Isotope Program
U.S. Department of Energy

U.S. Department of Energy Isotope Program Update and Perspective on Alpha-Emitters

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Outline:

- Introduction to the DOE Isotope Program
- Capabilities & Impact on the Dynamic Isotope Landscape
- High-Priority Medically Relevant α-emitters

U.S. DEPARTMENT OF ENERGY

Mission

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 the infrastructure required to produce and supply priority isotope products and related service

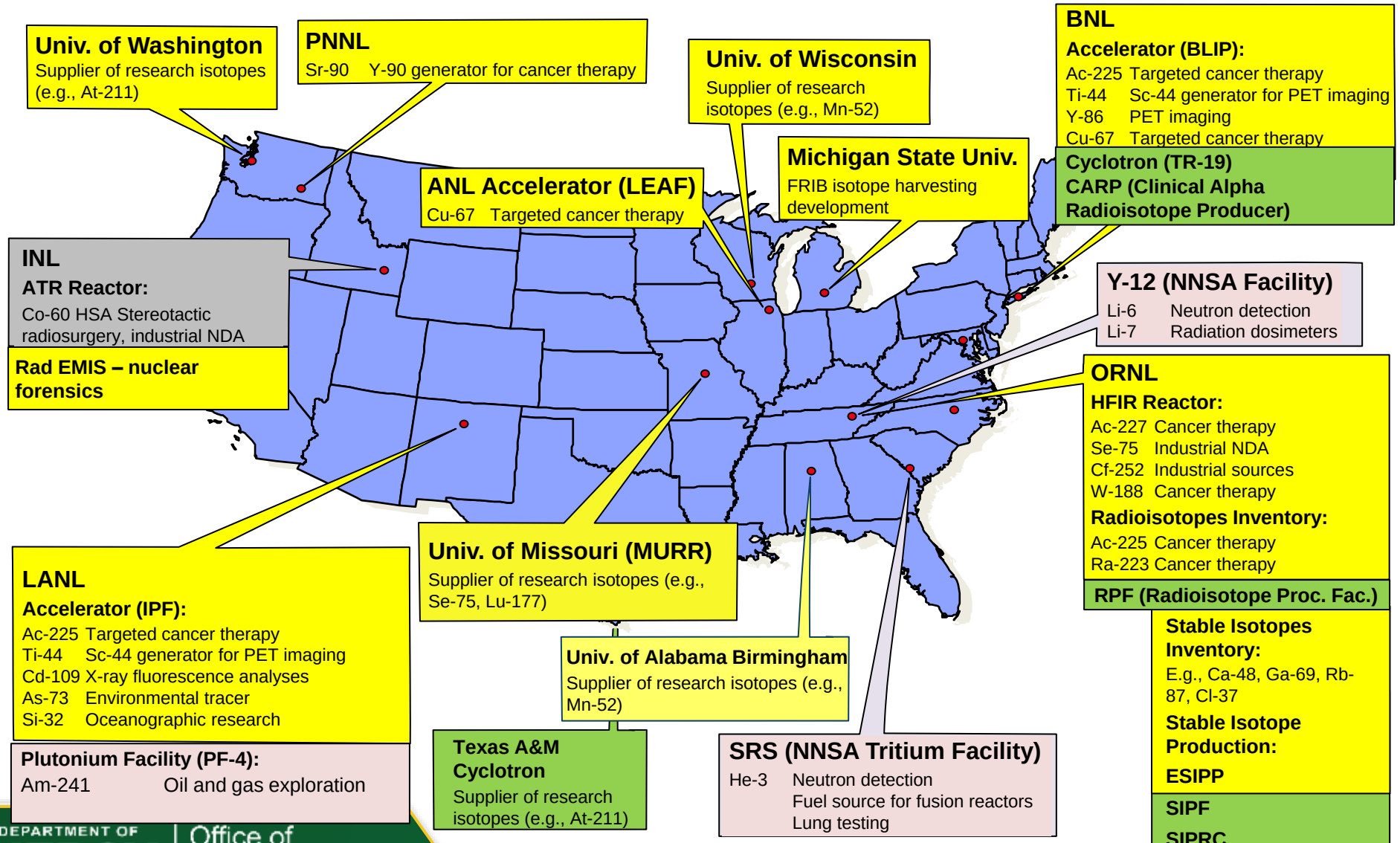
Conduct R&D on new and improved isotope production and processing techniques which can make available priority isotopes for research and application. Develop workforce.

Ensure robust domestic supply chains. Reduce U.S. dependency on foreign supply to ensure National Preparedness.

U.S. Government Role

- Research program enables advances and workforce development
- Coordinated isotope production capacity mitigates shortages
- Ability to nurture markets, provide high risk, or boutique isotopes
- Leverage world-class capabilities at national laboratories
- “Non-profit”, “No-compete”, research and government stature enables unique perspective
- Equal opportunity to access, technology
- DOE IP doesn’t produce all the material that is made into commercial sources and tends to focus on smaller sized sources

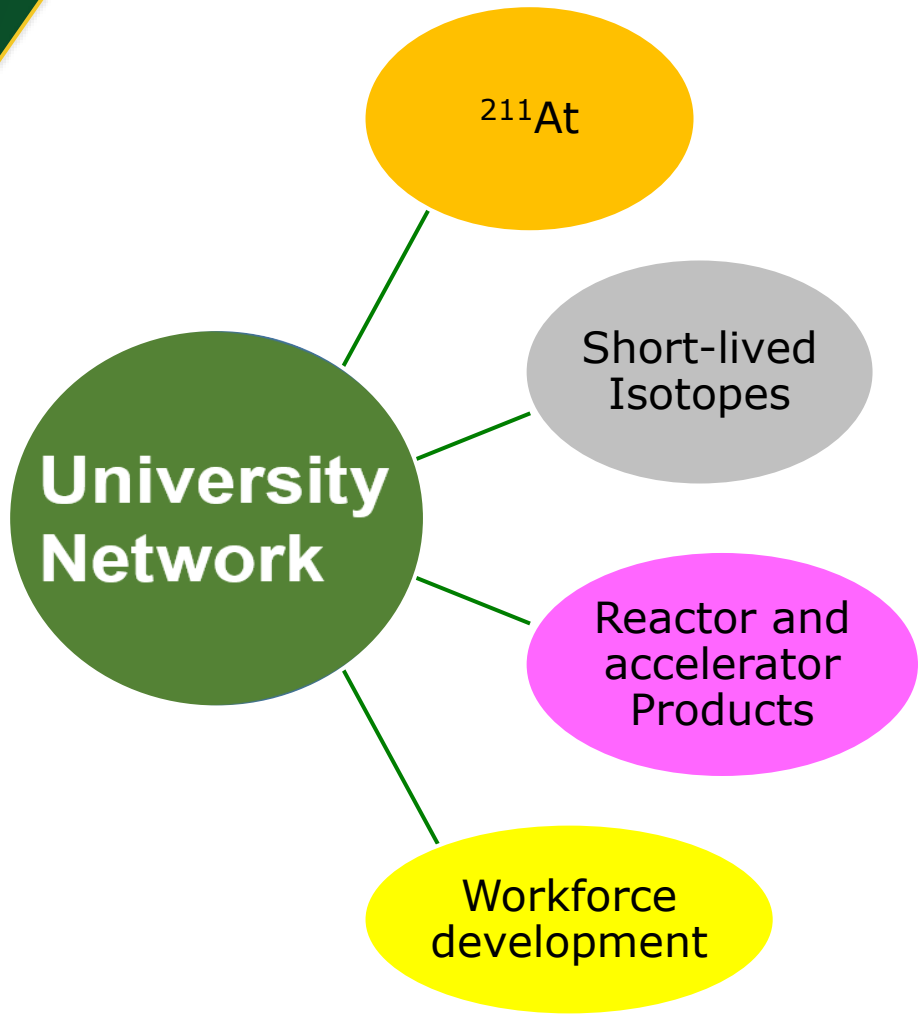
DOE IP Production Sites- 2024
Unique collection of accelerators, reactors, other capabilities



Green boxes under development

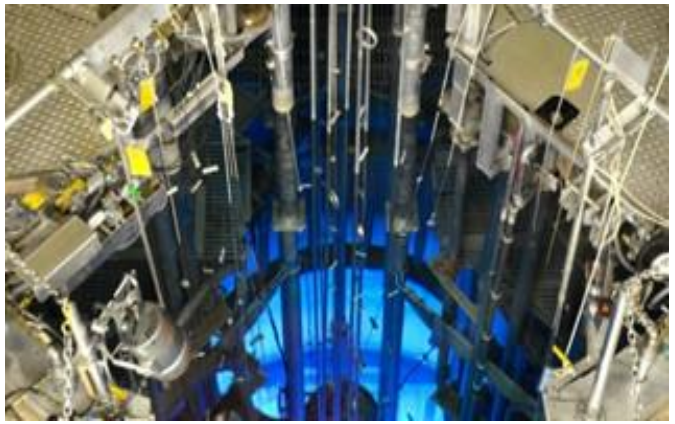
13/19 facilities added while under SC management

University Isotope Network

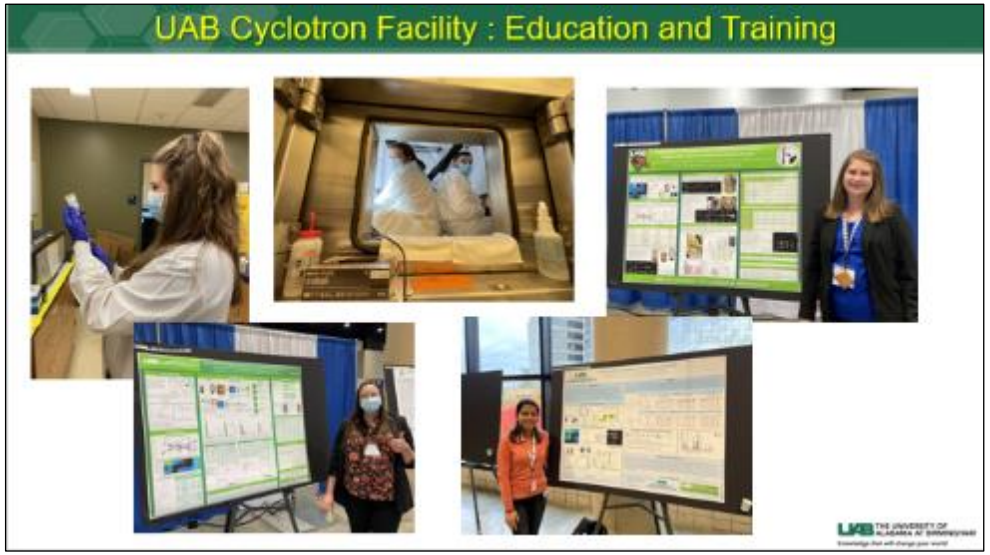


University Network continues to grow

- UW, UMO/MURR, MSU, **UAB, UWM, TAMU**

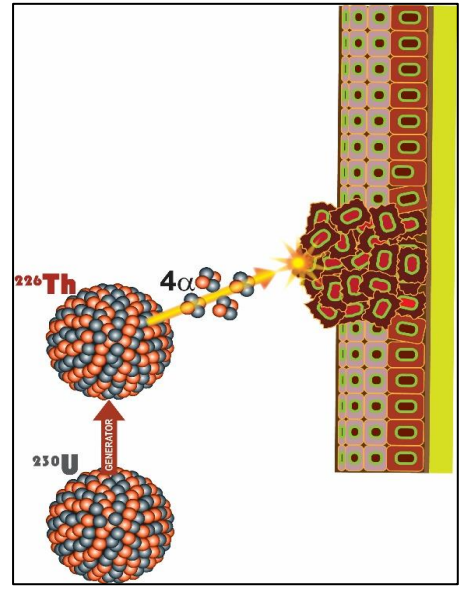


- Cost-effective
- R&D on isotope production
- Boutique isotope production
- Workforce development



Alpha Emitters: A High Priority

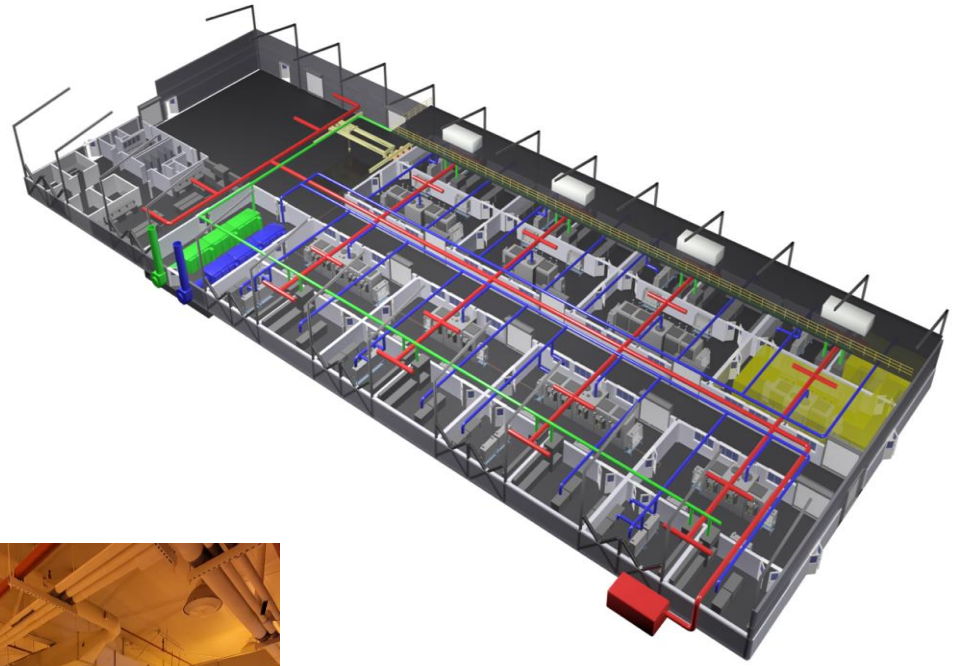
Radionuclide	Half-life
^{225}Ac	10 d
^{211}At	7.2 h
^{212}Bi	60 m
^{213}Bi	46 m
^{212}Pb	10.6 h
^{223}Ra	11.43 d
^{226}Th	31 m
^{227}Th	18.7 d
^{228}Th	1.9 y



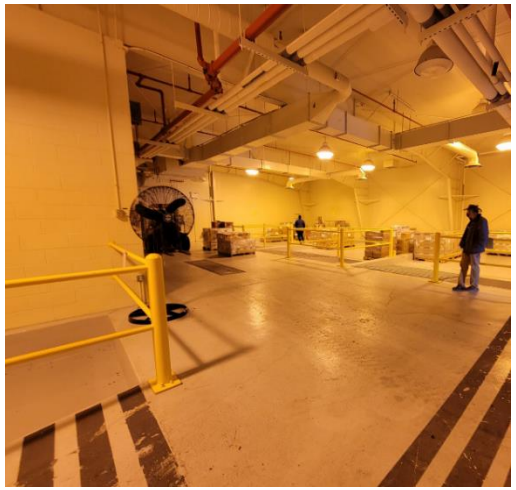
Artist rendering of a U-230/Th-226 generator currently under development

- Alpha emitters have been the highest priority for DOE IP for over 10 years.
- DOE IP produces or is developing production of all these isotopes.

Independence requires additional radiochemical processing



RPF

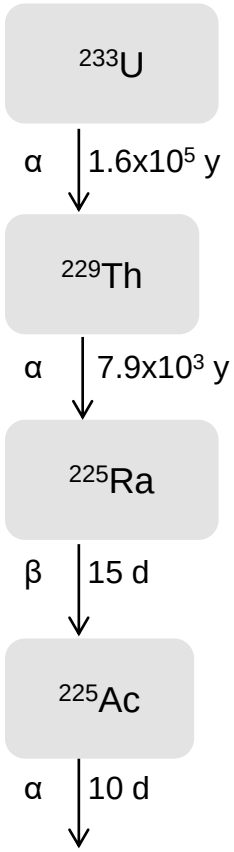


CARP

LANL

- **Radioisotope Processing Facility (RPF)** at ORNL for reactor target processing.
  - HAZCAT 2 nuclear facility with modular hot cells, cGMP cleanroom
  - Estimated TPC ~ $310-615M
  - CD-0 April 2021
- **Clinical Alpha Radionuclide Producer (CARP) Facility** for accelerator target processing at BNL
  - Haz Cat 3 facility in repurposed building. Estimated TPC ~ $60-80M
  - CD-0 December 2022
- **Radiochemical Processing Enhancements** at LANL: Add glove boxes and hot cells to new facility being constructed by NNSA/LANL

Ac-225 Cow Derived



- ORNL has been the main supplier of Ac-225 (via decay of existing Th-229 stock) since 1997
- >10 Ci (370 GBq) of ^{225}Ac shipped in >2000 packages since 1997
- Have submitted DMF and implementing cGMP
- Twelve 4-week milking campaigns are performed annually, with weekly customer shipments
- The present supply is fully subscribed and insufficient to meet the growing research and medical applications demands for Ac-225
- **Maintain standby list for small quantity/one-off requests**
- **Cancellations reallocated to others with priority given to existing domestic cow customers**

Ac-225 Accelerator Produced

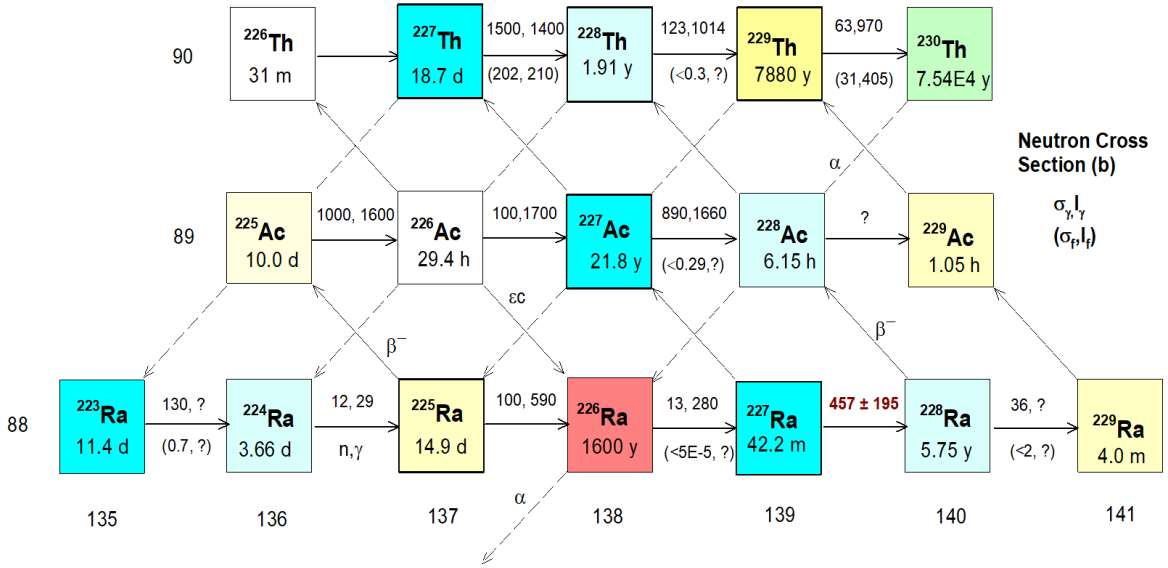
New world production record in September 2023!

Status and Update

- Effort initiated 2014
- First “batches” processed in 2018
- Consistently producing 50 mCi/batch after processing
- Up to 600 mCi present in current target design at EOB
- Amount of Ac-225 available is currently limited by:
  - Processing capabilities
  - Transit time between irradiation and processing sites
- Process is scalable by increasing target size and/or frequency of irradiations

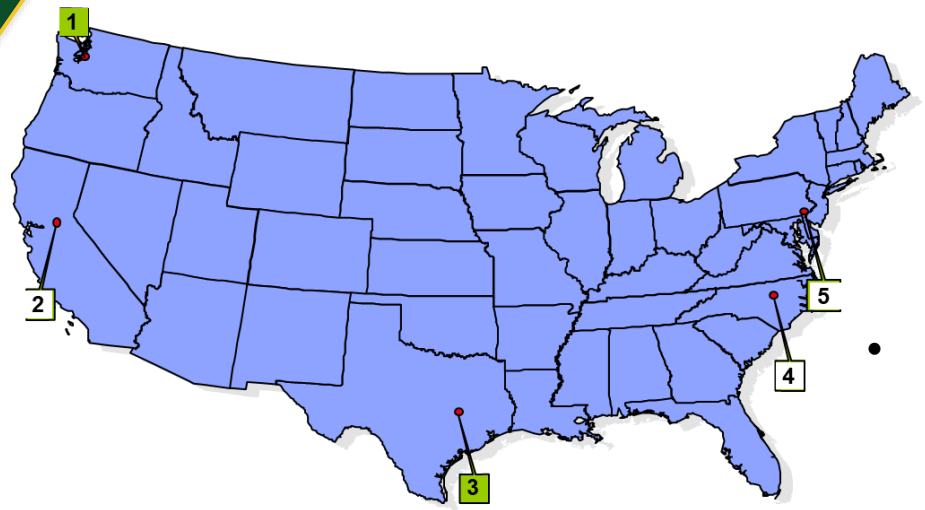
Ac-225 Alternative Production Routes

- ANL electron linac production route
  - $^{226}Ra(\gamma,n)^{225}Ra \rightarrow ^{225}Ac$
- BNL low energy cyclotron route
  - $^{226}Ra(p,2n)^{225}Ac$
- ORNL neutron production route
  - $^{226}Ra(3n,\gamma)^{229}Ra \rightarrow ^{229}Ac \rightarrow ^{229}Th$



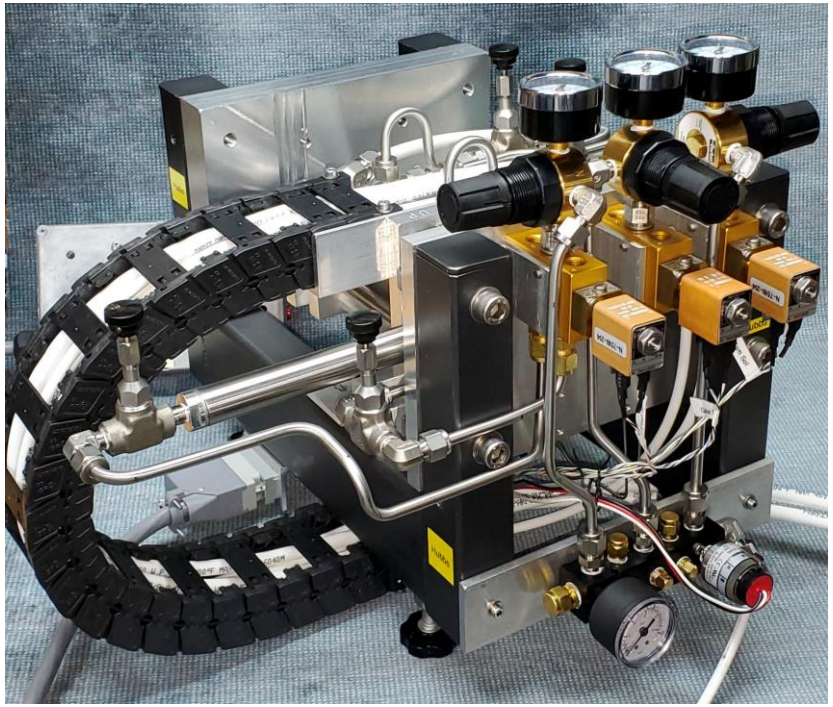
S. Hogle et al., Reactor Production of Thorium-229, Appl. Radiat. Isot. 114, 19 (2016)

At-211 Production Capabilities in the U.S.



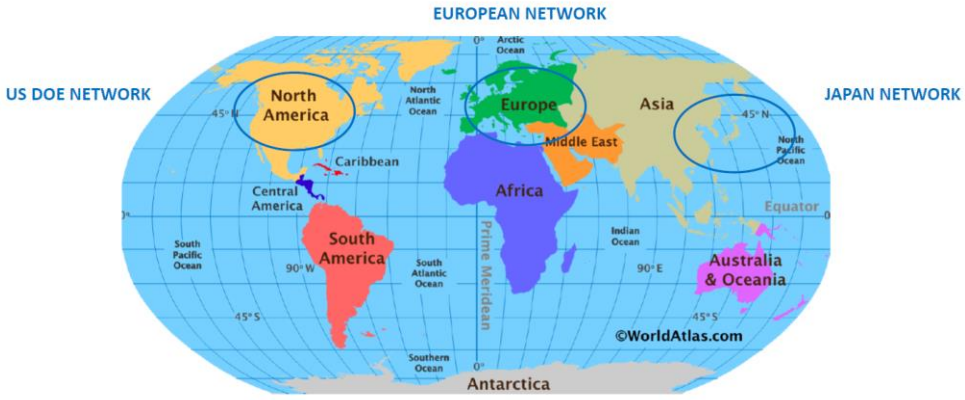
1. University of Washington
2. University of California - Davis
3. Texas A&M University
4. Duke University
5. University of Pennsylvania

- **Limited production capabilities for At-211**
  - **None of the DOE/NNSA National Laboratories used by DOE IP are suited to produce At-211.**
- **~250 university, hospital and research facility cyclotrons in the U.S. are capable of isotope production**
  - **Only 5 with potential to produce At-211**
- **Geographic distribution constraints driven by production batch yields and short physical half-life (7.2 h)**



World Astatine Community (WAC)

The WAC aims to facilitate communication, transfer of technology and collaborative research between the regional production networks, which each country or union has established. This allows for partnering to enable a global increase in astatine-211 production capacity; and motivation of the clinical interest of astatine-211 through increased availability.



....OPEN TO ANY NEW PARTNERS

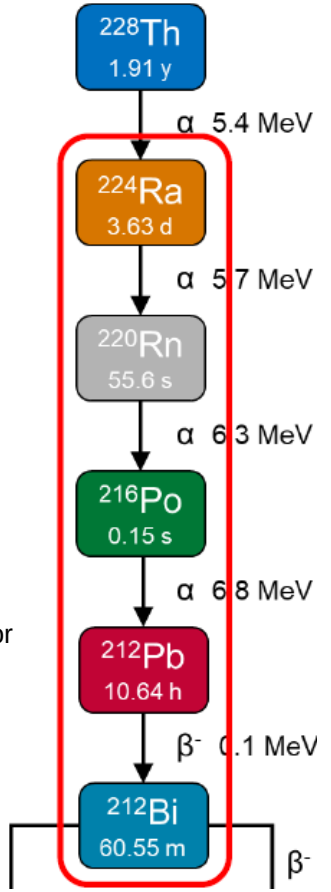
Pb-212 (Ra-224/Pb-212 Generator)

- Demand for Th-228 parent material and Ra/Pb generators is significantly increasing
- DOE IP is expanding both Th-228 and Ra/Pb generator availability in the U.S. to meet demand
- Optimizing current Th-228 and Ra/Pb generator supply from ORNL
  - Th-228
    - Dispensed ~690 mCi Th-228 in FY23
    - Plan to more than double the amount dispensed in FY24 on a monthly cadence
  - Ra/Pb Generators
  - Dispensed 10 generators in FY23
    - Monthly dispensing in FY24
- Added Ra/Pb generator production capabilities at PNNL
  - Capabilities for up to 20 mCi generators commenced in FY24 at both sites
- Work is underway at both sites to increase the generators to ~30 mCi each as an option

Th-228 cow is milked for Ra-224 at ORNL

Loading resin contacted with Ra-224 to fabricate a generator

PNNL generators in final packing step



Conclusions

- DOE IP ramped up its role in the supply of alpha-emitters with a goal of maximizing the domestic availability in 2012.
- A robust domestic supply of Ac-225, regionalized production of At-211, & increased availability of Th-228 and Ra-224/Pb-212 generators are being actively pursued with many sites scaling up production capabilities in response to increasing demand.
- Alternative production approaches and new R&D is being explored for all alpha-emitters.
- In response to increasing market demand DOE IP is increasing the processing capability of several DOE IP sites (CARP at BNL, Enhancements at LANL, RPF at ORNL)
- An increase in production sites and batch yields is required to realize the potential for success that At-211 offers.
  - Promote production and commercialization of At-211 by making technological advancements available to researchers and industry.

Correction!

During the workshop a question was asked regarding information contained in DOE IP product certificates of analyses for spallation-produced Ac-225. While the answer provided was accurate the author believes he incorrectly used the term radiochemical grade or research grade material when answering. As a correction, the material is supplied as an active pharmaceutical ingredient or API under a type 2 DMF (Drug Master File) filed with the US Food and Drug Administration. There is a large difference in the meaning behind the terminology and the regulatory burden associated with each.


Thank You!