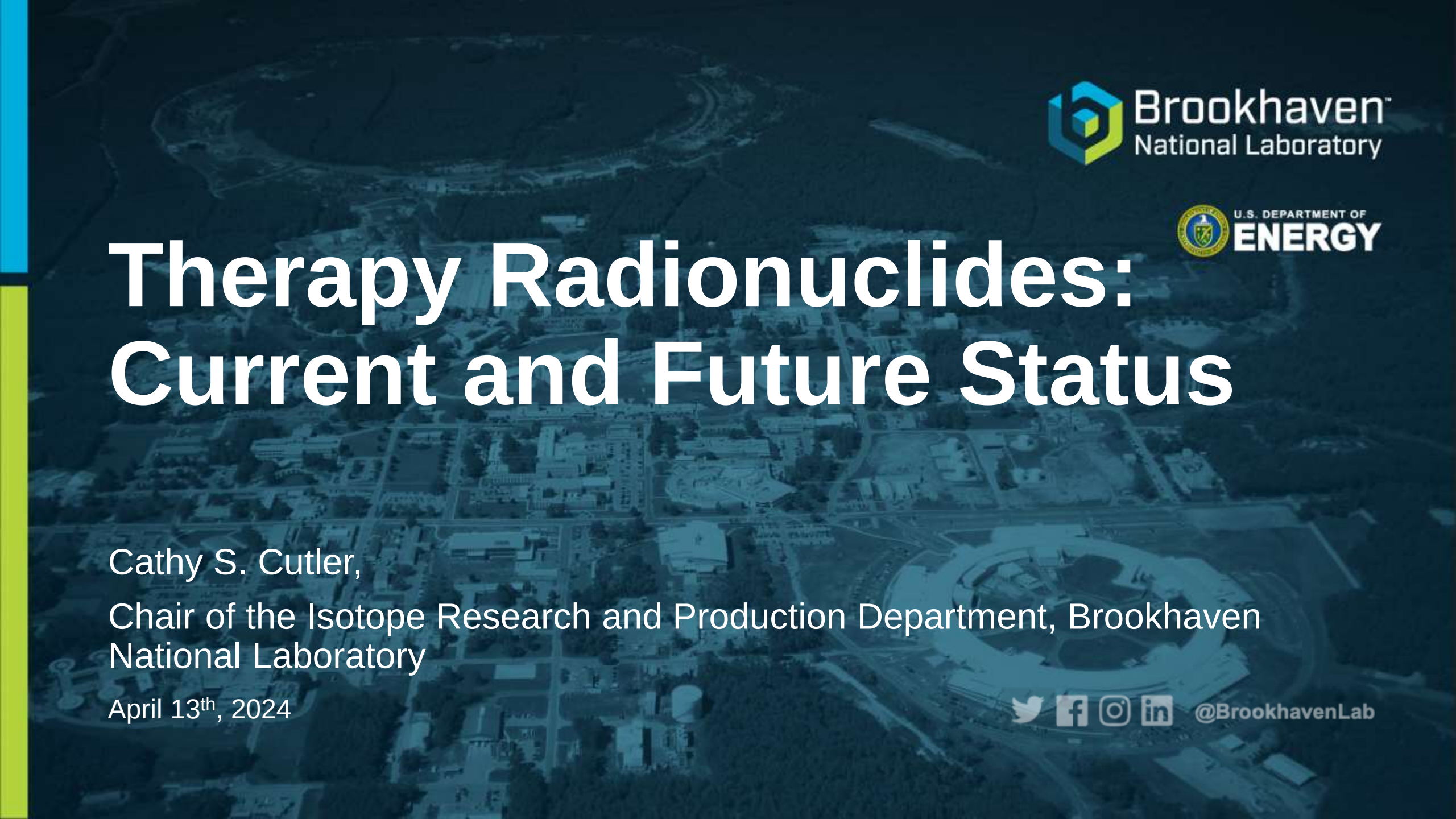

Therapy Radionuclides: Current and Future Status

Cathy S. Cutler,

Chair of the Isotope Research and Production Department, Brookhaven National Laboratory

April 13th, 2024

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Disclosures

- I have no financial or professional disclosures
- My background is in Inorganic chemistry and have been involved in isotope production at reactors, cyclotrons and accelerators and perform extractions from unwanted materials.
- Currently work as the Chair of the Isotope Research and Production Department at BNL.
- President-elect of the SNMMI

Clinical Trials

- Ac-225 23 trials, 15 are recruiting with multiple institutions, almost all in the US
- At-211 7 trials, 4 recruiting (1 in Japan and 3-4 at Fred Hutchinson Cancer Center)
- Cu-64, 28 studies, 8 recruiting all in the US
- Cu-67, 5 trials, 3 recruiting, Cu-67-SARTATE, Cu64/Cu-67-SAR-BBN, 64Cu-SAR-bisPSMA/67Cu-SAR-bisPSMA 64Cu-SAR-BBN
- Tb-161, 3 trials all recruiting, all outside of the US
- Lu-177 226 trials, 90 recruiting
- Zr-89 125 trials, 25 recruiting
- Ga-68 604 studies over 200 recruiting
- Lead-212 10 studies, 9 recruiting
- Lead-203, 5 studies none recruiting
- Sm-153, 17 studies, 1 recruiting
- Ra-223, 125 Studies, 19 recruiting
- Re-186, 7 trials, 2 recruiting
- Re-188, 10 trials, 2 recruiting
- Iodine-131, 345 studies, 23 recruiting
- As-72, 9 trials, 3 recruiting

Isotope Production

- US has tended to be highly reliant on foreign supply
- Harvested from waste materials
- Generator systems
- Reactors from (n, γ) reactions or fission
  - As neutrons have no charge thus probability much higher, targets tend to be smaller and easier to produce
- Accelerators using beams of protons, deuterons, alphas, electrons on targets etc.
  - Charged particles into a highly charged nucleus probability is much lower
  - Tend to have larger targets
  - Isotopes produced tend to be carrier free but not always

Challenges for Radioisotope Supply

- Reactor outages causing shortages in Mo-99/I-131/Lu-177
- Transportation
- Losing expertise
- Ongoing excursions
  - Russia major supplier (some cases sole source) of a range of radioactive and stable isotopes
    - Yb-176 is target material for NCA Lu-177; Ge-68 for Ga68 generators; Ac-225
    - Transportation, financial sanctions against Russia complicating isotope import
    - Potential for future nuclear-related sanctions

Major Isotope Production Reactors

SAFARI, NTP, South Africa

BR2, SCK-CEN, Belgium

HFR, NRG, Netherlands

Opal, ANSTO, Australia

MARIA, Polatom, Poland

MURR, Missouri, USA

LVR-15, UJV, Czech Republic

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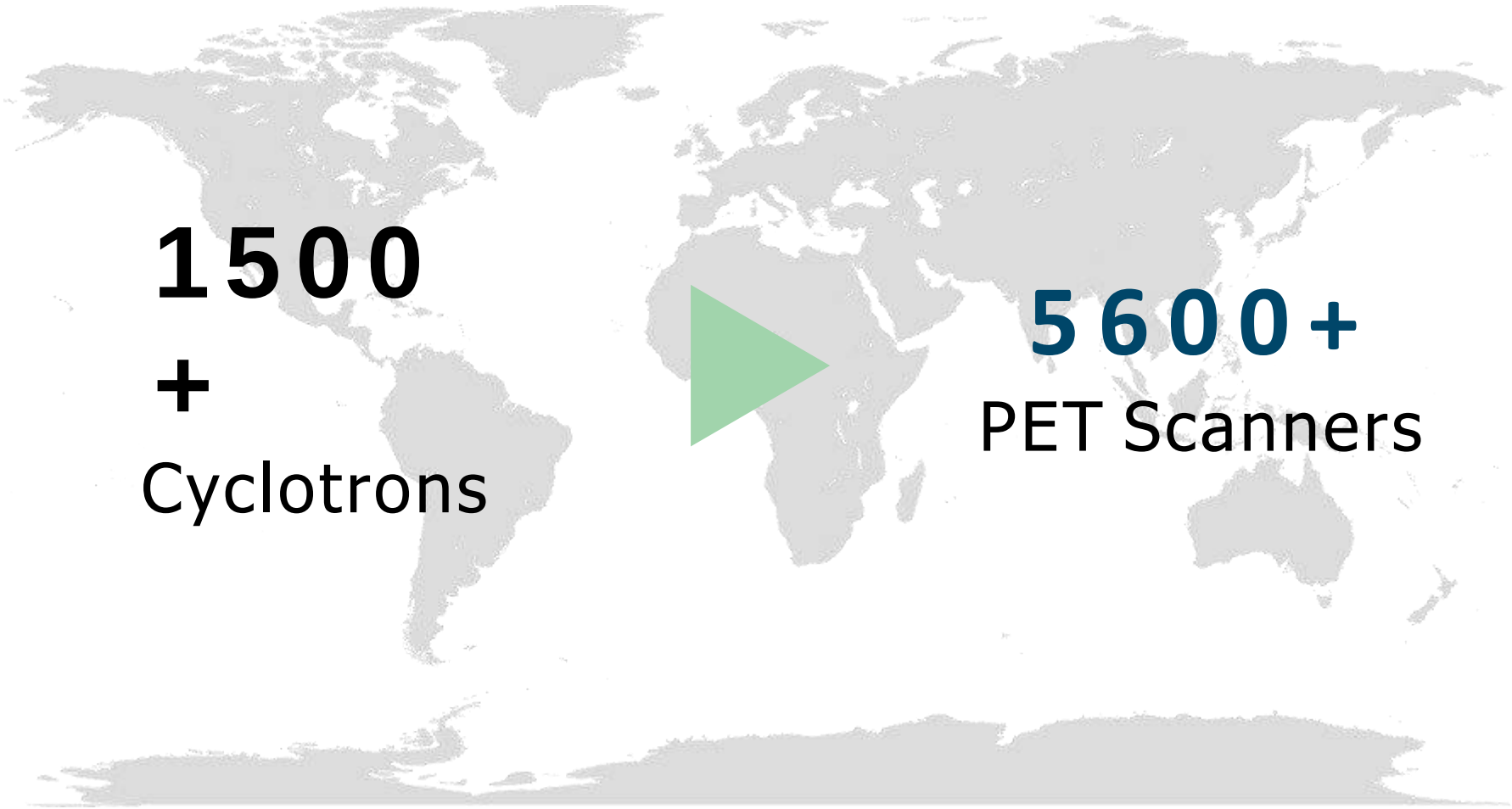
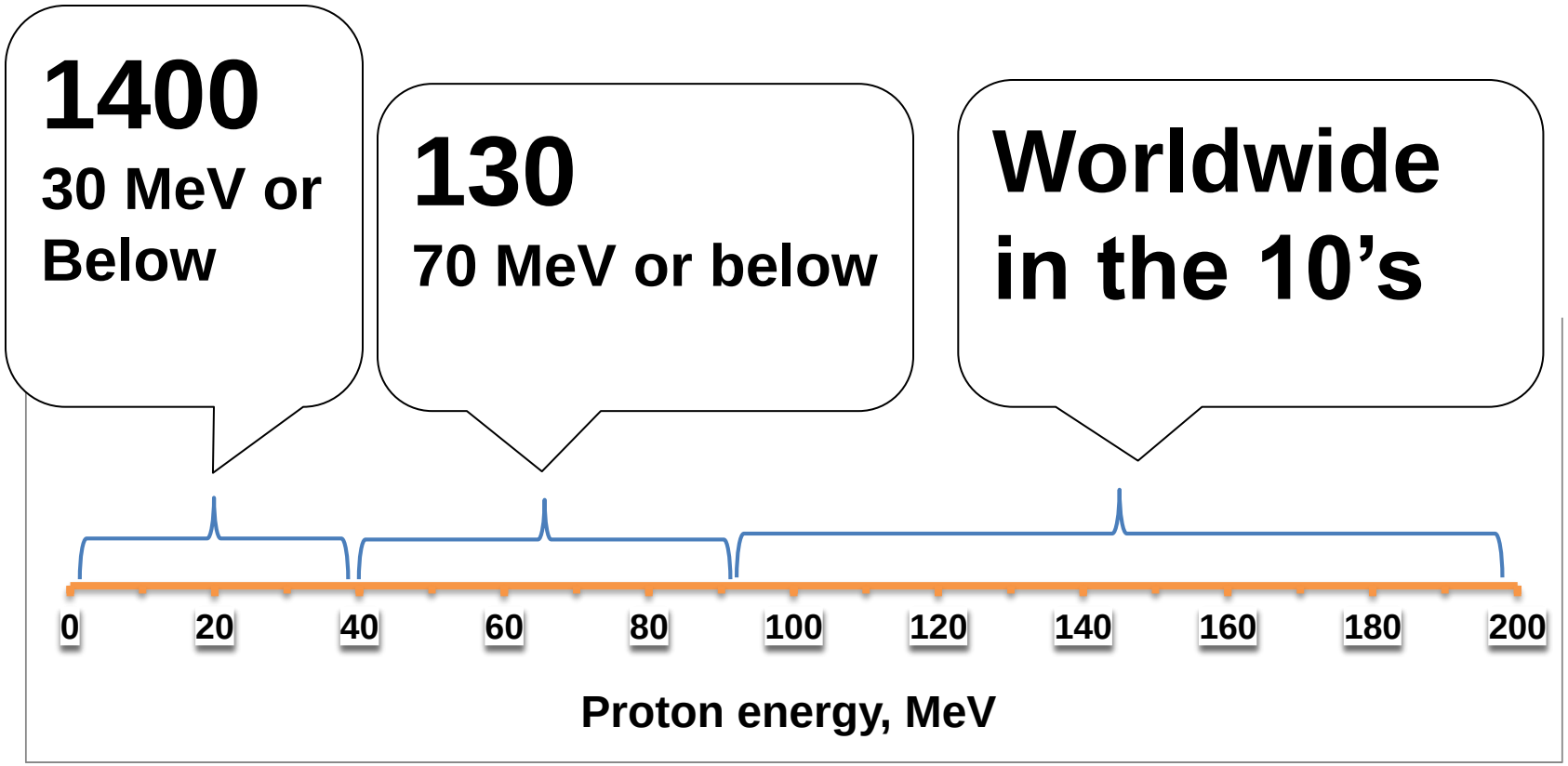


Paul-Emmanuel Goethals and Richard Zimmermann, MEDraysintell report “Cyclotrons used in Nuclear Medicine Report & Directory, Edition 2020” [27], updated by the authors to end of 2022, www.medraysintell.com (February 2023), IAEA

Breakdown of Cyclotrons Worldwide and Energy



Representative list of β- emitting Radionuclides

Radionuclide	Half-life	*Mean Eβ-** (keV)	*Mean Rβ-*** (mm)	*Eβ-** (max) (keV)	*Rβ-*** (max) (mm)
^{33}P	25.4 d	77	0.09	249	0.63
^{169}Er	9.4 d	99	0.14	350	1.1
^{177}Lu	6.7 d	133	0.23	497	1.8
^{67}Cu	61.9 h	141	0.26	575	2.1
^{131}I	8.0 d	182	0.39	610	2.3
^{153}Sm	46.8 h	224	0.54	805	3.3
^{198}Au	64.8 h	312	0.89	961	4.2
^{109}Pd	13.5 h	361	1.1	1028	4.5
^{186}Re	3.8 d	349	1.1	1077	4.8
^{165}Dy	2.3 h	440	1.5	1285	5.9
^{89}Sr	50.5 d	583	2.2	1491	7.0
^{32}P	14.3 d	695	2.8	1710	8.2
^{188}Re	17.0 h	764	3.1	2120	10.4
^{90}Y	64.1 h	935	4.0	2284	11.3

*Mean and maximum energy of beta particles emitted per disintegration (Kocher, 1981)

**Mean and maximum beta-particle range in water [data from p 206 in ICRU Report 37 (1984)]

Table from: Considerations in the selection of radionuclides for cancer therapy by Al Kassis and SJ Adelstein, pp767-794, in Handbook of Radiopharmaceuticals, edited by MJ Welch and CS Redvanly, Wiley 2003.

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Physical properties of Selected β- emitting Radionuclides

Radionuclide	Half-life	*Mean* $E\beta^{-*}$ (keV)	*Mean* $R\beta^{-**}$ (mm)	$E\beta^{-*}$ (max) (keV)	$R\beta^{-**}$ (max) (mm)	Imagable Photons
^{131}I	8.0 d	182	0.39	610	2.3	364 keV (82%) 637 keV (7%) 284 keV (6%)
^{177}Lu	6.7 d	133	0.23	497	1.8	208 keV (11.1%) 113 keV (6.6%)
^{67}Cu	61.9 h	141	0.26	575	2.1	93 keV (16%) 185 keV (49%)
^{90}Y	64.1 h	935	4.0	2284	11.3	511 keV β+ (0.017%)

*Mean and maximum energy of beta particles emitted per disintegration (Kocher, 1981)

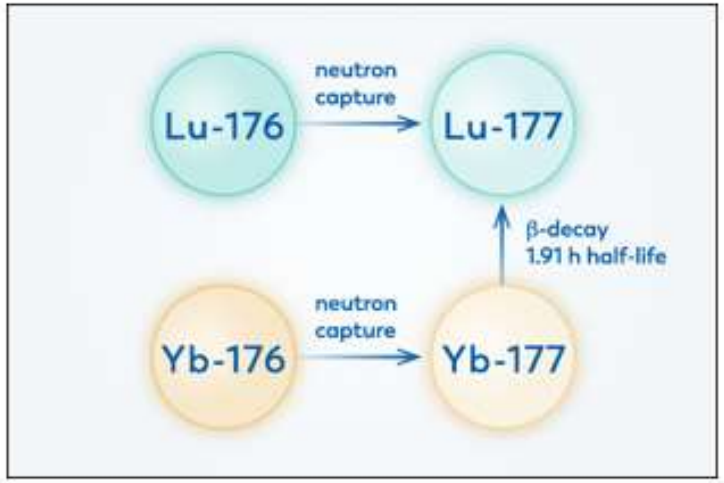
**Mean and maximum beta-particle range in water [data from p 206 in ICRU Report 37 (1984)]

Table from: Considerations in the selection of radionuclides for cancer therapy by Al Kassis and SJ Adelstein, pp767-794, in Handbook of Radiopharmaceuticals, edited by MJ Welch and CS Redvanly, Wiley 2003.

Production of ^{177}Lu

$^{176}Lu + n \rightarrow {}^{177}Lu + {}^{177m}Lu$

$^{176}Yb + n \rightarrow {}^{177}Yb \rightarrow {}^{177}Lu + \beta^-$



Challenges:

- ^{177m}Lu
- Reactor outages

Element	Target Isotope	% Natural Abundance	Cross section σ (barn)	Activation product	Decay Mode	$T_{1/2}$	Decay product	Specific Activity
Lu	^{176}Lu	2.59	2.8	^{177m}Lu	β^-, γ & IT	160.4 d	^{177}Hf (78.6 %) ^{177}Lu (21.4 %)	
			2090	^{177}Lu	β^-, γ	6.65 d	^{177}Hf	1.1 TBq/mg
Yb	^{176}Yb	12.76	2.85	^{177}Yb	β^-, γ	1.9 h	^{177}Lu	3 TBq/mg

Dash A, et al, *Nucl Med Mol Imag*. 2015 Jun;**49**(2):85-107

Commercial Sources of ^{177}Lu

Producer	Reactor(s)	Processing	nca/carrier
BWXT	Bruce Power (CANDU)	Canada	Yes/no
Curium	HFR	Netherlands (Monrol License)	Yes/no
Eckert & Ziegler	Br-2, HFR	Germany	Yes/no
Isotopia	BR-2, HFR McMaster	Israel Canada (AtomVie)	Yes/Yes
ITM-ITG (EndolucinBeta®)	BR-2, OPAL, FRM-2 HFR SAFARI ILL(FR)	Germany Australia-ANSTO	Yes/No
JSC Isotope	RIAR, other (Russia)	Russia	Yes/Yes
McMaster University	McMaster RR	Canada	Yes/Yes
US DOE/MURR	MURR	USA	Yes/Yes
Novartis – AAA/IDB	HFR INM? (Ru), MURR	Netherlands Indiana (2024?)	Yes/Yes
POLATOM (LutaPol)	Maria	Poland	No/Yes
BARC/BRIT	Dhruva	India	Yes/Yes
SHINE (IOCB Prague License)	MURR	USA	Yes/No

Other producers: PARS (Iran), CMR(Russia), Perkin-Elmer (U.S.) and others

Slide Courtesy of Ira Goldman

^{67}Cu Production

- ^{67}Zn(n,p)^{67}Cu
  - Need fast neutrons
  - Enriched ^{67}Zn target (4% nat. abundance)
- ^{68}Zn(p,2p)^{67}Cu
  - Enriched ^{68}Zn (18% nat. abundance)
  - Need 30+ MeV protons
  - Coproduction of ^{64}Cu
- ^{68}Zn(γ,p)^{67}Cu
  - Electron linac
  - Enriched ^{68}Zn target (18% nat. abundance)
  - High specific activity (15 TBq/mg)
  - No coproduction of ^{64}Cu

Commercial Sources of ^{67}Cu

Producer	Reaction
NorthStar	$^{68}Zn(\gamma,p)^{67}Cu$
Iotron	$^{68}Zn(\gamma,p)^{67}Cu$
Idaho Accelerator Center	$^{68}Zn(\gamma,p)^{67}Cu$

Properties of the Therapeutic Radionuclides

Radionuclide	^{177}Lu	^{67}Cu	^{47}Sc	^{161}Tb
Half-life (d)	6.644	2.576	3.349	6.906
Type of Decay (%)	β^- (100%)	β^- (100%)	β^- (100%)	β^- (100%)
Mean particle energy	133.6 keV	135.9 keV	161.9 keV	154.3 keV
Progeny	^{177}Hf (stable)	^{67}Zn (stable)	^{47}Ti (stable)	^{161}Dy (stable)
Imageable photons (keV)	112.9 (6.23%); 208.37 (10.4%)	184.6 (49.6%); 91.3 (7.6%); 93.3 (3%)	159.4 (68.3%)	74.6 (10.2%)

Champion, at al., *Theranostics*, 2016. **6**(10), 1611-1618
Naskar and Lahiri, *Front. Med*. 2021, **8**, 2021
Chernysheva, et al., *Curr Radiopharm* 2021; **14**(4), 359-373

Second Attendance Verification Code

6338

Alpha Therapeutic Agents

Alpha Emitters

- Ability to deliver target-specific radiation dose due to short & well defined track length (<100 µm)
- High linear energy transfer (LET) properties of alpha can be therapeutically effective in cells with low sensitivity to low-LET radiation (Quality factor = 5)
- Also effective against dormant tumor cells in G_0 phase
- Cytotoxicity at both high and low-dose rates
- Works in hypoxic tissues
- Overcome required resistance
- ***Limited use due to availability, complexation chemistry needs development, requires specialized facilities for handling***

Alpha Radionuclide Properties

Radionuclide	Half-life	E_α(keV)	Accompany γ-emission: energy (keV) and branching (%)
^{149}Tb	4.12 h	4077	B^+, γ = 352
^{211}At	7.21 h	5867	γ = 79
^{212}Bi	60.6 min	8785	γ = 727
^{213}Bi	45.7 min	8378	γ = 440
^{223}Ra	11.4 d	5348^{avg}	γ = 269
^{224}Ra	3.62 d	5094^{avg}	γ = 241
^{225}Ac	9.92 d	5450^{avg}	γ = 86
^{227}Th	18.7 d	5562^{avg}	γ = 236 (11.5%)

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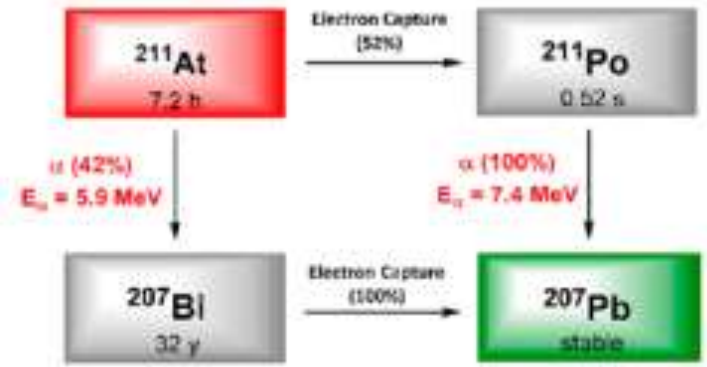
Astatine-211

- Production of At-211 (7.2 h)
  - Cyclotron $^{209}Bi(\alpha,2n)^{211}At$ (21-29 MeV)
  - Requires moderate energy (peak cross section ~26 MeV) alpha particle beam
  - Need high current beam to provide clinical quantities

- Production of Rn-211 (14.6 h) (in development)
  - Proton spallation of U or Th
  - Requires high energy proton beam
  - Low yield
  - Limited number of accelerators



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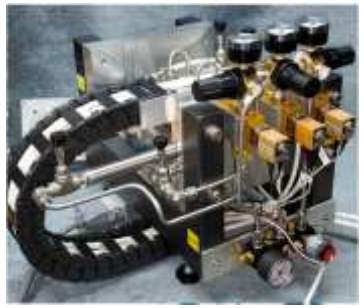
At-211 Production Capabilities in the U.S.

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 hours)



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Evolving Strategy for At-211

- DOE IP recognizes that the production and isolation of At-211 can be challenging. However, we believe that success dramatically increases with cooperation.
- Generation of a notable new literature and general knowledge of the stability and robustness of the product supply chain to encourage clinical evaluation and eventual adoption.
- Maximize the UIN's capability to support U.S. domestic At-211 researchers.
  - Continue to develop production capability at the university sites via grant funding.
  - Gas trapping and generator development can extend shipping range, two approaches are being explored.
  - Explore opportunities for commercialization of At-211 with U.S. private industry.
  - Explore opportunities for development of bench-top accelerators optimized for At-211 production.
- Promote international cooperation and technology exchange.
- World Astatine Community – Unveiled at the 12th International Symposium for Targeted Alpha Therapy, representatives from United States, Japan and the European Union announced the World Astatine Community (WAC) a collaborative effort to share astatine production technology

Commercial Sources of At-211

Nusano's proprietary, high-current ion source technology:

- Generates heavy ions, He^{++} & $^2H^+$, to greatly increase yield & efficiency
- Beam enables production of broad array of radioisotopes
- Annual preventive maintenance vs. monthly downtime

- Ionetix 30 Mev Cyclotron produces first At-211 at facility in April 2023

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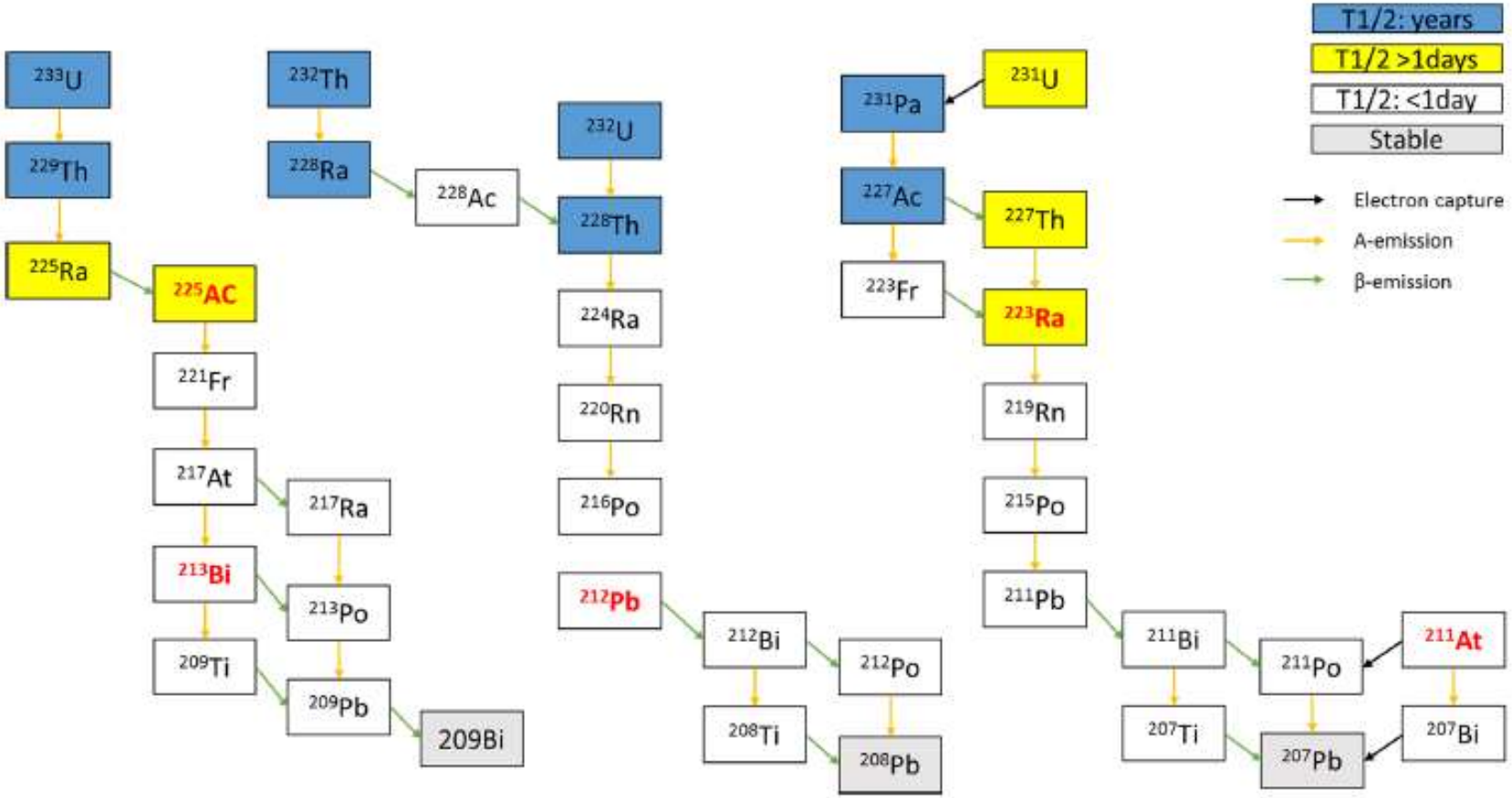

M. Makvandi et al (2018) Targeted Oncology 13: 189-203

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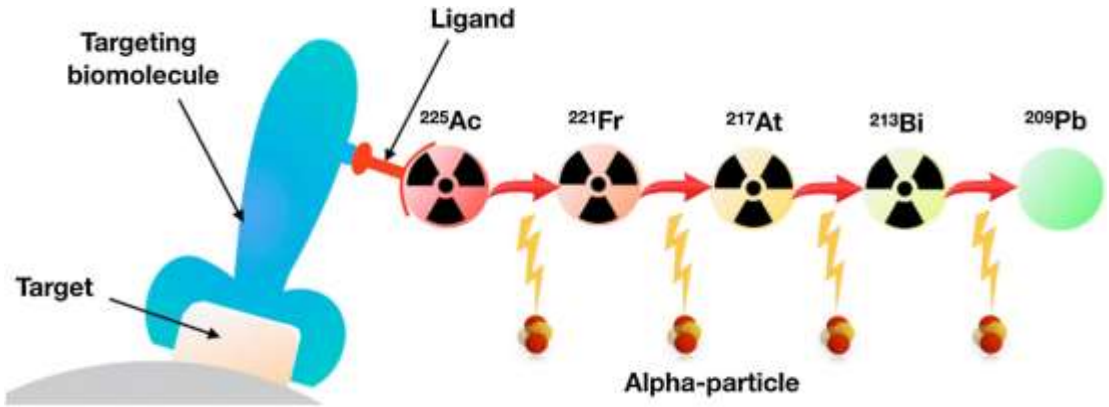
Actinium-225 (9.2 d) Demand

- **27 molecules** labeled with ^{225}Ac are presently under development, among which 13 have already reached human test level[1]
- The first ^{225}Ac-radiopharmaceutical has entered the clinical phase III stage and might **reach the market by 2028**
- **Patient doses**, as informed by clinical trials, are estimated at **1.1-2.4 mCi per patient** kg[2]
- Considering pre-injection decay, **~80 Ci** at end of bombardment would be sufficient to treat 100,000 patients each year



^{225}Ac emits four α-particles down to stable ^{209}Pb [3]

[1]Zimmermann, R., Is Actinium Really Happening? *J Nucl Med*, Aug 2023
[2]Jang, A., et al., Targeted Alpha-Particle Therapy: A Review of Current Trials, *Int. J. Mol. Sci.* 2023, 24(14), 11626.
[3]Pallares, R.M, Abergel, R.J., Development of radiopharmaceuticals for targeted alpha therapy: Where do we stand?, *Front. Med. 2022, Vol.9*

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Overview of ongoing targeted alpha therapy clinical trials [3]

Radiopharmaceutical	Ligand	Cancer type	Special notes	Clinical trial*
^{211}At-BC8-B10	BC8-B10, antibody targeting CD45	Different types of acute leukemia or myelodysplastic syndrome		NCT03128034, phase I/II, recruiting (2017) NCT03670966, phase I/II, recruiting (2019) NCT04083183, phase I/II, recruiting (2020)
^{225}Ac-Lintuzumab	Lintuzumab, antibody targeting CD33	Acute myeloid leukemia	In combination with other chemotherapeutic agents	NCT03441048, phase I, recruiting (2018) NCT03867682, phase I/II, recruiting (2020) NCT03932318, phase I/II, not yet recruiting (2023)
^{212}Pb-DOTAMTATE	DOTAMTATE, somatostatin analog	Somatostatin positive neuroendocrine tumors		NCT03466216, phase I, recruiting (2018) NCT05153772, phase II, recruiting (2021)
BAY2315497 (^{227}Th)	Antibody targeting PSMA	Metastatic castration resistant prostate cancer	In combination with darolutamide	NCT03724747, phase I, active but not recruiting (2018)
^{225}Ac-FPI-1434	FPI-1175, antibody targeting insulin-like growth factor-1 receptor (IGF-1R)	Advanced solid tumors		NCT03746431, phase I/II, recruiting (2019)
BAY2701439 (^{227}Th)	Antibody targeting HER2	Advanced cancers expressing the HER2 protein		NCT04147819, phase I, recruiting (2020)
JNJ-69086420 (^{225}Ac)	H11B6, antibody targeting human kallikrein-2 (hk2)	Advanced and metastatic prostate cancer		NCT04644770, phase I, recruiting (2020)
^{225}Ac-J591	J591, monoclonal antibody against PSMA	Hormone-sensitive metastatic prostate cancer	In combination with androgen deprivation therapy	NCT04946370, phase I/II, recruiting (2021) NCT05567770, phase 1, not yet recruiting (2022)
^{225}Ac-PSMA-I&T	PSMA-I&T, small molecule targeting PSMA	Castration-resistant prostate cancer		NCT05219500, phase II, recruiting (2021)
^{211}At-OKT10-B10	OKT10, antibody targeting CD38	Plasma cell myeloma in patients undergoing stem cell transplantation	In combination with different chemotherapeutic agents and/or total body irradiation	NCT04466475, phase I, recruiting (2022) NCT04579523, phase I, not recruiting yet (2022)
^{225}Ac-DOTA-M5A	M5A, anti-carcinoembryonic antigen (CEA) antibody	CEA positive advanced and metastatic colorectal cancer		NCT05204147, phase I, recruiting (2022)
^{212}Pb-DOTAM-GRPR1	Gastrin-releasing peptide receptors (GRPR) antagonist	Several GRPR1-expressing tumors		NCT05283330, phase I, not recruiting yet (2022)
^{225}Ac-DOTA-daratumumab	Daratumumab, antibody targeting CD38	Refractory plasma cell myeloma		NCT05363111, phase I, recruiting (2022)
^{225}Ac-FPI-1966	Vofatamab, antibody targeting fibroblast growth factor receptor 3 (FGFR3)	FGFR3-expressing advanced solid tumors		NCT05363605, phase I/II, recruiting (2022)
RYZ101 (^{225}Ac)	Somatostatin analog peptide	Somatostatin receptor expressing gastroenteropancreatic neuroendocrine tumors		NCT05477576, phase I/II, recruiting (2022)
^{225}Ac-MTI-201	MTI-201, peptide targeting melanocortin 1 receptor (MC1R)	Metastatic uveal melanoma		NCT05496686, phase I, recruiting (2022)
^{212}Pb-Pentixather	Pentixather, CXC-chemokine receptor 4 (CXCR4)-directed peptide	Atypical lung carcinoid tumors		NCT05557708, early phase I, not recruiting yet (2022)

*The year in the clinical trial row refers to the date when the clinical study was (or is expected to be) initiated.

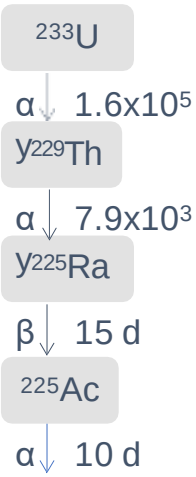
Th-229 Generator Sources

- Generator Th-229 Sources
  - ORNL, US 130 mCi of Th-229
  - JRC, Karlsruhe, Germany 40 mCi of Th-229
  - IPPE, Russia 130 mCi of Th-229 generator
  - CNL, Canada 5-10 mCi of Th-229

Challenge is the supply of all together is only 1.2-1.7 Ci

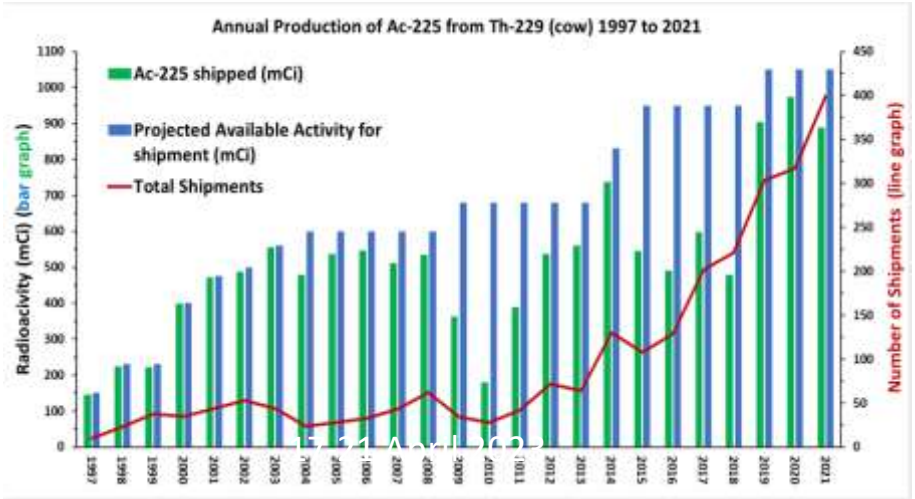
Actinium-225 Production at ORNL

- ORNL has been the main supplier of ^{225}Ac (via decay of existing ^{229}Th stock) since 1997
- >10 Ci of ^{225}Ac shipped in >2000 packages
- Approximately 1 Ci of ^{225}Ac is harvested annually from 130 mCi ^{229}Th stock at ORNL
- Thirteen 4-week campaigns are performed per year, with weekly customer shipments
- **Present supply fully subscribed**



Rationale for pursuing additional routes for production of ^{225}Ac

- The present supply is insufficient to meet the growing research and medical applications demands for ^{225}Ac



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Future Th-229 Sources

TerraPower (US)

Mining medical isotopes from nuclear waste (acs.org)

"Still, the amount of available ^{225}Ac is at the mercy of natural processes that happen over a very long time. The natural decay of ^{233}U and ^{229}Th is steady and reliable but also incredibly slow. ^{233}U has a half-life of 160,000 years, and the half-life of ^{229}Th is 8,000 years. The long half-lives mean that every year, a kilogram of 233U yields only about 5 mg of ^{229}Th, which can then decay into the medically valuable actinium. From the remaining ^{233}U that Isotek is set to dispose, TerraPower is on track to receive all the thorium that can be extracted during processing, Bolon says. That means TerraPower will get at least 45 g of ^{229}Th a year, enough to provide 50 to 100 times as much ^{225}Ac as the DOE is able to provide." (9 Ci/year)

Last year TerraPower announced a $750 million investment from Korea for nuclear technology and nuclear medicine isotope production

Agreement with Cardinal Health to distribute Ac-225 from generators

Collaboration with PanTera

Viable ^{225}Ac Production Routes

Facility	Nuclear Reaction
Reactor (thermal neutrons)	$^{226}Ra(3n,\gamma)^{229}Ra \rightarrow ^{229}Ac \rightarrow ^{229}Th$
Accelerator (photons via electrons)	$^{226}Ra(\gamma,n)^{225}Ra \rightarrow ^{225}Ac$
Accelerator (low energy particles)	$^{226}Ra(p,2n)^{225}Ac$ $^{226}Ra(\alpha,n)\ ^{229}Th$ $^{226}Ra(p,pn)\ ^{225}Ra$ $^{232}Th(p,x)\ ^{229}Th$
Accelerator (high energy protons)	**$^{232}Th(p,x)^{225}Ac$** $^{232}Th(p,x)^{225}Ra \rightarrow ^{225}Ac$
Accelerator (high energy neutrons)	$^{226}Ra(n,2n)\ ^{225}Ra$
Hot Cell Facility (^{233}U processing)	^{229}Th decay to ^{225}Ac

Processing Facilities at BNL: Latest News

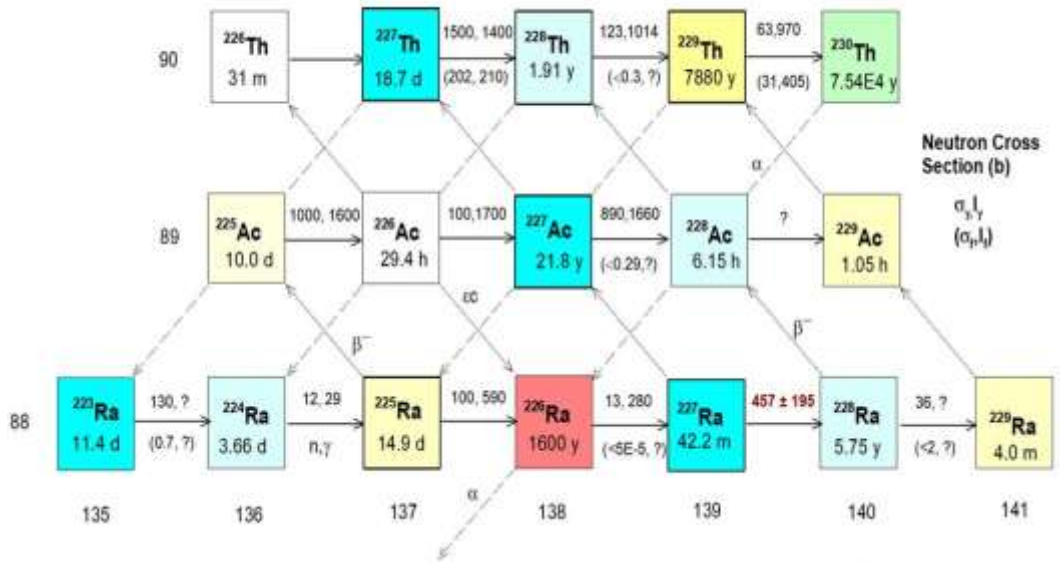
- Commissioned new AP hot cells for processing of Ac-225 to meet growing demand
- AP hot cells in routine operations
- A major milestone was achieved!

BNL put 112 mCi of Ac-225 into inventory by irradiation and processing all conducted onsite (BLIP and AP hot cell) – great accomplishment!

- DOE IP now has two processing sites: ORNL and BNL
- DMF filed in December 2023.

Alternative Routes of Production Under Investigation

- Electron linac production route
  - $^{226}Ra(\gamma,n)^{225}Ra \rightarrow ^{225}Ac$
- Low energy cyclotron route
  - $^{226}Ra(p,2n)^{225}Ac$
- 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)

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Sources of Ac-225 from Ra-226

Ra-226 based:

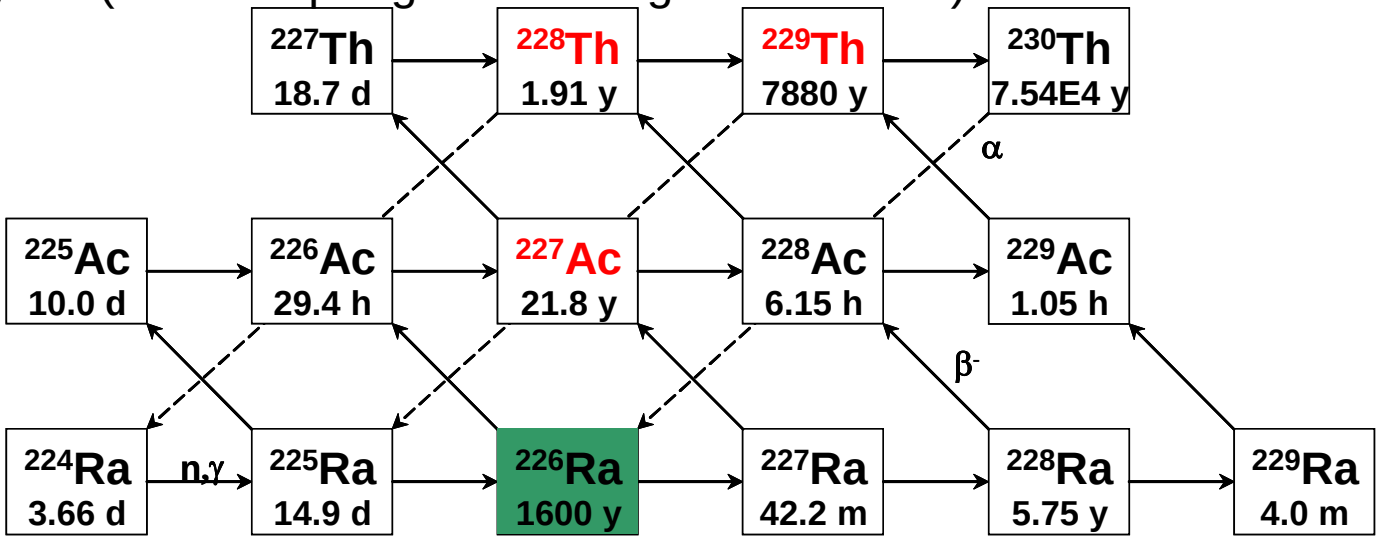
- Alfarim,
  - AZIsotopes,
  - BWXT/TRIUMF,
  - DOE
  - Eckert & Ziegler,
  - Global Morpho Pharma,
  - PanTera (IBA/SCK)
  - Ionetix,
  - CNL/ITM,
  - Nihon Medi-Physics,
  - Niowave,
  - NorthStar Medical,
  - SpectronRx, others

Photonuclear Routes of Production

- IBA September 20, 2021 Proton therapy developer Ion Beam Applications (IBA) and Belgian nuclear research center SCK CEN have partnered to enable the production of the medical radioisotope actinium-225 (Ac-225). Together, the companies will evaluate the technical and economic feasibility of producing large quantities of Ac-225. SCK CEN and IBA plan to undertake the construction and commissioning of a production unit on the SCK CEN site in Mol, Belgium.
- Niowave photonuclear production from Ra-226. Niowave is operating a closed-loop cycle to domestically produce high-purity Ac-225 and other alpha emitters from Ra-226 using a superconducting electron linear accelerator. The commercial-scale system will produce **10 Ci per week** of Ac-225 from a nitrate-based solution of Ra-226. Niowave's superconducting linacs can handle higher production output (>500 Ci per year using a 20 MeV, 210 kW beam) than any other method.
- Northstar indicates they will be producing Ac-225 from Ra-226 by the end of the calender year. Using electron accelerator photonuclear route to irradiate Ra-226 to produce Ac-225. Have stated up to 10 Ci of Ac-225 production in 2 years. Have a supply agreement in place with Point Biopharma Global Inc.

Reactor Production of Alpha-Emitting Radioisotopes

- **Radium-226 target**
  - Limited quantities (no longer a commercial market; recover from old, unwanted sources)
- **Actinium-227 product**
  - High yield (>1 Ci per g of Ra in high flux reactor)
- **Thorium-228 product**
  - High yield (>50 Ci per g of Ra in high flux reactor)
- **Thorium-229 product**
  - Low yield (>10 mCi per g of Ra in high flux reactor)



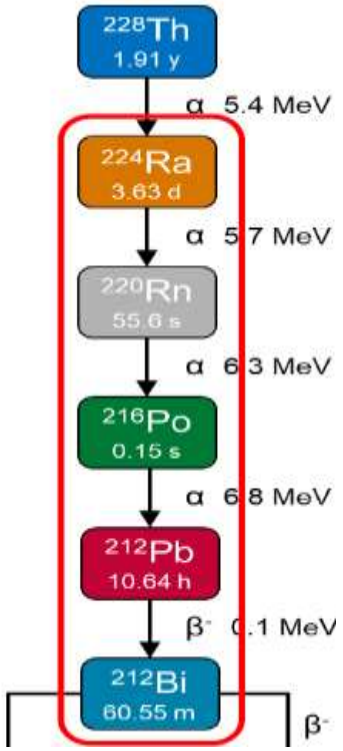
Pb-212 (Supplied as a Pb-212/ Bi-212 Generator)

- Generator demand is increasing
- DOE IP is expanding generator availability in the U.S. to meet demand
- Optimizing current supply from ORNL
  - FY22: record production year of 10 campaigns with 20 generators shipped (≤ 16 mCi each)
  - FY23: production plan for 12 campaigns with plan for 20-24 generators (≤ 16 mCi each)
- Building on R&D for supply from PNNL
  - In FY21, set up & demonstrated the process up to ~3 mCi level
  - In FY22, scaled up to clinically relevant levels (11-19 mCi)
  - In FY23, PNNL is working towards supply of Pb-212 generators (≤ 16 mCi each) on a monthly basis
- Work is underway at both sites to increase generator capacity to ~30 mCi each
  - Completion targeted in early FY23 for ORNL
  - Latter half of FY23 for PNNL

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



Brookhaven National Laboratory

Summary

- The interest in therapeutic radionuclides is growing in leaps and bounds
- The production is increasing making radionuclides more readily available
  - DOE IP has ramped up its role in the supply with a goal of maximizing the domestic availability.
  - Several commercial companies are pursuing production
- A robust domestic supply of Ac-225, regionalized production of At-211, and increased availability of Pb-212 generators are being actively pursued in the U.S.
- Alternative production approaches are 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, API at LANL, RPF at ORNL)

Questions?