)/ ^{213}Bi
  - ^{211}At (7 h, accelerator produced)
  - ^{223}Ra (11 d)
  - ^{227}Th (19 d)/^{223}Ra

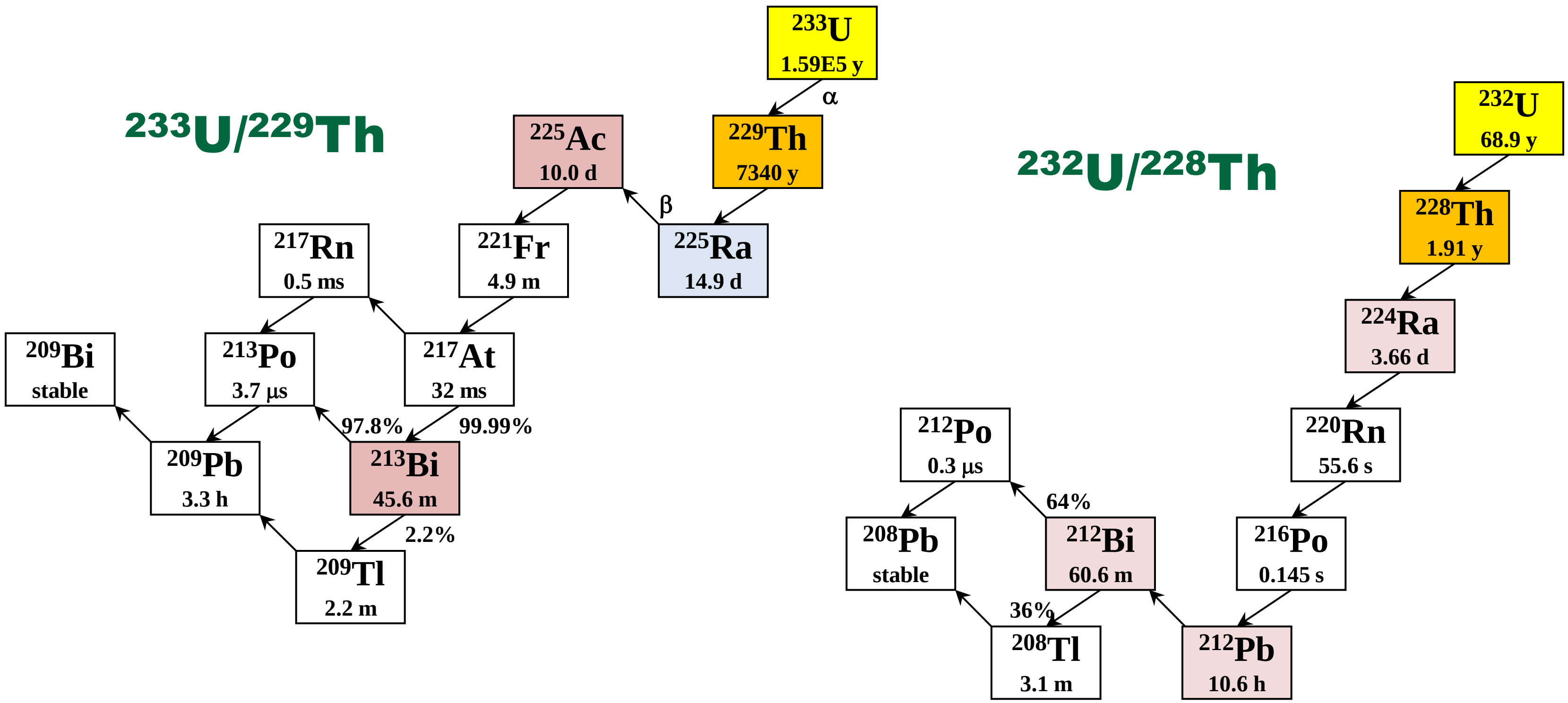


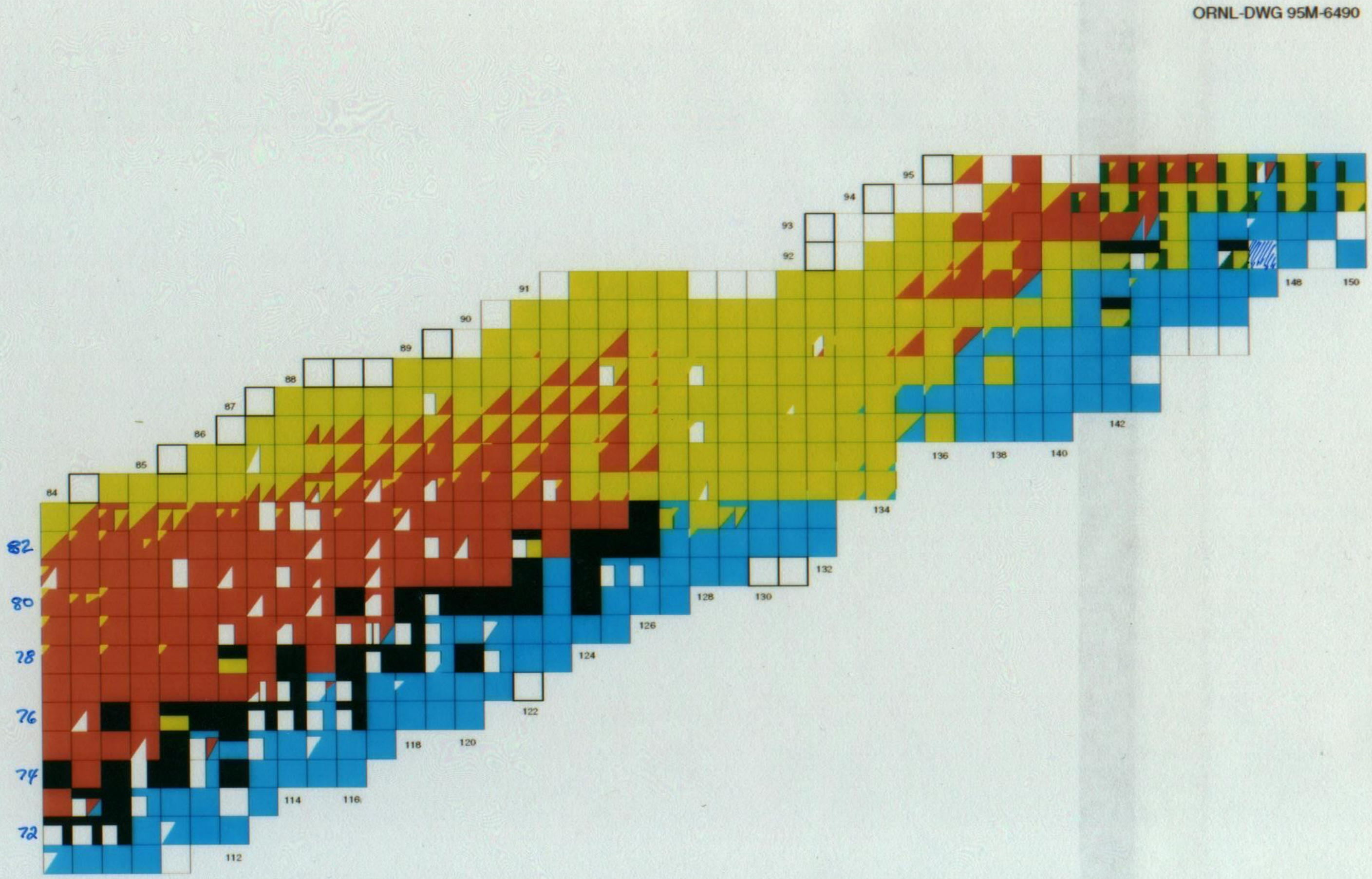
Radioimmunotherapy

ORNL ^{225}Ac /^{213}Bi Generator

Availability of $^{225}Ac/^{213}Bi$ and $^{224}Ra/^{212}Pb$ generator systems through natural decay of ^{229}Th and ^{228}Th

- Radiochemical extraction from ^{229}Th and ^{228}Th sources




ORNL-DWG 95M-6490
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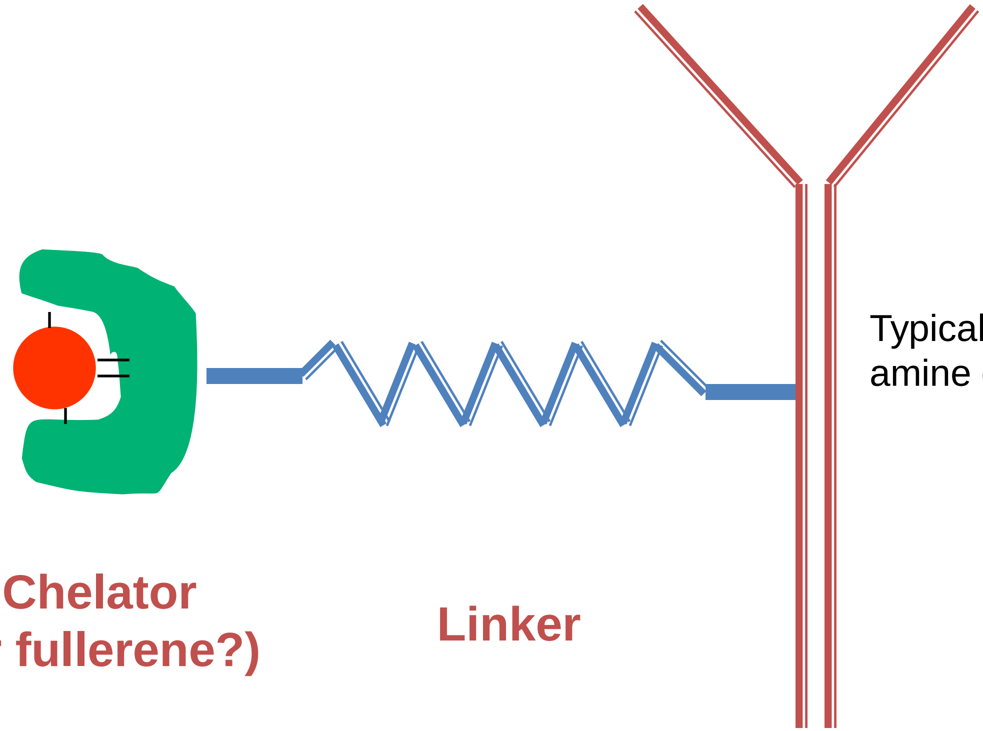
Radioimmunotherapy (RIT) Concept

Radionuclide



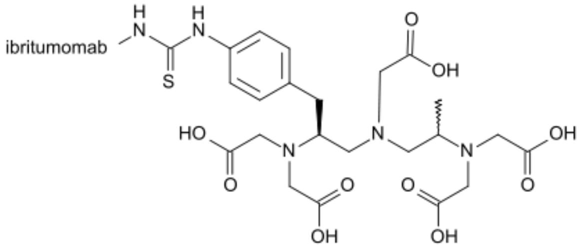
Typical attachment to
amine group on Lysine

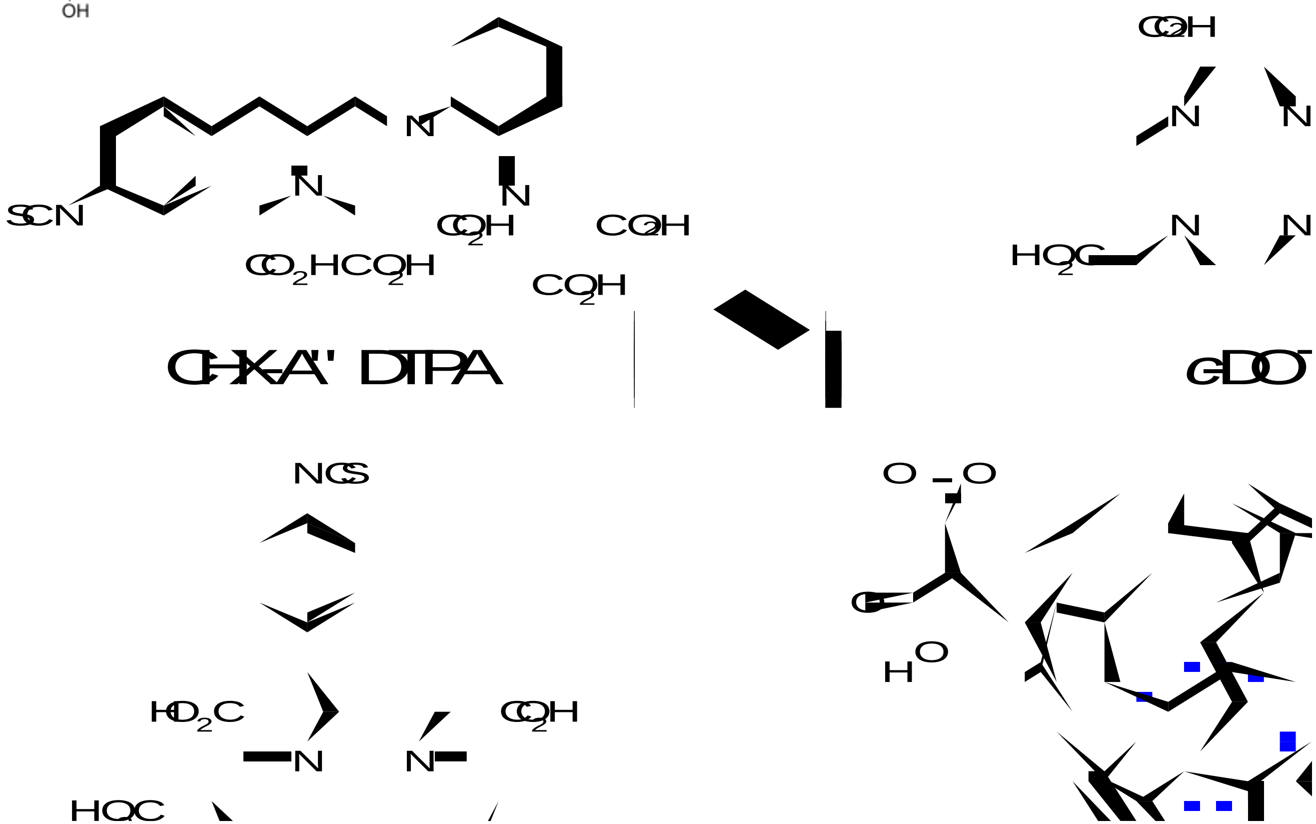
Chelator
(or fullerene?)

Linker

Method for Targeting Cancer
Cell Epitopes:
Antibody or Fragment, Peptide

Polyaminocarboxylate (PAC) Chelators and Fullerenes





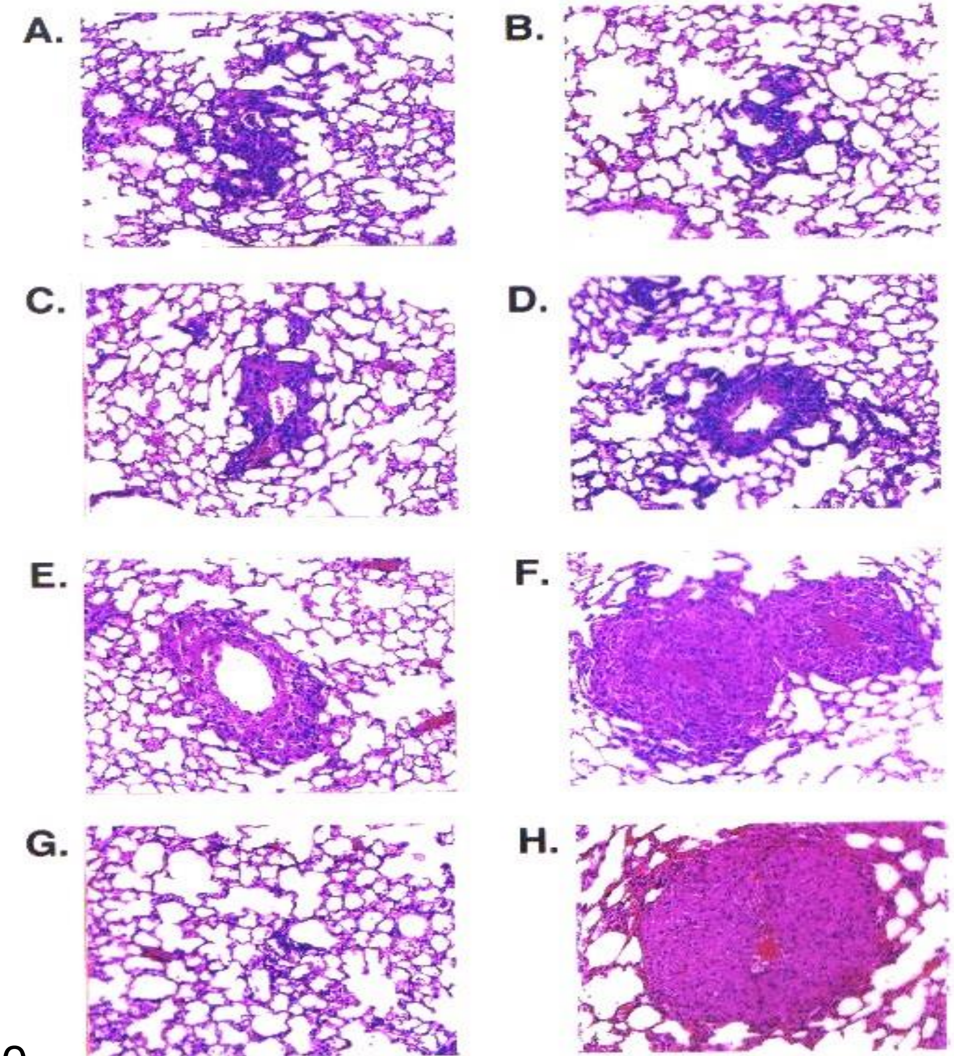
treated control

Day 0

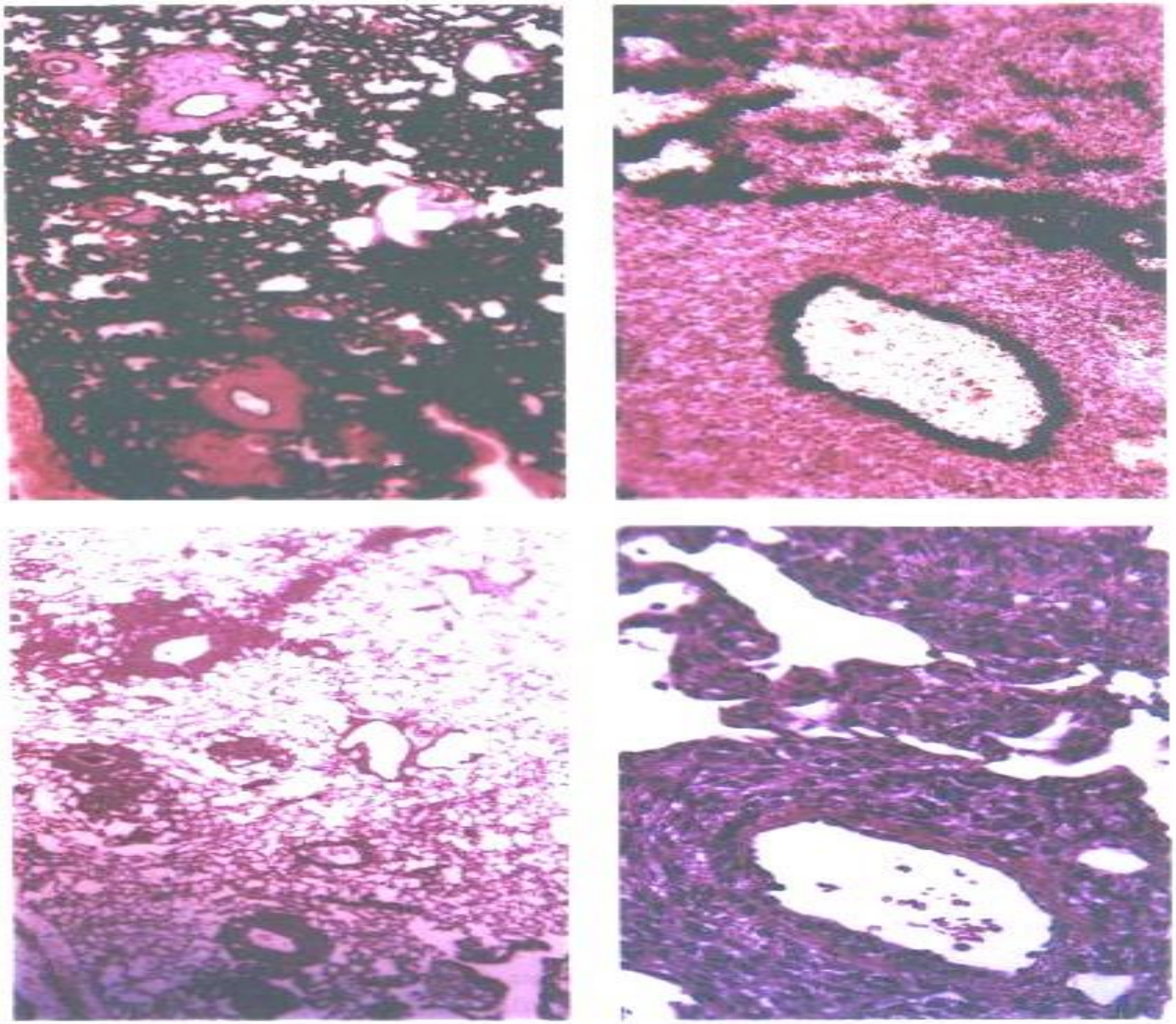
Day 1

Day 3

Day 5

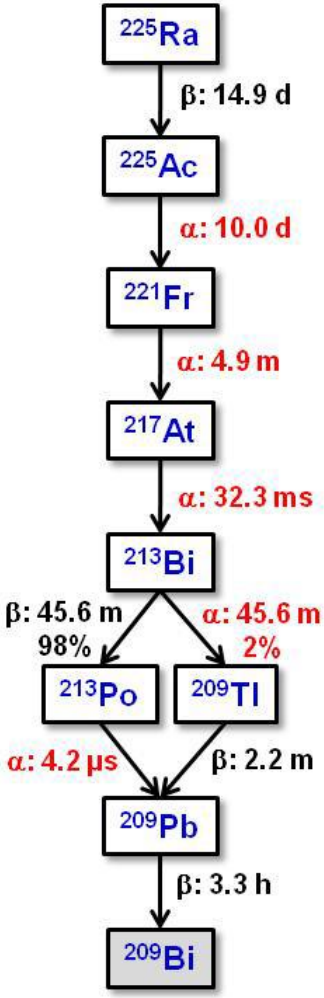


Kennel and Mirzadeh, 2000



Kennel and Mirzadeh, 2000

^{225}Ac - A Promising Isotope for α-Therapy



Cancer type	Radioconjugate	Phase	No. of patients
Leukemia	^{213}Bi-HuM195mAb	Phase I	18
Leukemia	^{213}Bi-HuM195mAb	Phase I/II	31
Leukemia	^{225}Ac-HuM195mAb	Phase I	18
Lymphoma	^{213}Bi-rituximab	Phase I	12
Melanoma	^{213}Bi-9.2.27mAb	Phase I (intralesional)	16
Melanoma	^{213}Bi-9.2.27mAb	Phase I (systemic)	38
Glioma	^{213}Bi-Substance P	- Phase I	2 6+19
Neuroendocrine tumours (GEP-NET)	^{213}Bi-DOTATOC	Phase I	25

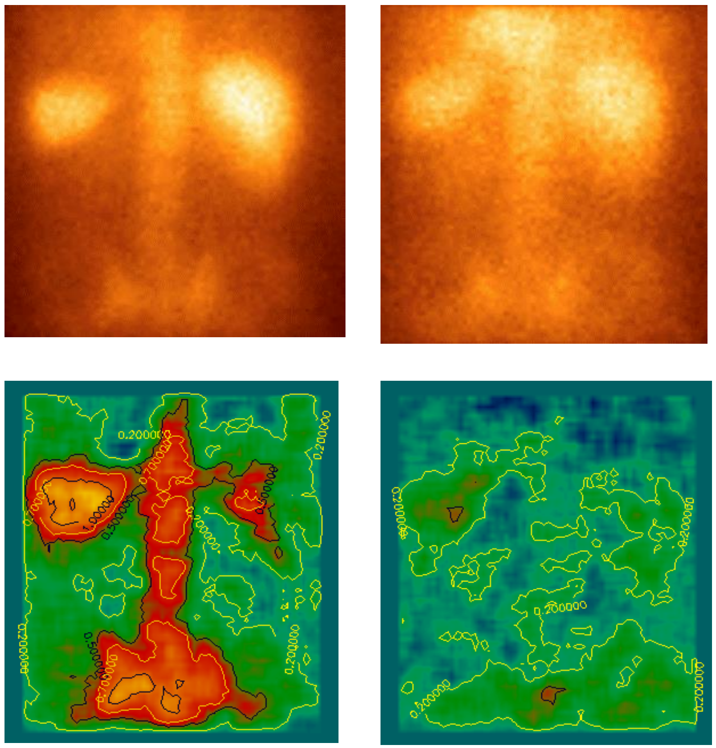
Table from: International Atomic Energy Agency. Technical Meeting Report "Alpha Emitting Radionuclides and Radiopharmaceuticals for Therapy" IAEA, 24-28 June **2013**.

Treatment of Acute Myelogenous Leukemia (AML) with Bismuth-213

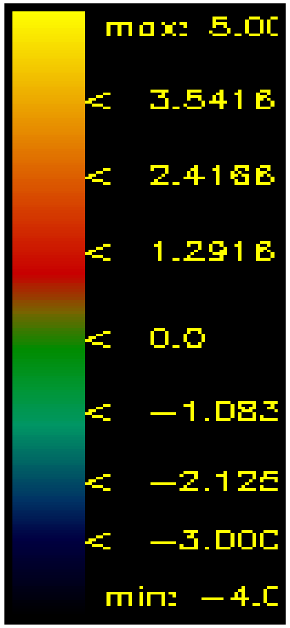
Dose 1 *Dose 4*

Posterior 60-Minute Summation

Rate/Minute



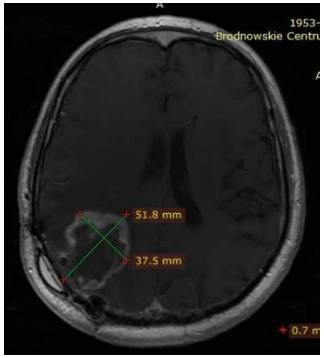
Patient No. 4



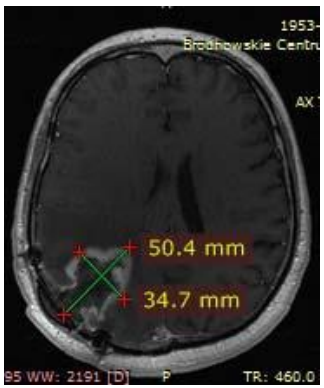
Courtesy of Actinium Pharmaceutical Inc. and Sloan Kettering Cancer Center, NY

Peptide receptor α-therapy of glioblastoma with Bi-213

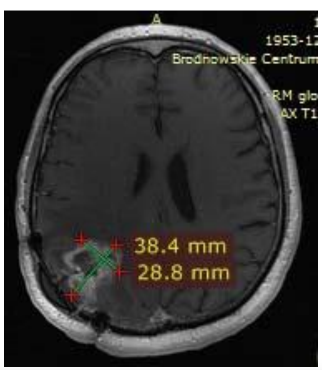
Courtesy of Alfred Morgenstern at ITU



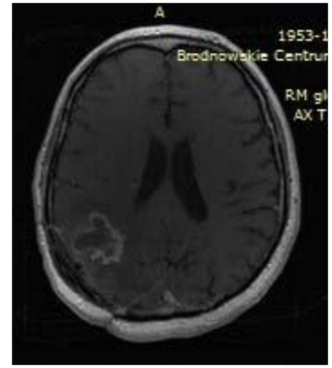
Before treatment



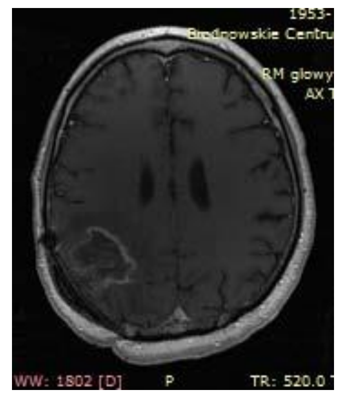
5 weeks post 1st treatment



5 weeks post 2nd treatment



7 weeks post 3rd treatment



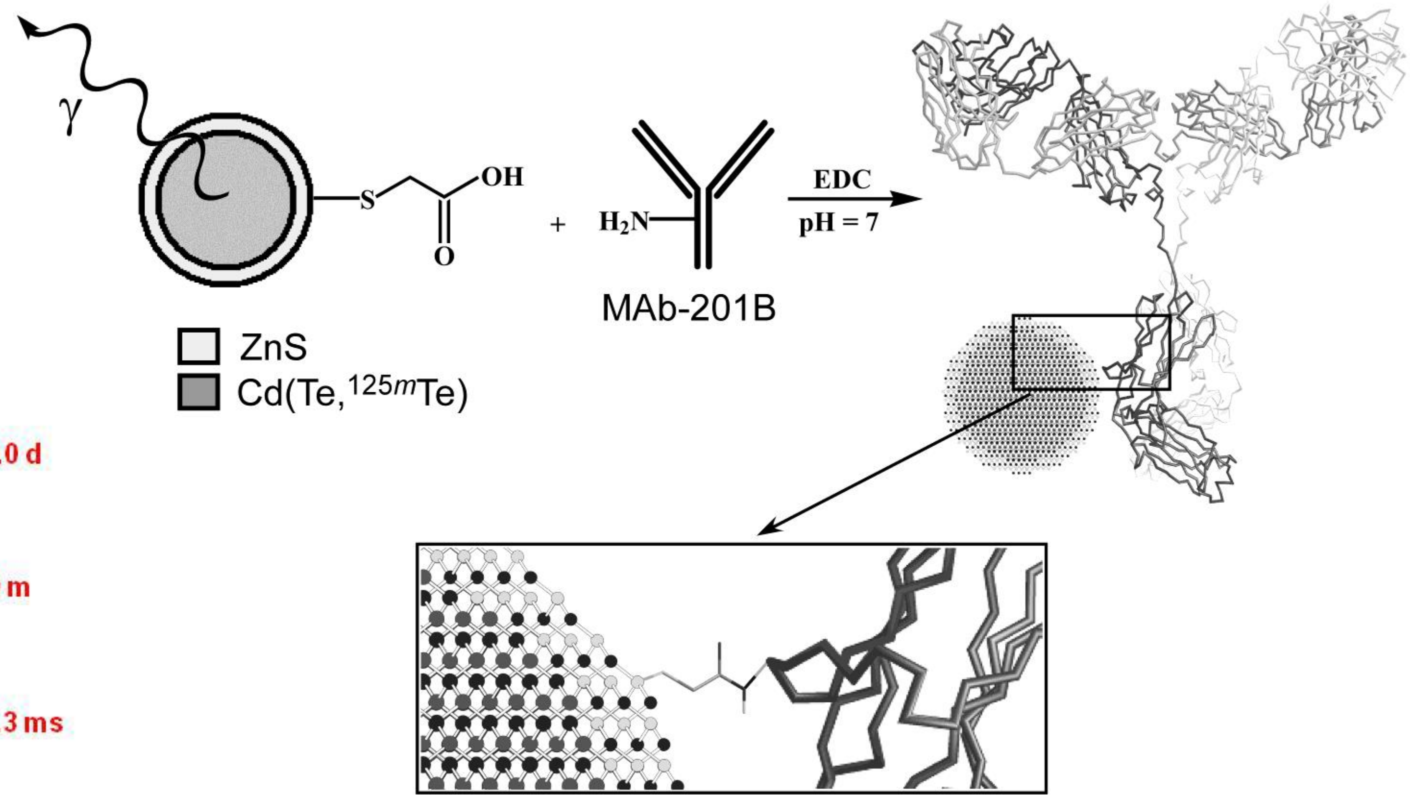
9 weeks post 4th treatment

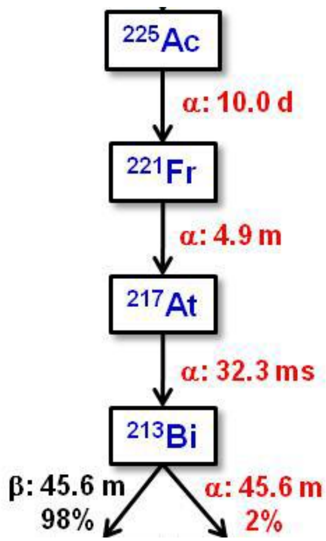
treatment continued to date : 5 cycles)

Overall survival:>23 months

Patient 6 – Glioblastoma grade IV (male, 59 y)

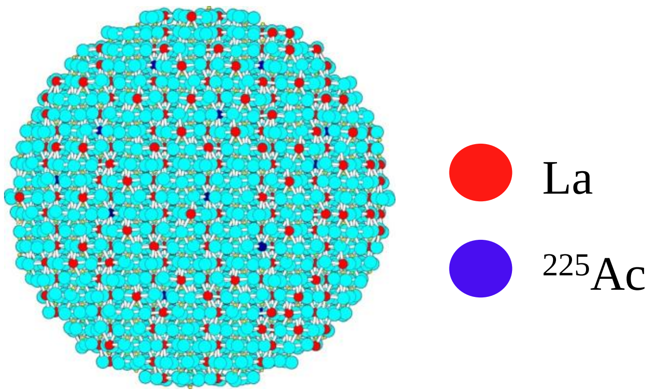
Nanoparticles Platform for in-vivo Delivery of Radionuclides



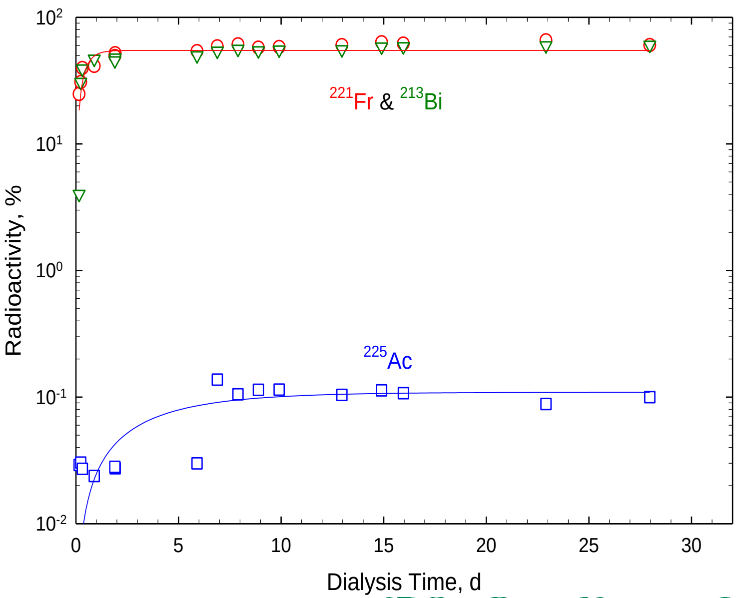


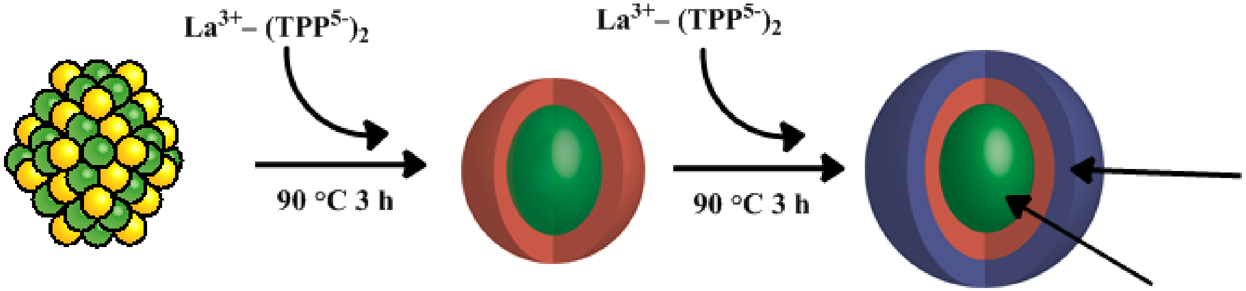
$LaPO_4$ Nanoparticles Platform for in-vivo Delivery of Actinium-225

Isotope	Half-life	α-Energy (MeV)	α-Recoil Energy (keV)	Recoil Range (nm)
^{225}Ac	10 d	5.829	107	20
^{221}Fr	4.9 m	6.341	116	22
^{217}At	32.3 ms	7.067	130	24
^{213}Bi	46 m	8.376	154	29



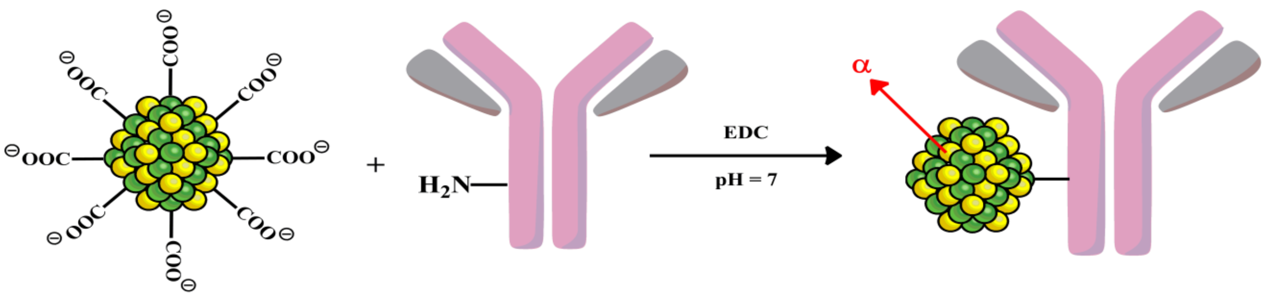
In-vitro Release of ^{225}Ac, ^{221}Fr and ^{213}Bi from $La(^{225}Ac)PO_4$ NPs

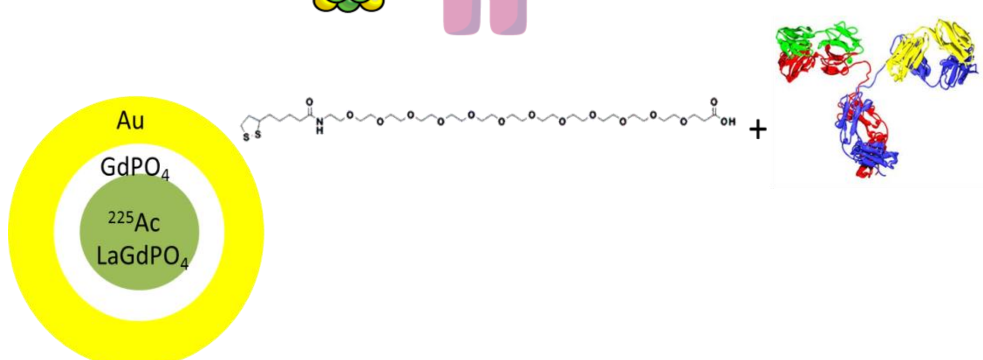




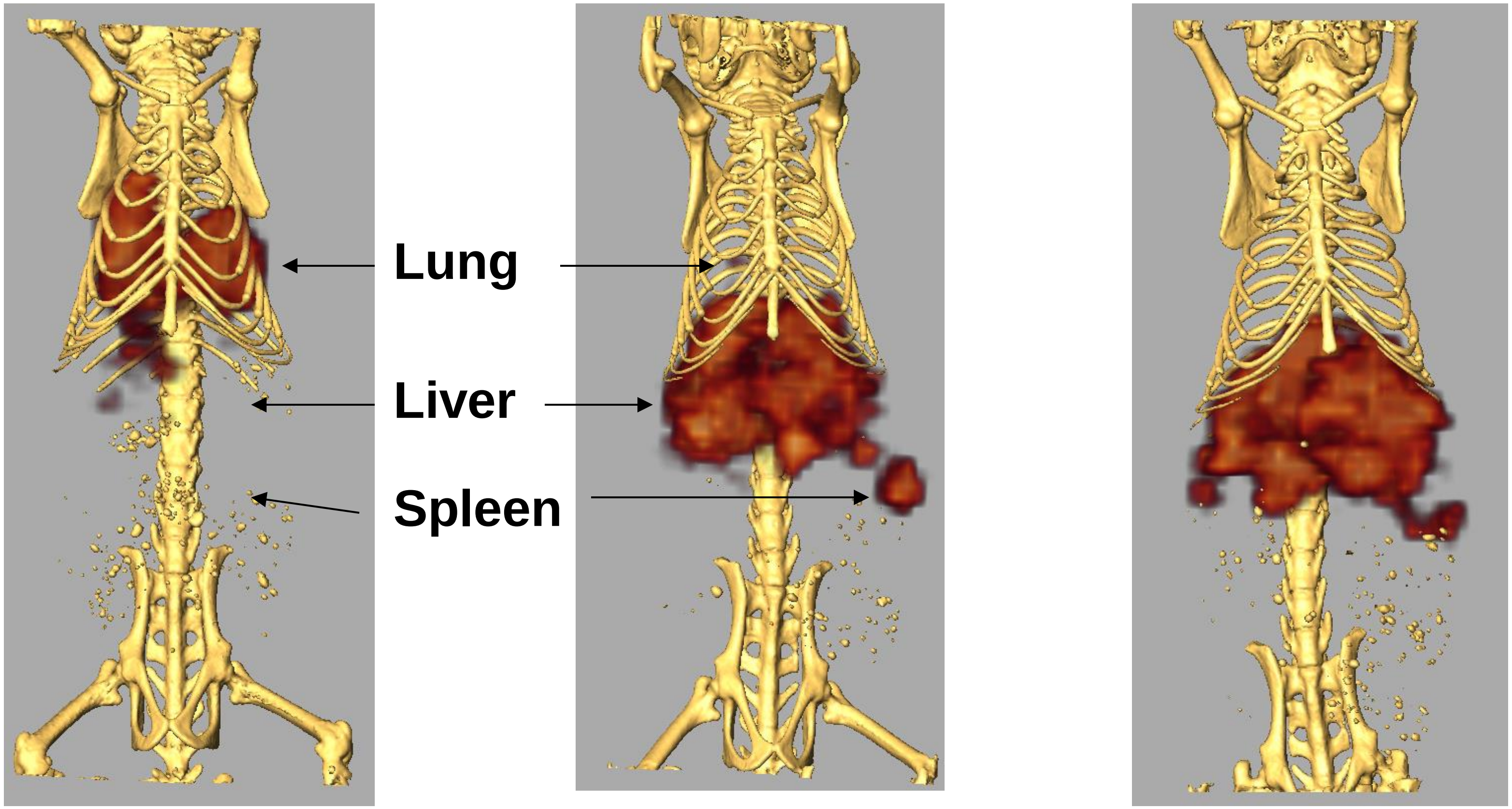
$GdPO_4$ Shells

$LaGd(^{225}Ac)PO_4$ Core





SPECT/CT of $^{225}AcLaPO_4$ Targeted Nanoparticles



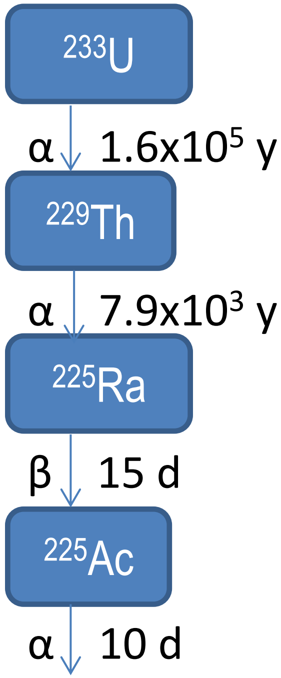
MAb 201B-NP

MAb 201B-NP & cold MAb

MAb 14-NP control

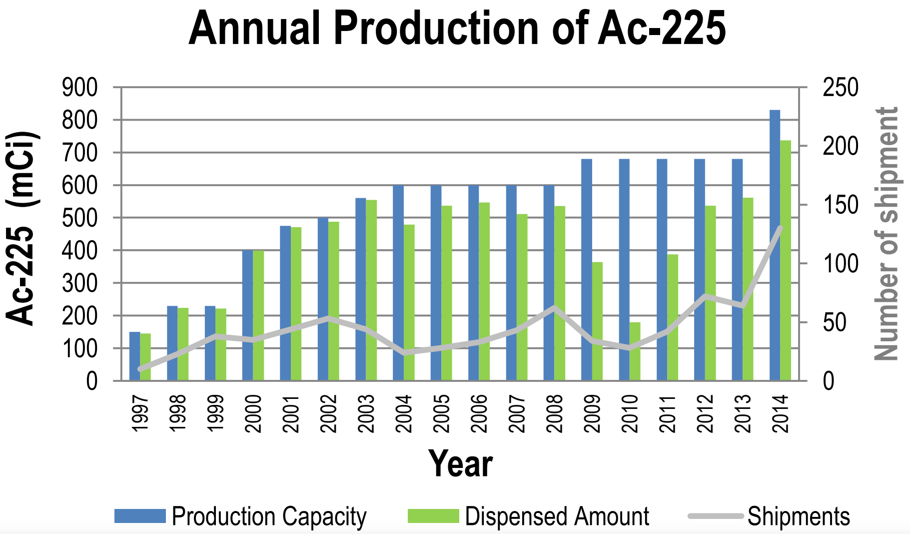
Background of Actinium-225 Production at ORNL

- ORNL has been the main supplier of ^{225}Ac (via decay of existing ^{229}Th stock) since 1997, with an annual budget of $1.8 M.
- 700-900 mCi of ^{225}Ac is harvested annually from 130–mCi ^{229}Th stock at ORNL.
- 6-12 campaigns are performed per year, and campaign 126 is currently underway

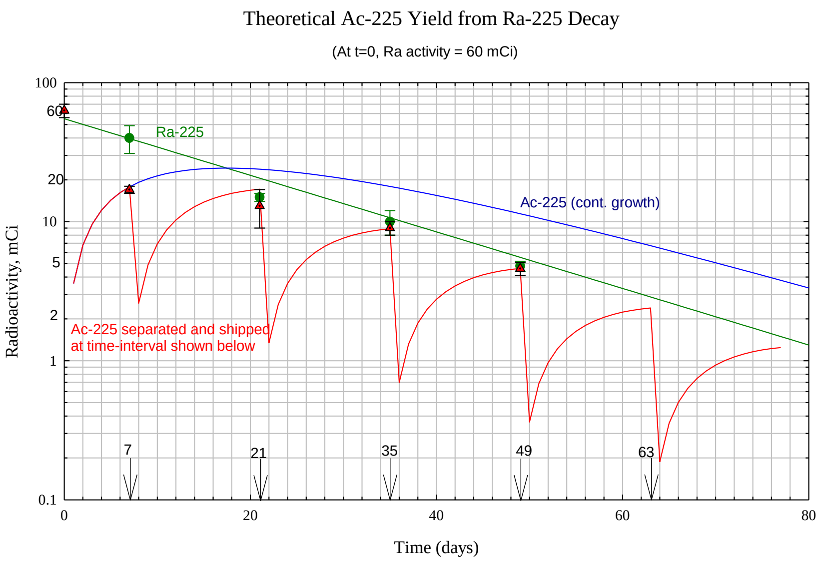


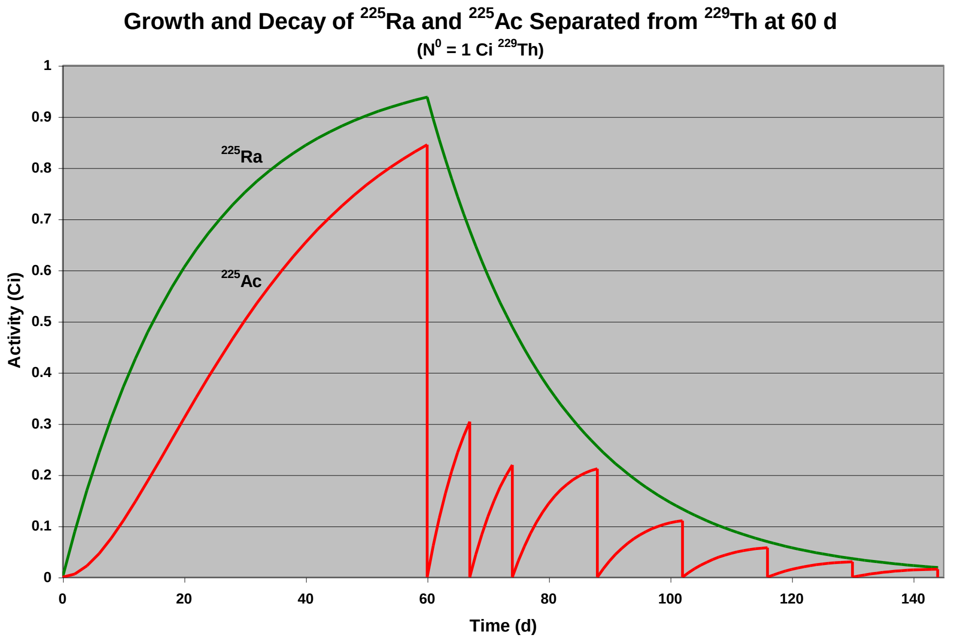
Rationale for R&D related to production of ^{225}Ac

- The present supply of ^{225}Ac is insufficient for current medical and research demands of ~6 Ci/year.



Production ^{225}Ac from Decay of ^{229}Th





New Initiatives to Enhance Production of Ac-225

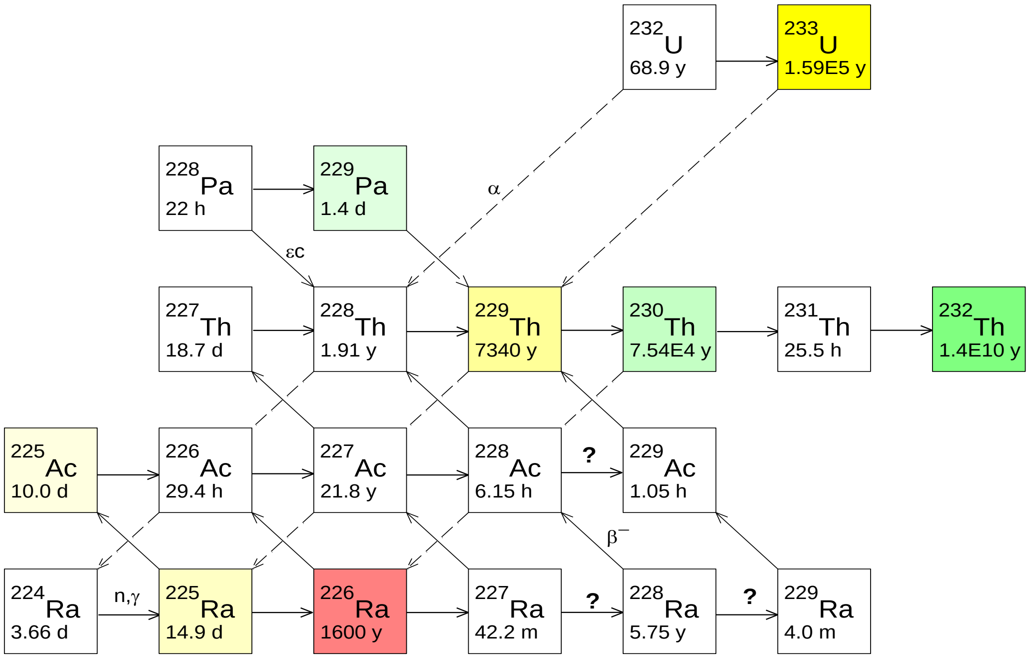
- Direct production of ^{225}Ac in a high energy proton accelerator
- Reactor Production of ^{229}Th at ORNL High Flux Isotope Reactor (Nuclear Data)
- Production of ^{229}Th via low energy protons (Nuclear Data)

Direct production of ^{225}Ac in a proton accelerator

The new collaboration between ORNL, BNL and LANL aims at developing a plan for full-scale production and stable supply of ^{225}Ac by irradiating ^{232}Th targets in the BNL BLIP and LANL IPF, and target processing at ORNL

ORNL Contributions:

- Develop the processing chemistry
- Evaluate yields and impurities
- Construct and evaluate $^{225}Ac/^{213}Bi$ Generator
- Provide Ac and generator to selected customers for in vivo evaluation



1st publication of tri-lab efforts: Griswold et al, Large Scale Accelerator Production of ^{225}Ac: Effective Cross Sections for 78-192 MeV Protons Incident on ^{232}Th Targets (in print, App. Rad. Isot., 2016)

Challenges Associated with Accelerator-Based Production of ^{225}Ac -- Complex Chemistry

Thorium Target Mass :
1-10 g – initial mass, 50-100 g – anticipated for Ci-level targets

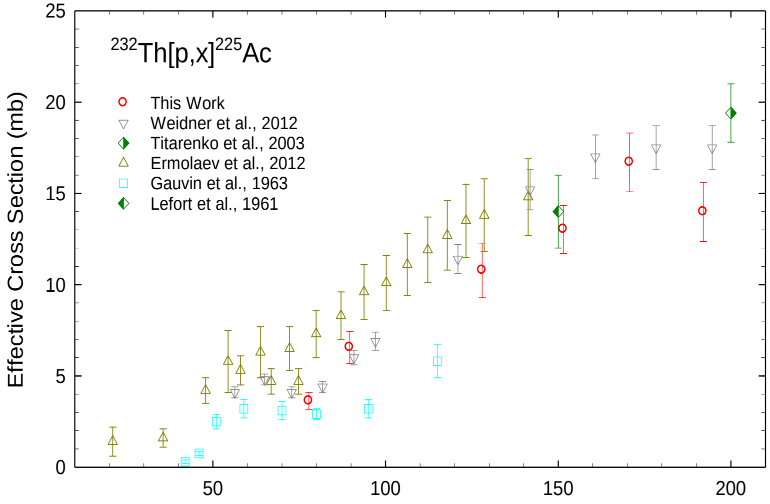
Production of Radiolanthanides:
Significant challenge to separate trivalent Ln-isotopes from ^{225}Ac (specifically ^{140}La and ^{141}Ce)

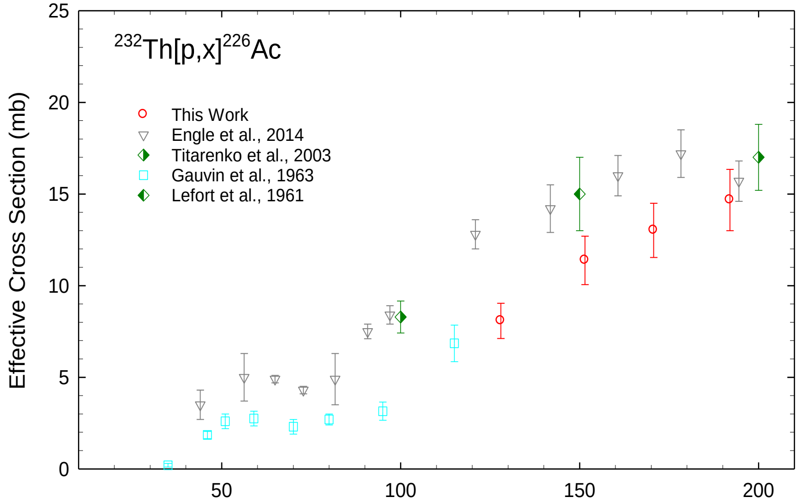
Production of large quantities of fission products:
In the 100-200 MeV proton energy range, for every mCi of ^{225}Ac, 12.5 mCi of fission products are produced

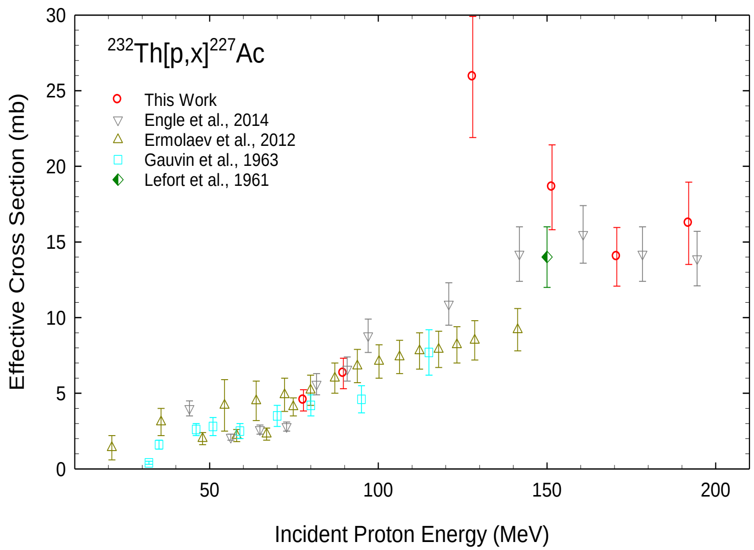
Timing: The $^{227}Ac/^{225}Ac$ ratio (~0.2% at EOB) gets worse with time

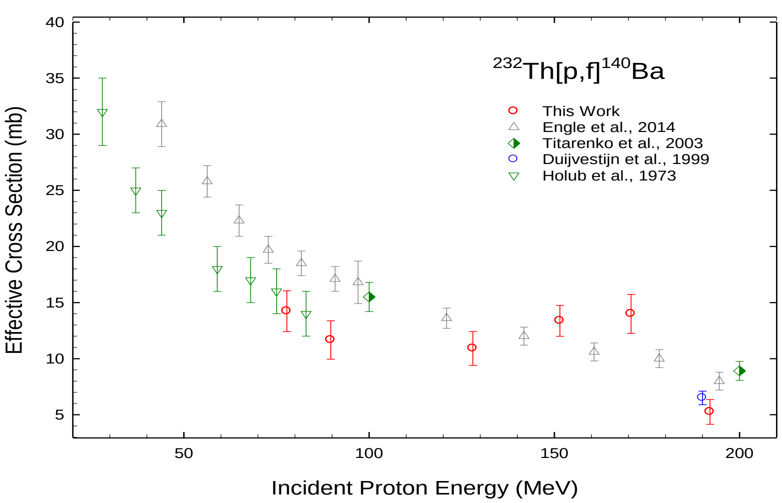
Toxicity: Biological toxicity of minute amount of 0.2% ^{227}Ac in ^{225}Ac is not evaluated

Accelerator Production of ^{225}Ac (cont.)

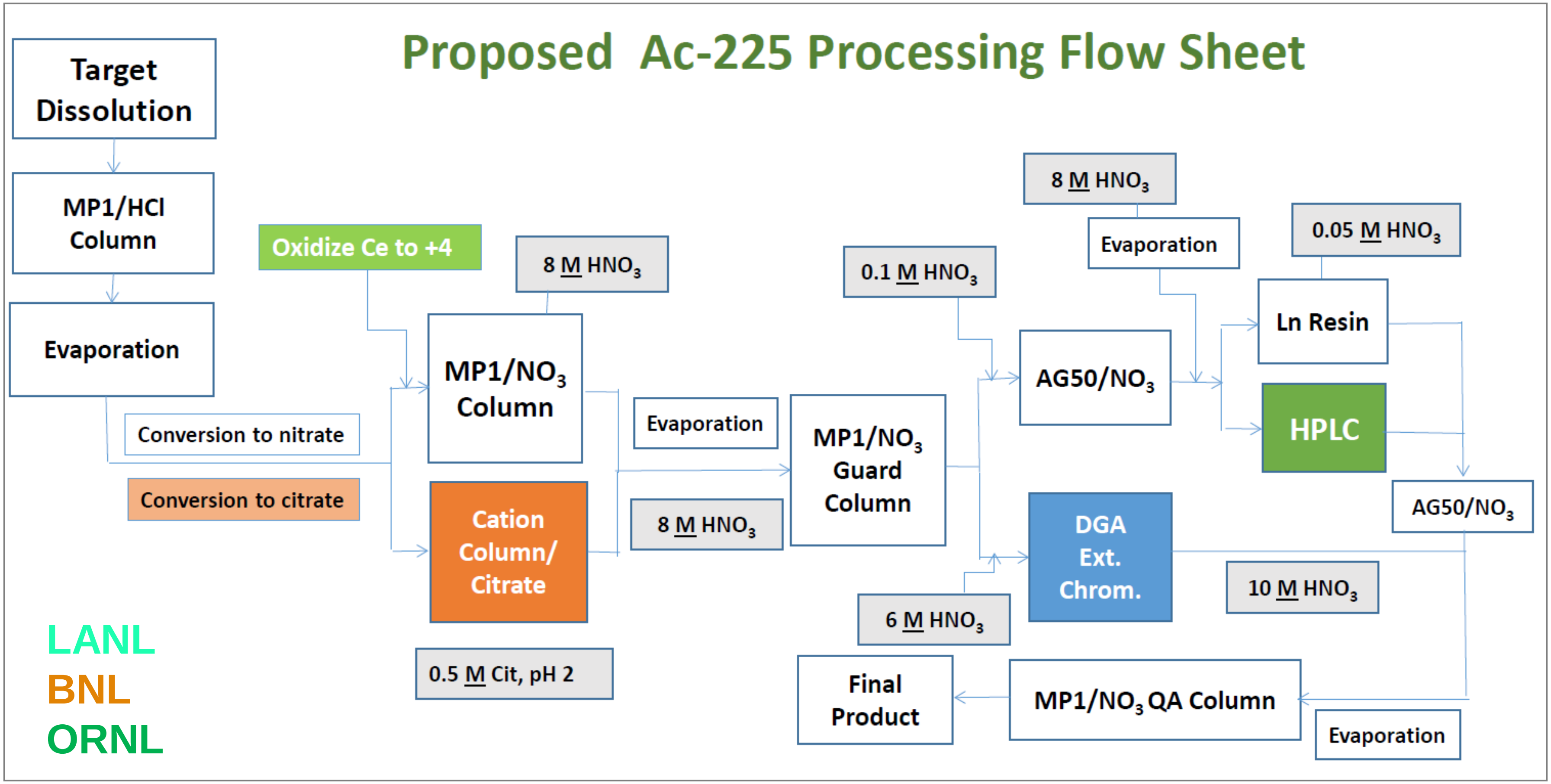








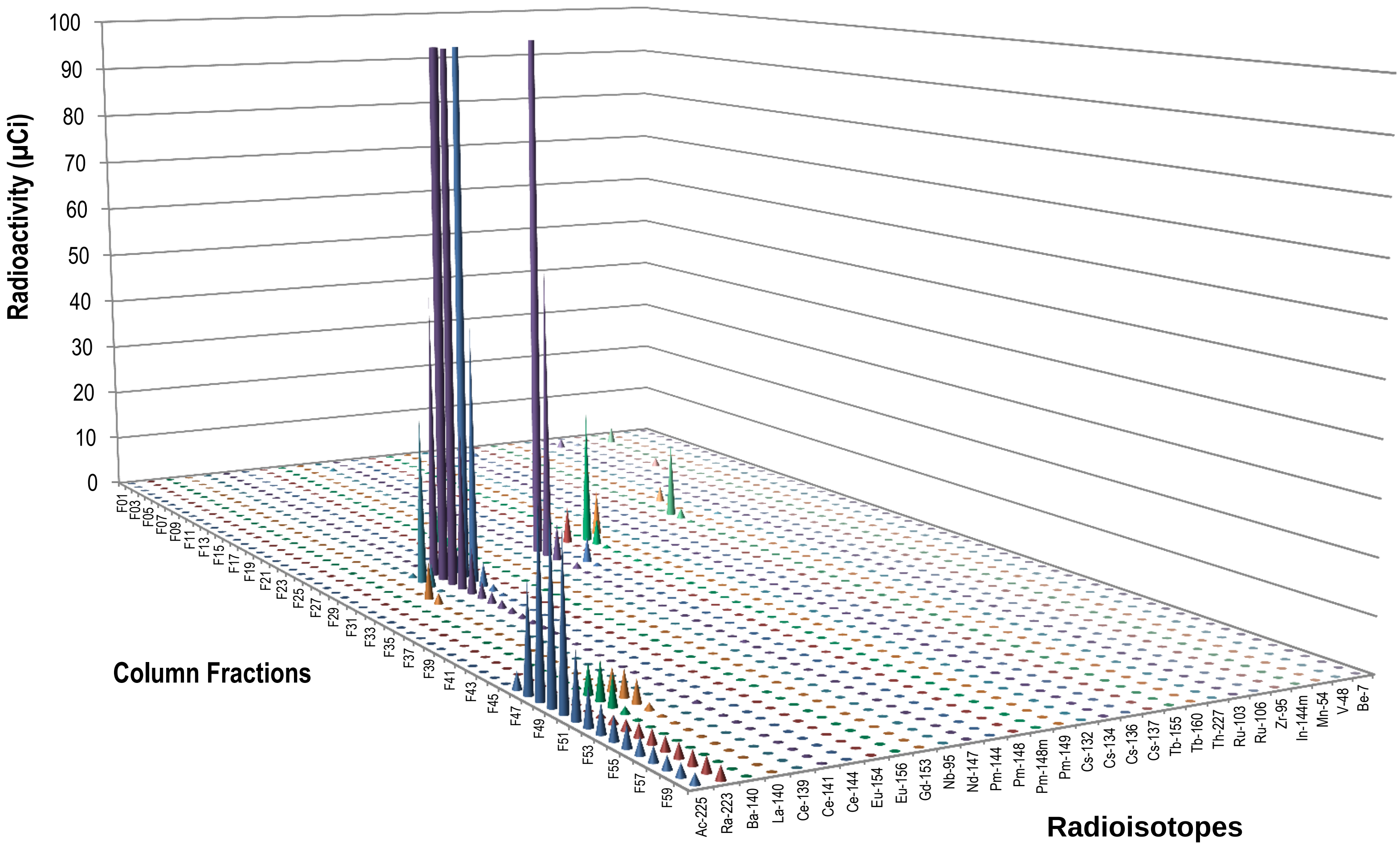
Chemical Process for Accelerator-Produced ^{225}Ac



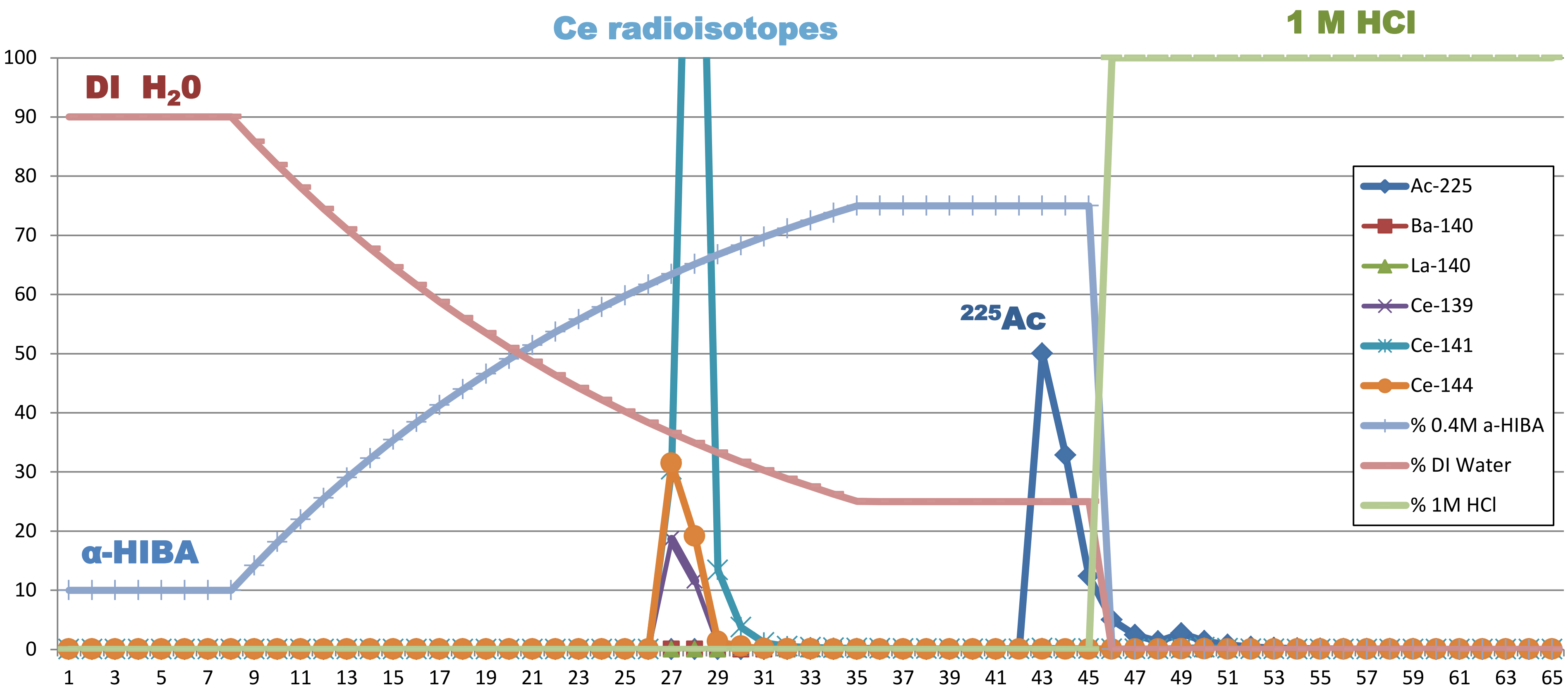
For a 10 day irradiation of a 5 g cm^{-2} ^{232}Th target at IPF or BLIP, yield of ^{225}Ac is ~1.5 Ci at EOB with ~0.2% contamination from ^{227}Ac

Radionuclide	Yield at EOB			
	IPF: 250 μA, 90 MeV		BNL: 100 μA, 192 MeV	
	(Ci)	(GBq)	(Ci)	(GBq)
^{225}Ac	1.5	5.6×10^{1}	1.5	5.7×10^{1}
^{226}Ac	N/M	N/M	3.2	1.2×10^{2}
^{227}Ac	2.7×10^{-3}	1.0×10^{-1}	3.1×10^{-3}	1.1×10^{-1}
^{227}Th	6.3	2.3×10^{2}	1.9	7.0×10^{1}
^{228}Th	2.2×10^{-1}	8.1×10^{0}	8.0×10^{-2}	2.8
^{99}Mo	1.8×10^{1}	6.7×10^{2}	5.4	2.0×10^{2}
^{140}Ba	3.1	1.2×10^{2}	4.6×10^{-1}	1.7×10^{1}
^{139}Ce	1.1×10^{-2}	4.1×10^{-1}	1.6×10^{-2}	5.9×10^{-1}
^{141}Ce	1.4	5.2×10^{1}	3.5×10^{-1}	1.3×10^{1}
^{143}Ce	1.4	5.1×10^{1}	1.6	5.8×10^{1}
^{144}Ce	9.0×10^{-2}	3.5	3.3×10^{-2}	1.2

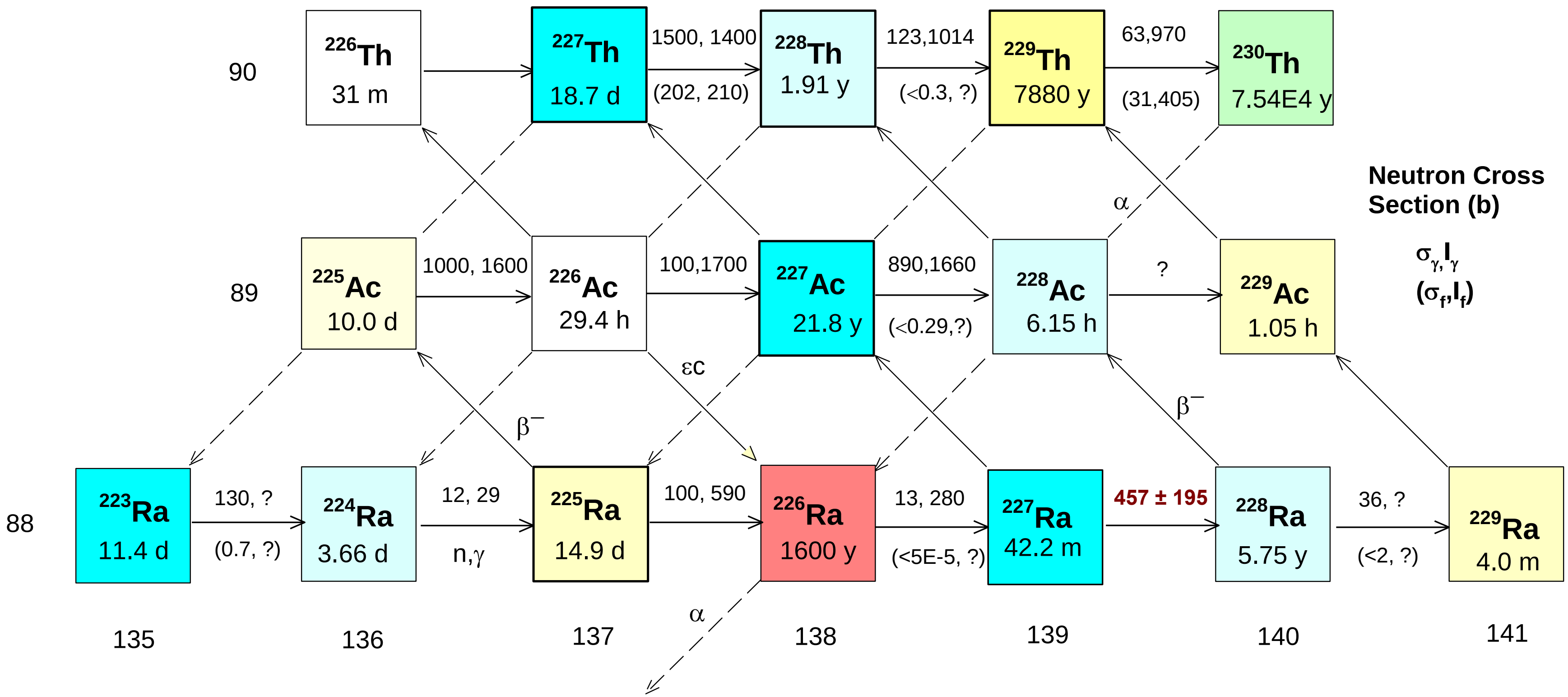
HPLC Separation of ^{225}Ac from ^{140}La and other radiolanthanides, showing only major radioactive species



Second HPLC Separation of ^{225}Ac From ^{140}La – Gradient and Chromatogram

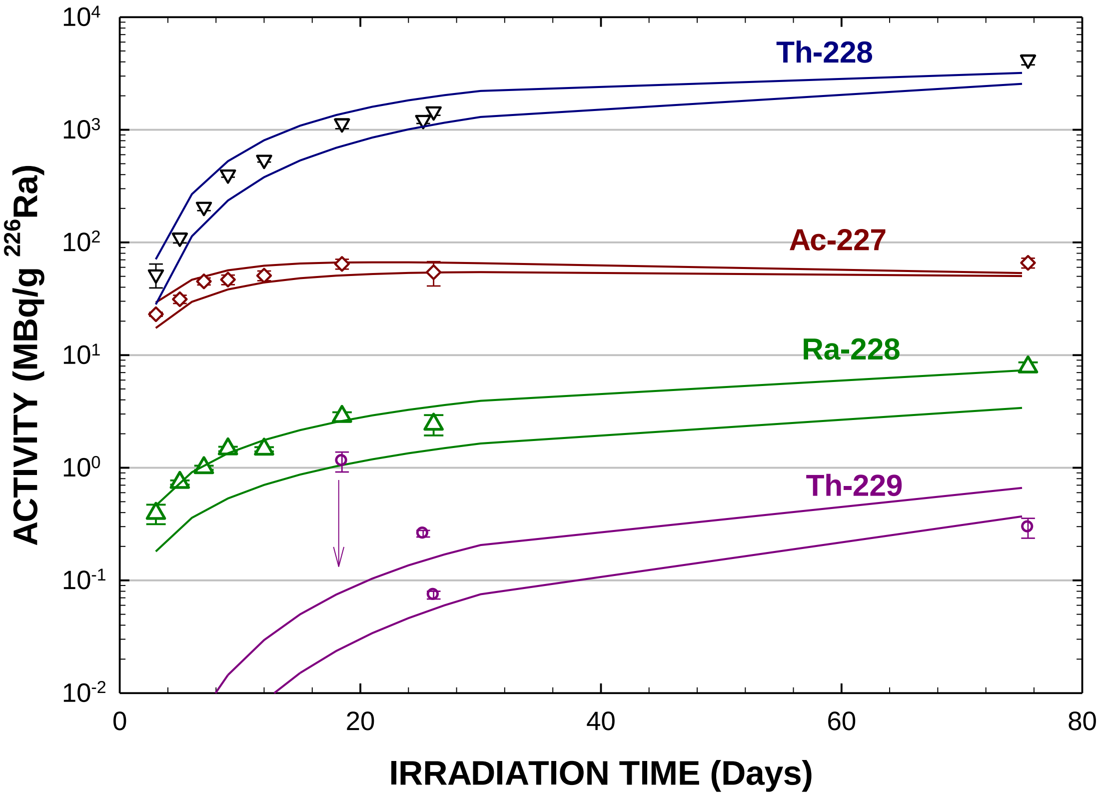


Reactor production of Th-229



1st term of cross-section refers to thermal and 2nd term to resonance integrals. The values in parenthesis are fission cross-sections at thermal and epi-thermal neutrons, respectively

Reactor Production of Thorium-229



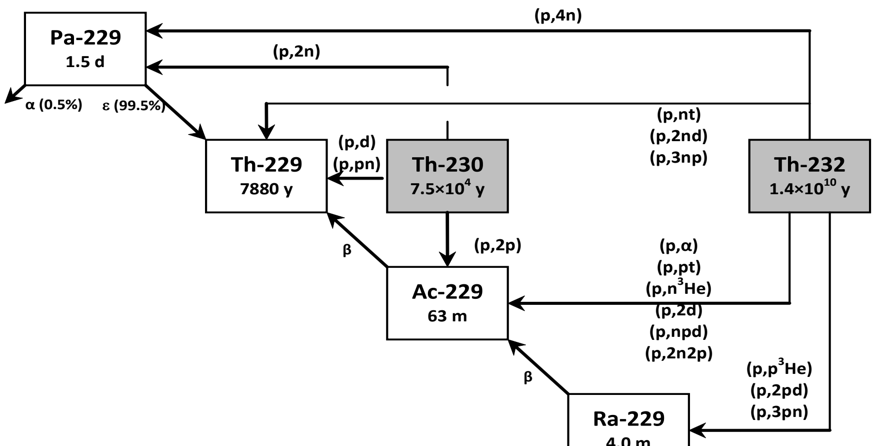
- Projected ^{229}Th yield for 6 cycle irradiations: 18-23 mCi per g of ^{226}Ra, with ^{228}Th and ^{227}Ac contaminations of 3000 and 50 times larger.

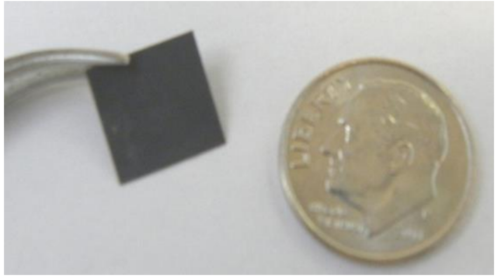
- 20 mCi of ^{229}Th will generate ~140 mCi of ^{225}Ac per year

Reactor Production of Thorium-229, Hogle, et al., ARI, 114, 19-27 (2016)

Production of ^{229}Th via Proton-induced Reactions on ^{232}Th

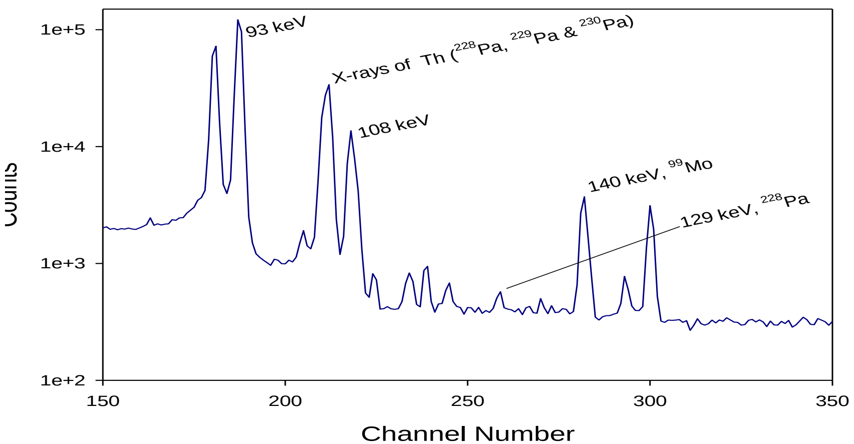
Thorium Proton Bombardment Reaction Block Diagram



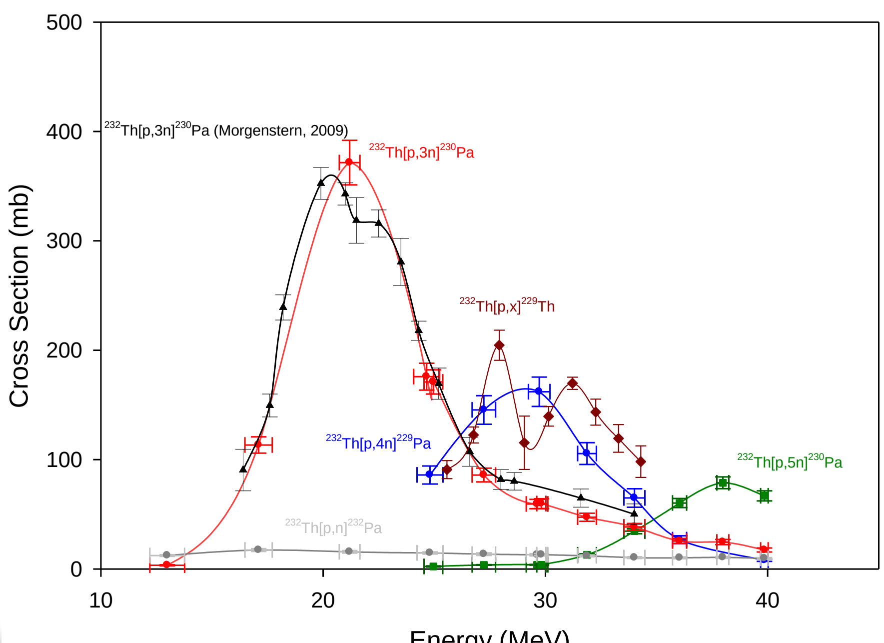


γ-Ray Spectrum of Purified Pa Fraction

(Th230-2, PaPPT-T5, 6/15/2011)



Various Excitation Functions for Proton Bombardment of ^{232}Th



Production of ^{229}Th via Proton-induced Reactions on ^{232}Th

Summary

- Excitation function for the ^{232}Th[p,4n]^{229}Pa reaction has been measured with good precision; excitation function peaks at 28 MeV, 150 mb.

- Measurements of thick target production show cross section is dominated by the following two reactions:

  ^{232}Th[p,4n]^{229}Pa(1.5 d, *EC*)^{229}Th

  ^{232}Th[p,α]^{225}Ac(63 m, *β*)^{229}Th

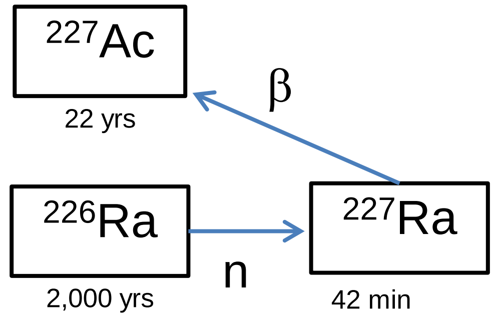
- Irradiating 1 gram of ^{232}Th (~0.5 mm) for 1 year at 100 μA of 35 MeV protons and exiting at 25 MeV would yield ~28 mg of ^{229}Th (5.6 mCi).

Future Work

- Additional nuclear data for short-lived ^{229}Ac is necessary to determine cross section of ^{232}Th[p,α]^{229}Ac reaction
- The thick target yield from ^{230}Th target expected to be 3-5 times greater than from ^{232}Th target

^{227}Ac production: larger scale pilot demonstration

- **^{227}Ac is made via irradiation of ^{226}Ra targets at HFIR**



Building 3047 cleanup

- **ORNL entered into a production R&D phase shortly after hosting the 2013 International TAT conference**

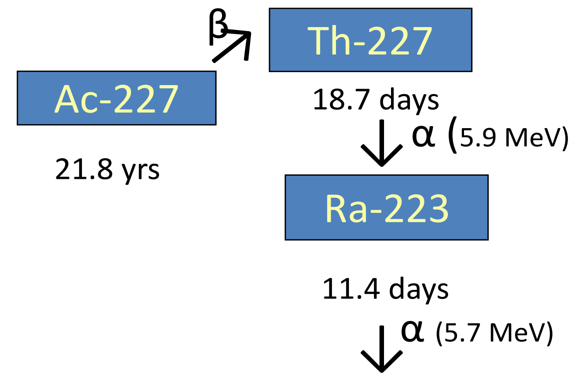
Preliminary feasibility R&D was followed by two years of

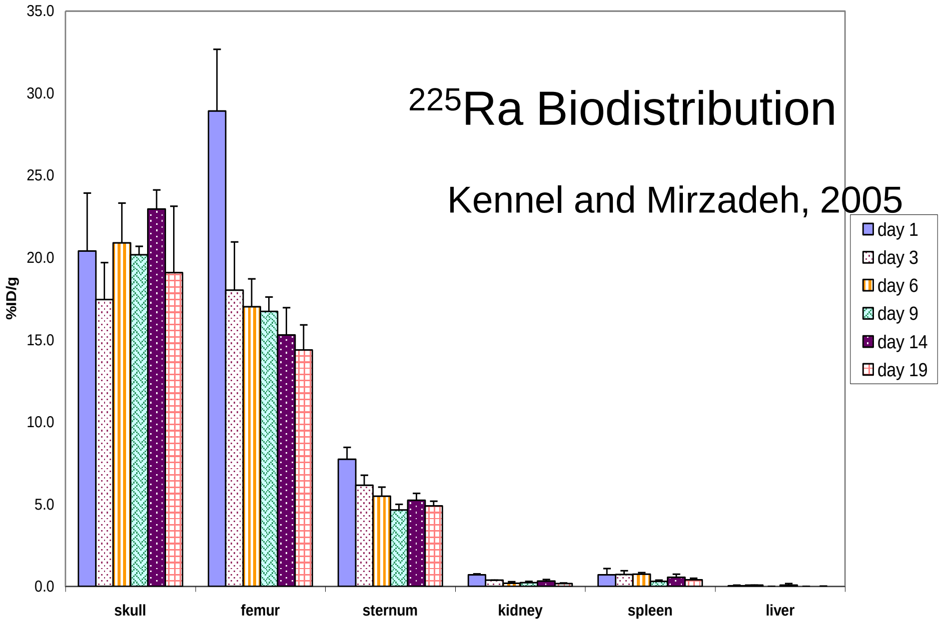
1st HFIR Rabbit containing 2 Ra pellets

1st 50-mg ^{226}Ra pellet

Xofigo, 1st approved "targeted" alpha therapy (TAT) for treatment of advanced prostate cancer

- Prostate cancer is the second leading cause of cancer death in American men, behind lung cancer
- ^{223}Ra targets new bone growth, like Ca
- ^{223}Ra is derived from an ^{227}Ac generator





Ra-226 target design

- Up to 13 pellets can be stacked in a welded-aluminum rabbit for irradiation at HFIR
- Total $RaCO_3$/Al volume: ~1.3 cm^3
- Total Ra-226 mass: 0.7 g (0.749 g of $RaCO_3$)
- aluminum mass: 2.748 g
- Ra-226 mass limit based on heat calculations and the target temperature during irradiation (dose rates will limit Ra-226 mass per target to about 600 mg)

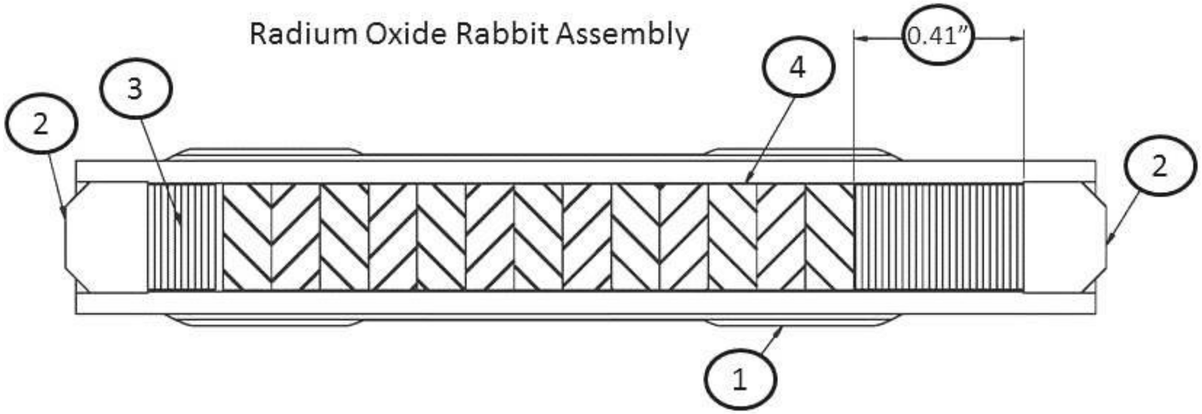
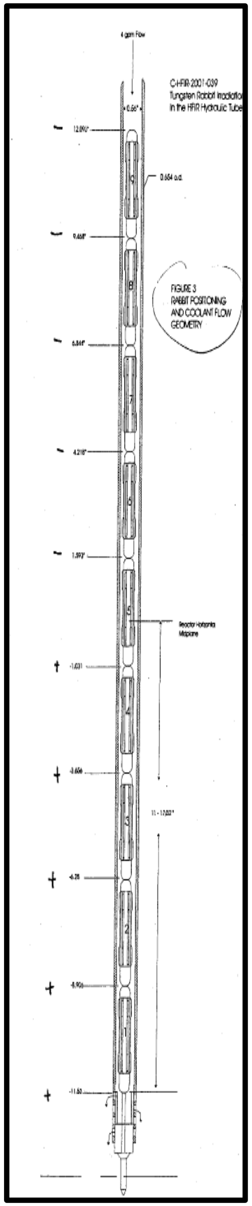
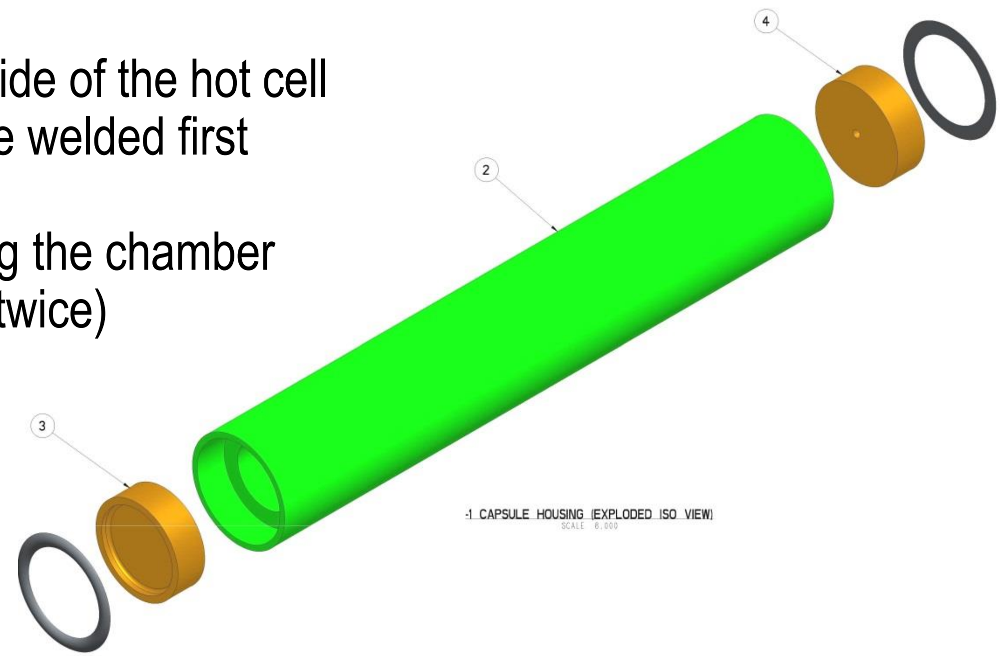


Figure 5. Configuration of 13 RaO/Al pellets for irradiation at HFIR. Some of the components include; 1) finned aluminum rabbit, 2) rabbit end caps (aluminum), 3) fill material – aluminum foil or quartz wool, and 4) radium oxide pellets (13) – 0.250" diameter and 0.125" thick.

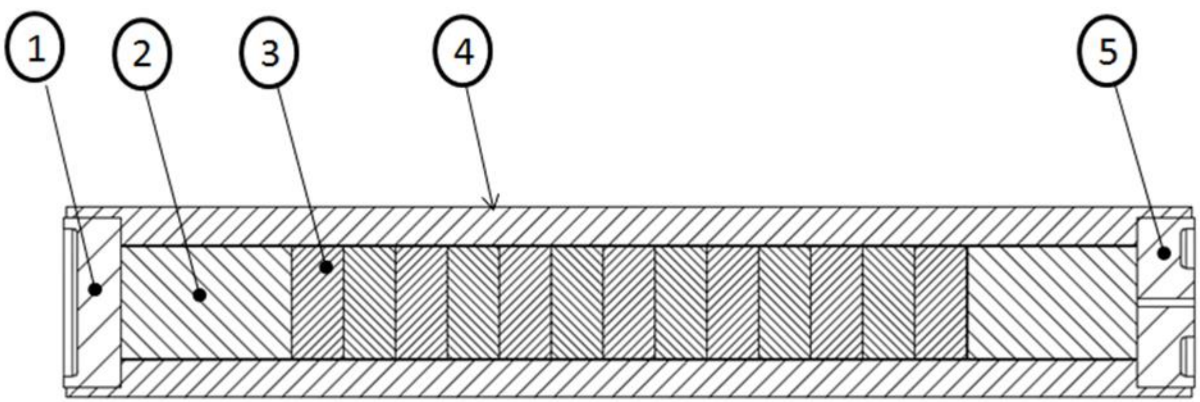


New HFIR-HT rabbit design

- Changes were made to the rabbit design to facilitate the in-cell welding process
- The bottom cap will be EB-welded outside of the hot cell
- The circumference of the top cap will be welded first
  - under a helium cover gas
- The plug will be welded after evacuating the chamber and backfilling with high-purity helium (twice)



1) Bottom End Cap
2) Spacer
3) Radium Oxide pellets
4) Rabbit Body
5) Top End Cap



- Body is aluminum alloy 6061
- End caps are 4047 aluminum (required for welding)

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