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U.S. DEPARTMENT OF ENERGY

Update on the BNL Isotope Program

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Chair of Isotope Research and Production Department (IP)

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DOE Isotope Program Mission

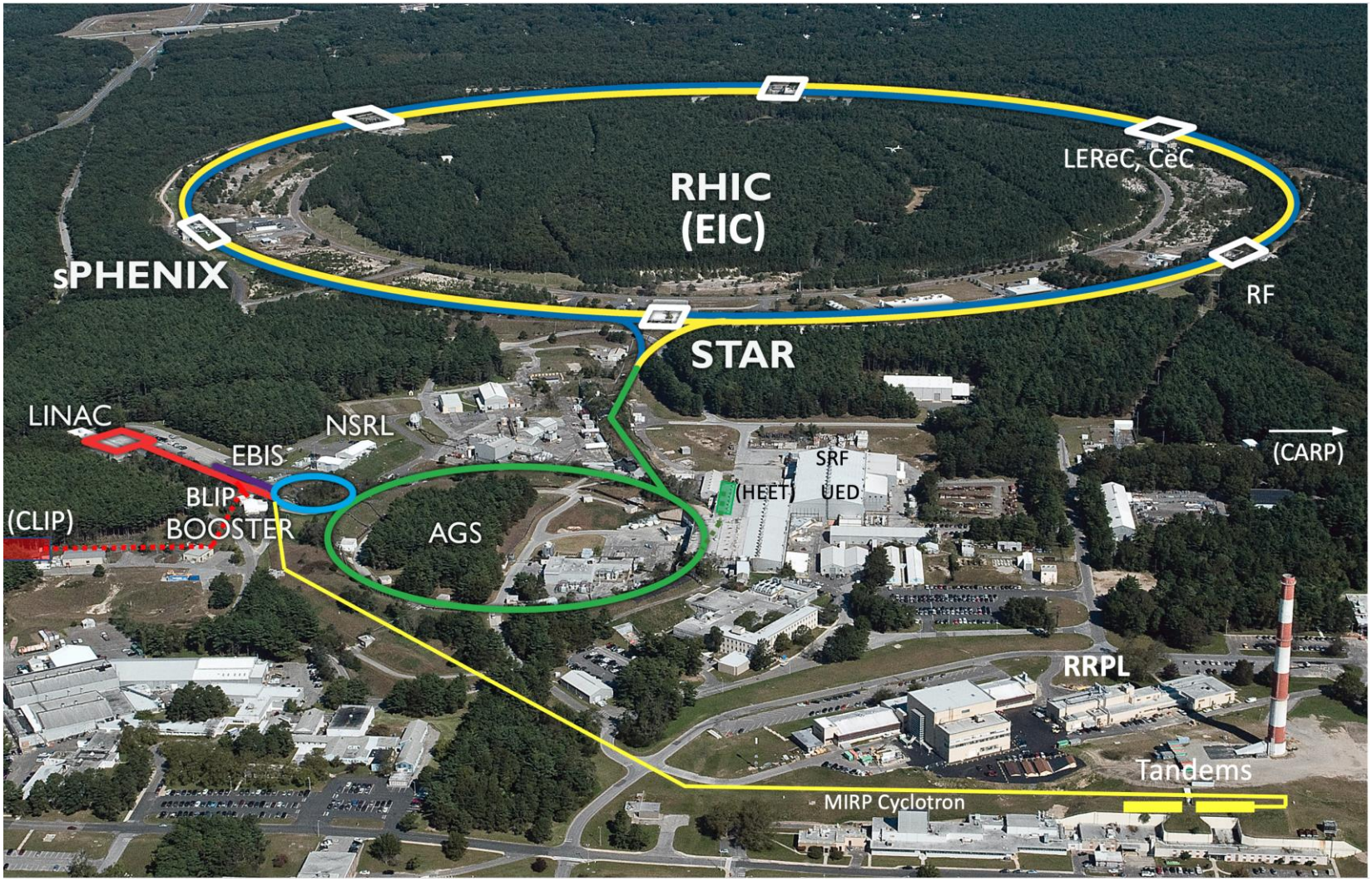
Produce and/or distribute radioactive and stable isotopes that are in short supply; includes by-products, surplus materials and related isotope services

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

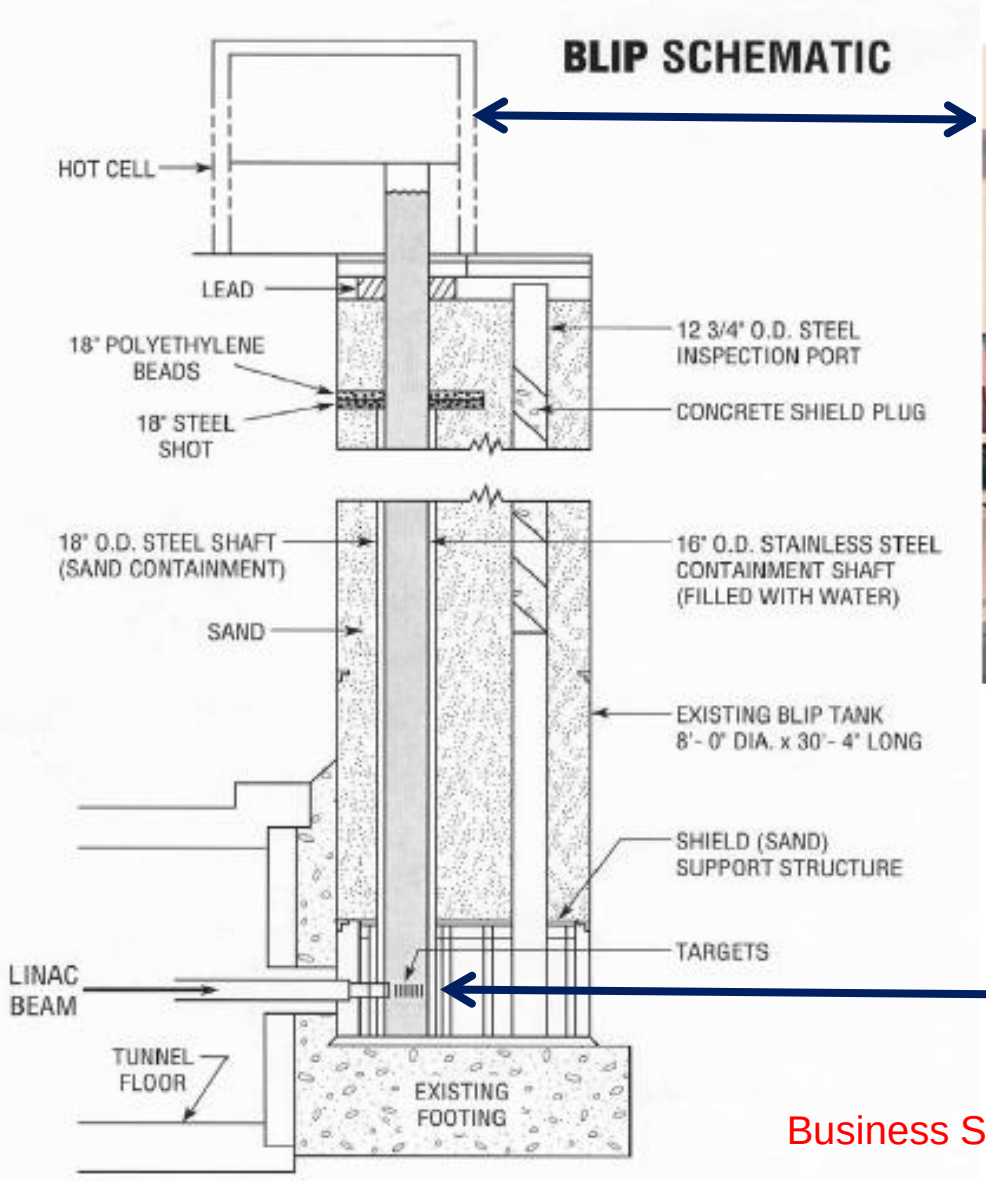
Conduct R&D on new and improved isotope production and processing techniques which can make available priority isotopes for research and application. Develop workforce.

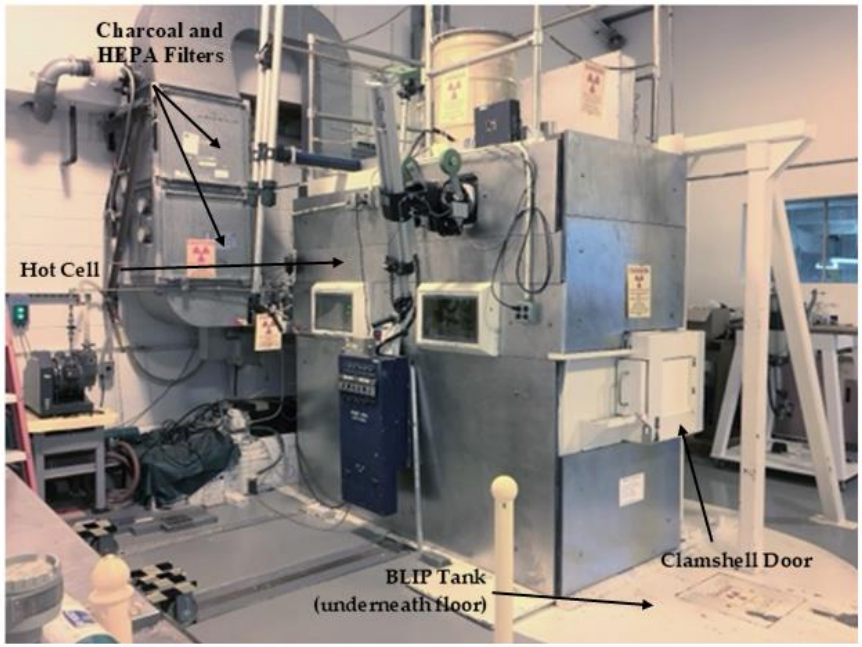
Ensure robust domestic supply chains. Reduce U.S. dependency on foreign supply to ensure National Preparedness.

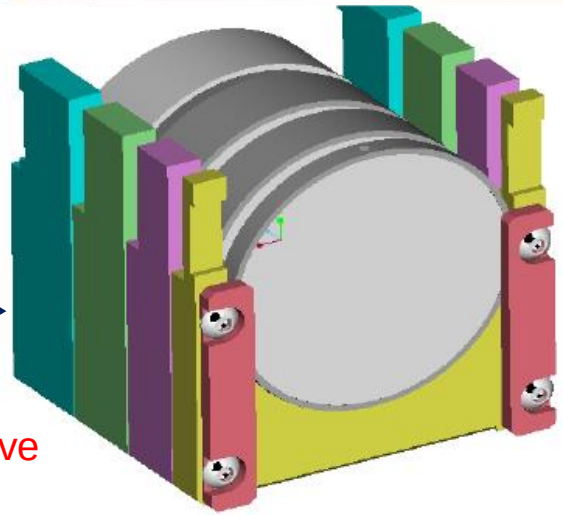
Collider-Accelerator Department facilities



Brookhaven Linac Isotope Producer







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Building 801(Houses the RRPL) Radionuclide Research and Production Laboratory

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Radioisotope Laboratories, Manufacturing (TPL)

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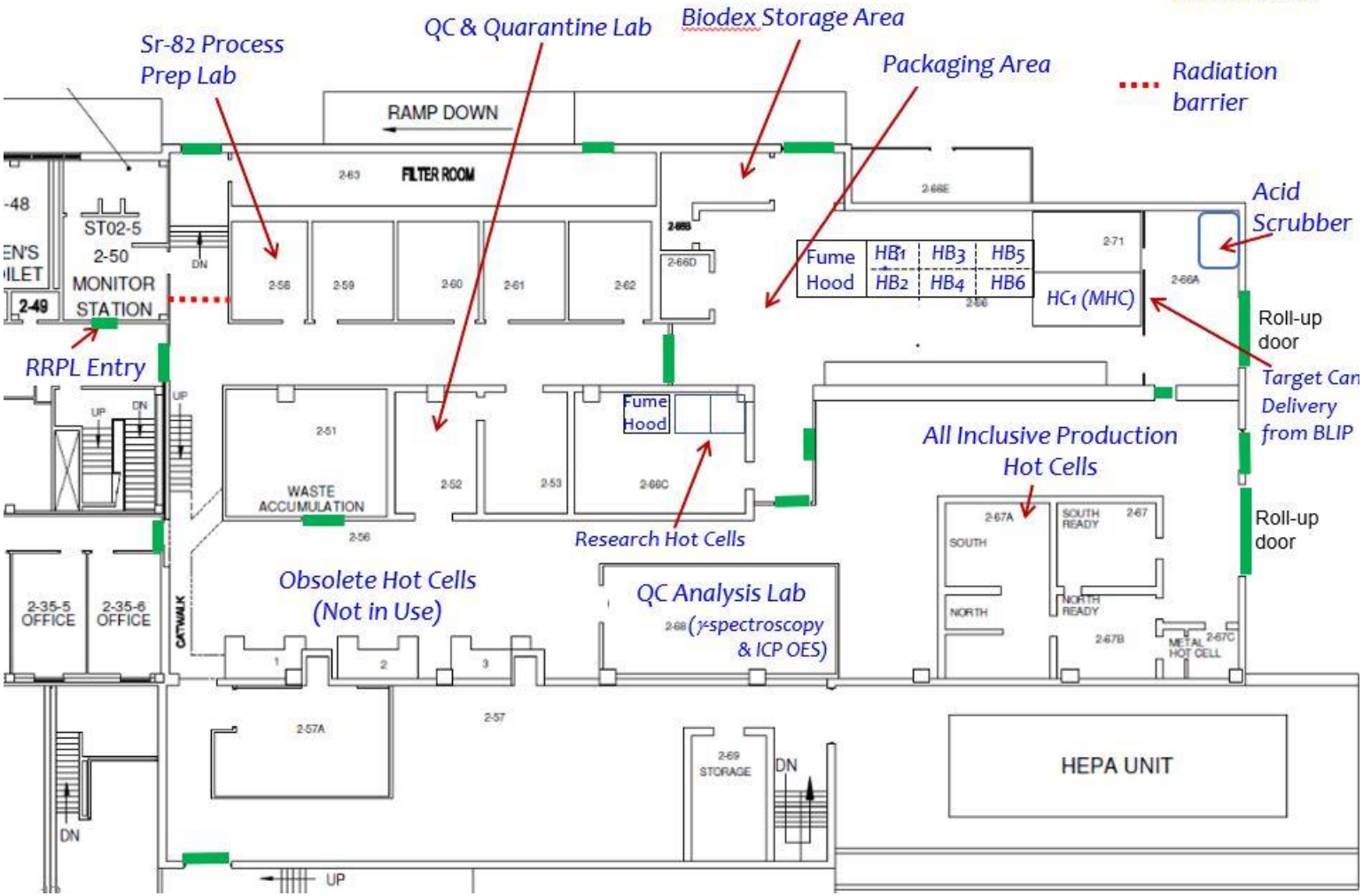

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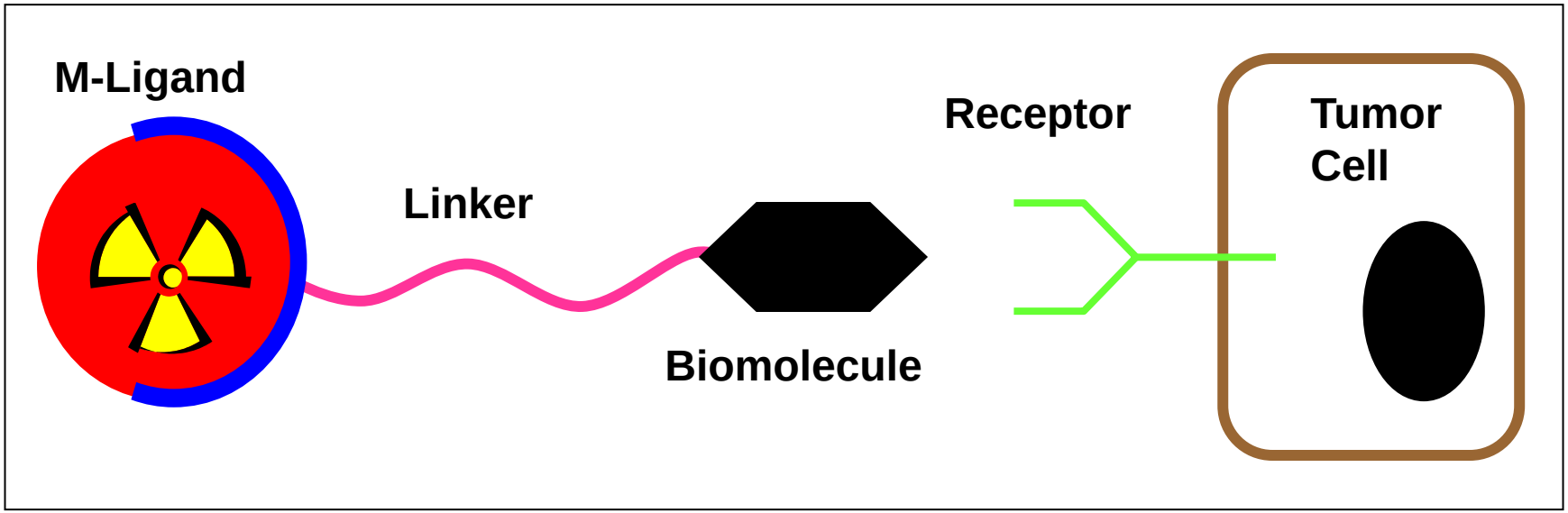
Targeted Approaches

- Bifunctional Chelating Agent
- Requires high specific activity



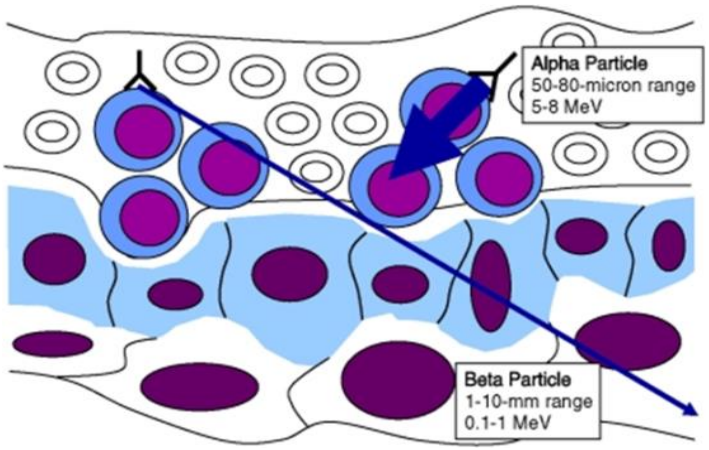
Physicochemical characteristics of β-emitters and α-emitters

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

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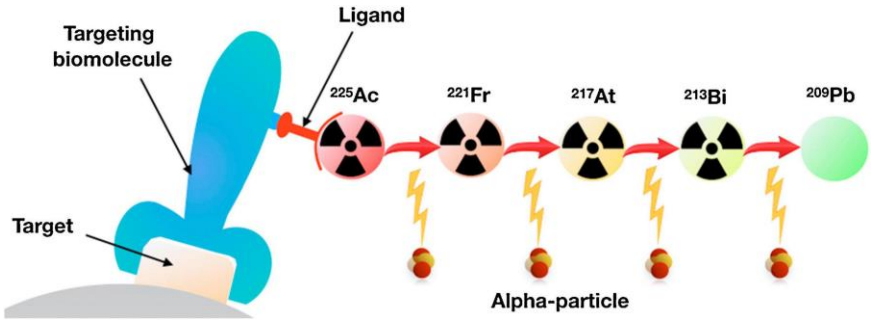
Slide courtesy of Dr. M. McDevitt, Memorial Sloan Kettering

Actinium-225 (half-life=9.92 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 **1.1-1.2 mCi per patient-kg**[2]
- Recent estimate of annual global ^{225}Ac use: **670 Ci for 2 million patient doses per year** (ref 1)



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

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.

[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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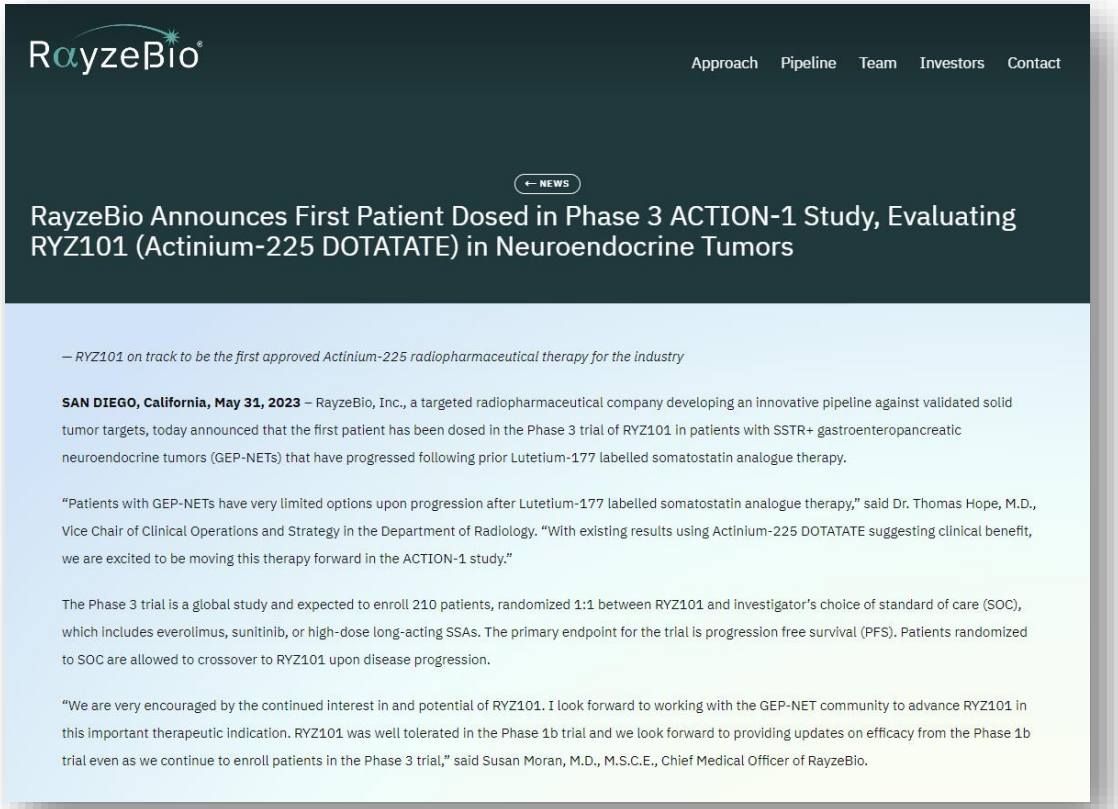
MARKET DRIVERS: What is fueling this growth?

1. Rising Demand for Clinical Applications

- Favorable preclinical and clinical results for targeted alpha therapy, with Ac-225 leading the way
- New clinical trials initiating, existing clinical trials progressing, and drug development underway
- Each phase requires substantially more Ac-225, especially when tied to prevalent illnesses (e.g., prostate cancer)



RayzeBio

Approach Pipeline Team Investors Contact

← NEWS

RayzeBio Announces First Patient Dosed in Phase 3 ACTION-1 Study, Evaluating RYZ101 (Actinium-225 DOTATATE) in Neuroendocrine Tumors

— RYZ101 on track to be the first approved Actinium-225 radiopharmaceutical therapy for the industry

SAN DIEGO, California, May 31, 2023 – RayzeBio, Inc., a targeted radiopharmaceutical company developing an innovative pipeline against validated solid tumor targets, today announced that the first patient has been dosed in the Phase 3 trial of RYZ101 in patients with SSTR+ gastroenteropancreatic neuroendocrine tumors (GEP-NETs) that have progressed following prior Lutetium-177 labelled somatostatin analogue therapy.

"Patients with GEP-NETs have very limited options upon progression after Lutetium-177 labelled somatostatin analogue therapy," said Dr. Thomas Hope, M.D., Vice Chair of Clinical Operations and Strategy in the Department of Radiology. "With existing results using Actinium-225 DOTATATE suggesting clinical benefit, we are excited to be moving this therapy forward in the ACTION-1 study."

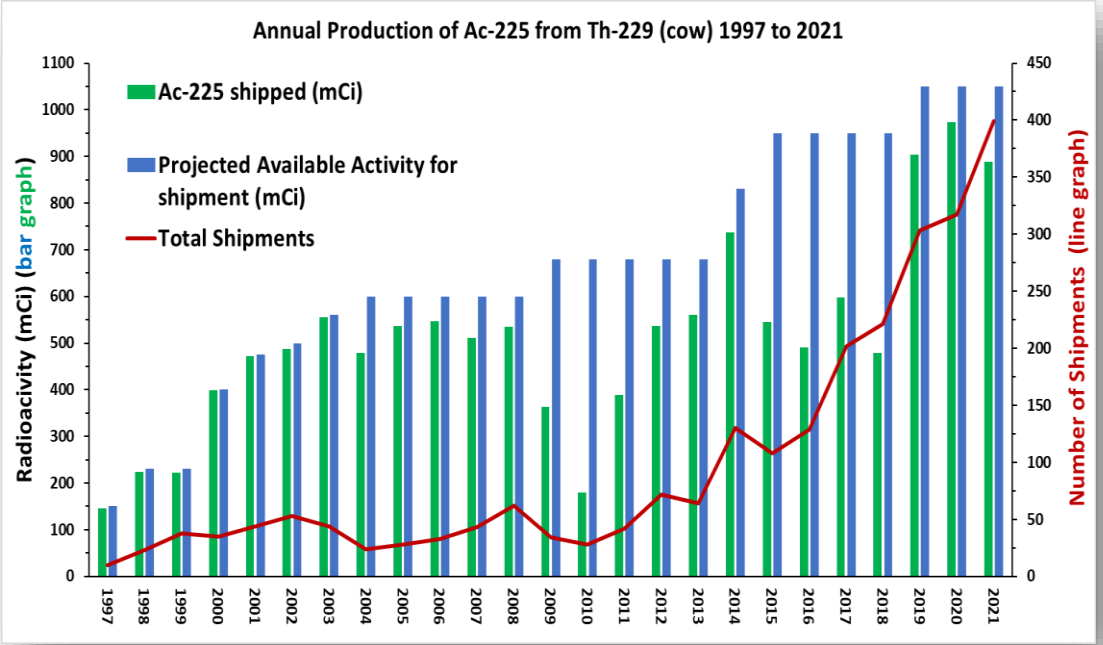
The Phase 3 trial is a global study and expected to enroll 210 patients, randomized 1:1 between RYZ101 and investigator's choice of standard of care (SOC), which includes everolimus, sunitinib, or high-dose long-acting SSAs. The primary endpoint for the trial is progression free survival (PFS). Patients randomized to SOC are allowed to crossover to RYZ101 upon disease progression.

"We are very encouraged by the continued interest in and potential of RYZ101. I look forward to working with the GEP-NET community to advance RYZ101 in this important therapeutic indication. RYZ101 was well tolerated in the Phase 1b trial and we look forward to providing updates on efficacy from the Phase 1b trial even as we continue to enroll patients in the Phase 3 trial," said Susan Moran, M.D., M.S.C.E., Chief Medical Officer of RayzeBio.

MARKET DRIVERS: What is fueling this growth?

2. Limited Supply of Other Ac-225 Sources

- The global supply of Th-229-derived Ac-225 is fully subscribed, including ORNL's inventory
  - ORNL Th-229 limit of 1 Ci/year
- Future/alternative n.c.a. Ac-225 supplies are not fully developed and ready for mass production and distribution (e.g., cyclotron-based, additional Th-229 cows, electron beam)



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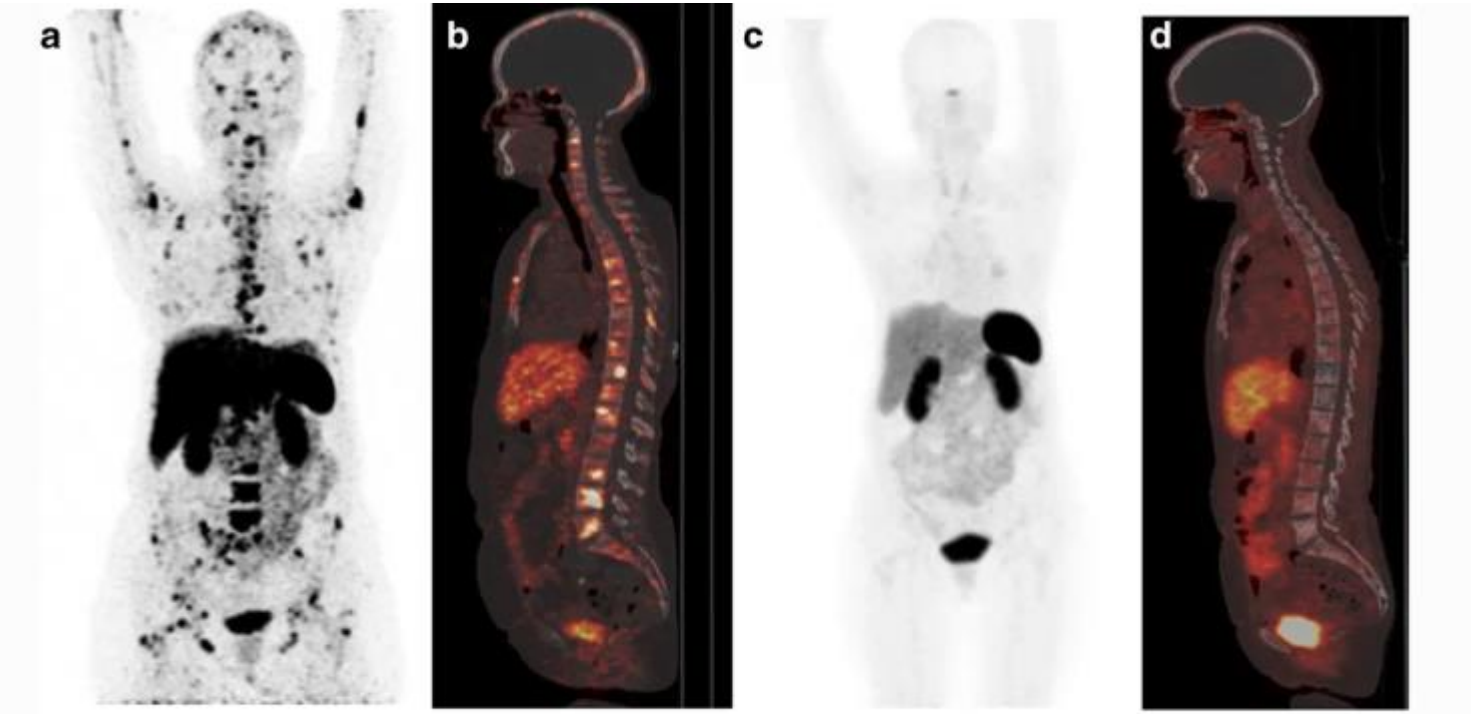
Broadening horizons with ^{225}Ac-DOTATATE targeted alpha therapy for gastroenteropancreatic neuroendocrine tumour patients stable or refractory to ^{177}Lu-DOTATATE PRRT: first clinical experience on the efficacy and safety



Baseline ^{68}Ga-DOTANOC PET/CT MIP and sagittal Image

Post 2 cycles of ^{225}Ac-DOTATATE therapy, Interim ^{68}Ga-DOTANOC PET/CT MIP and sagittal image

Balla S., et.al Eur J Nucl Med Mol Imaging: 2020 47(4) 934-946
doi: 10.1007/s00259-019-04567-2

Basis of the Tri-Lab Effort: Leveraging Unique DOE Isotope Program Facilities, Capabilities and Expertise to Address 225Ac 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) 165 μA intensity to targets at incident energies ranging from 66-202 MeV

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Processing Facilities at BNL: Latest News

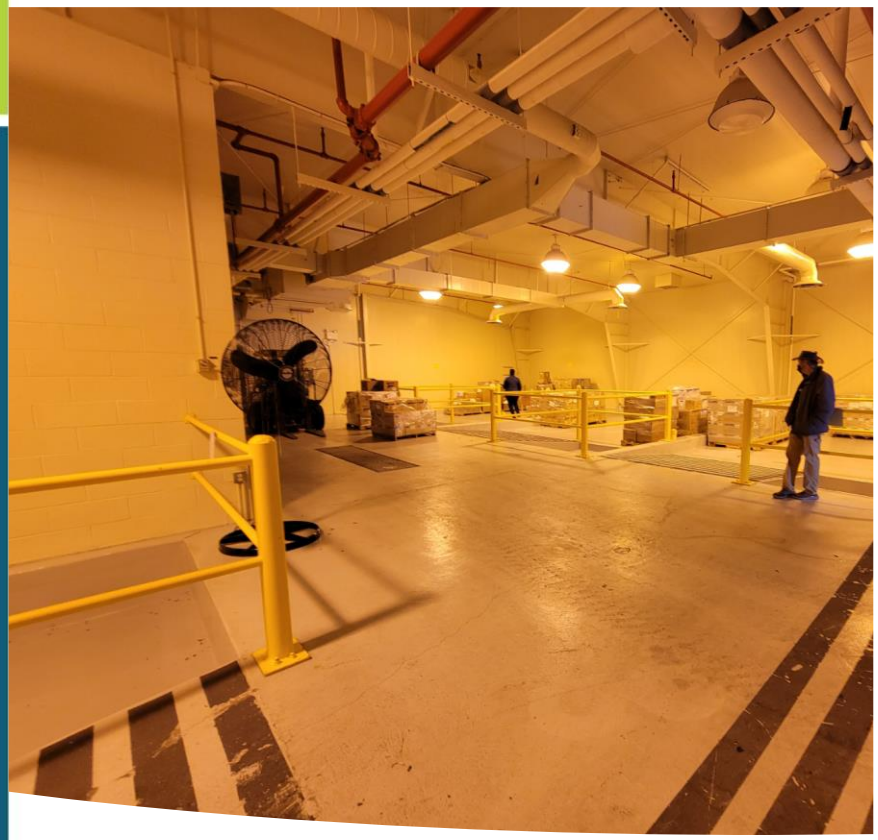
- Commissioned new AP hot cells for processing of Ac-225 to meet growing demand
- AP hot cells in routine operations
- A major milestone was achieved in March 2023!

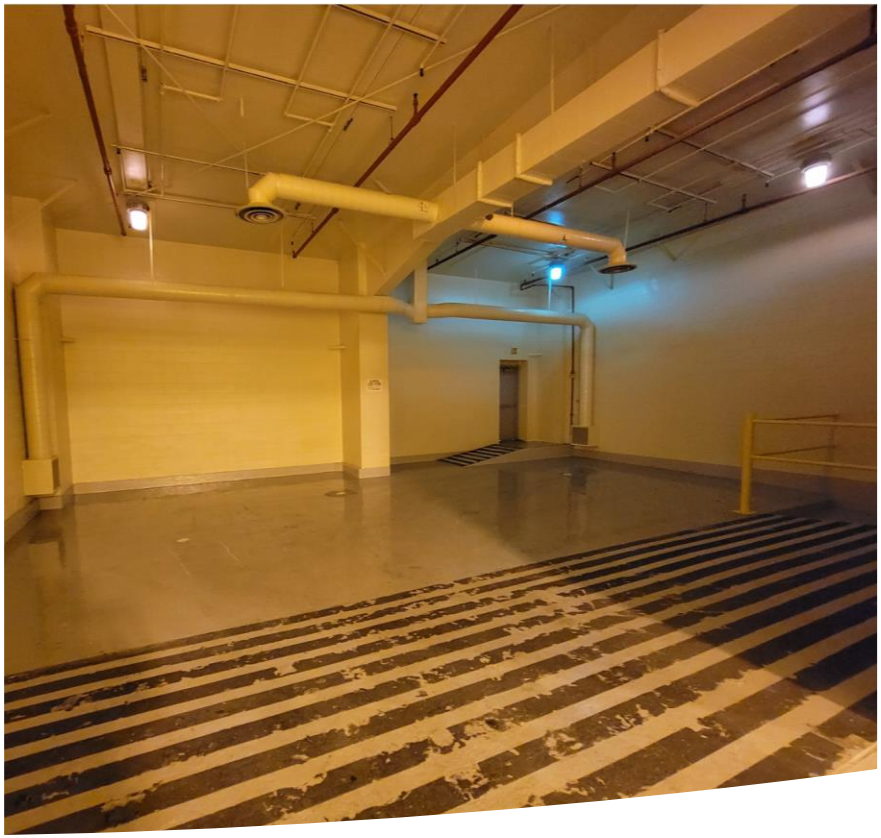
MIRP put 112 mCi of Ac-225 into inventory by irradiation and processing all conducted here onsite (BLIP and AP hot cell) – great accomplishment!

- DOE IP now has two processing sites: ORNL and BNL
- Consist of three hot cells, two ready rooms, dedicated ventilation, acid scrubber system, clamshell for target introduction to reduce dose to operators.

Clinical Alpha Radionuclide Producer (CARP)

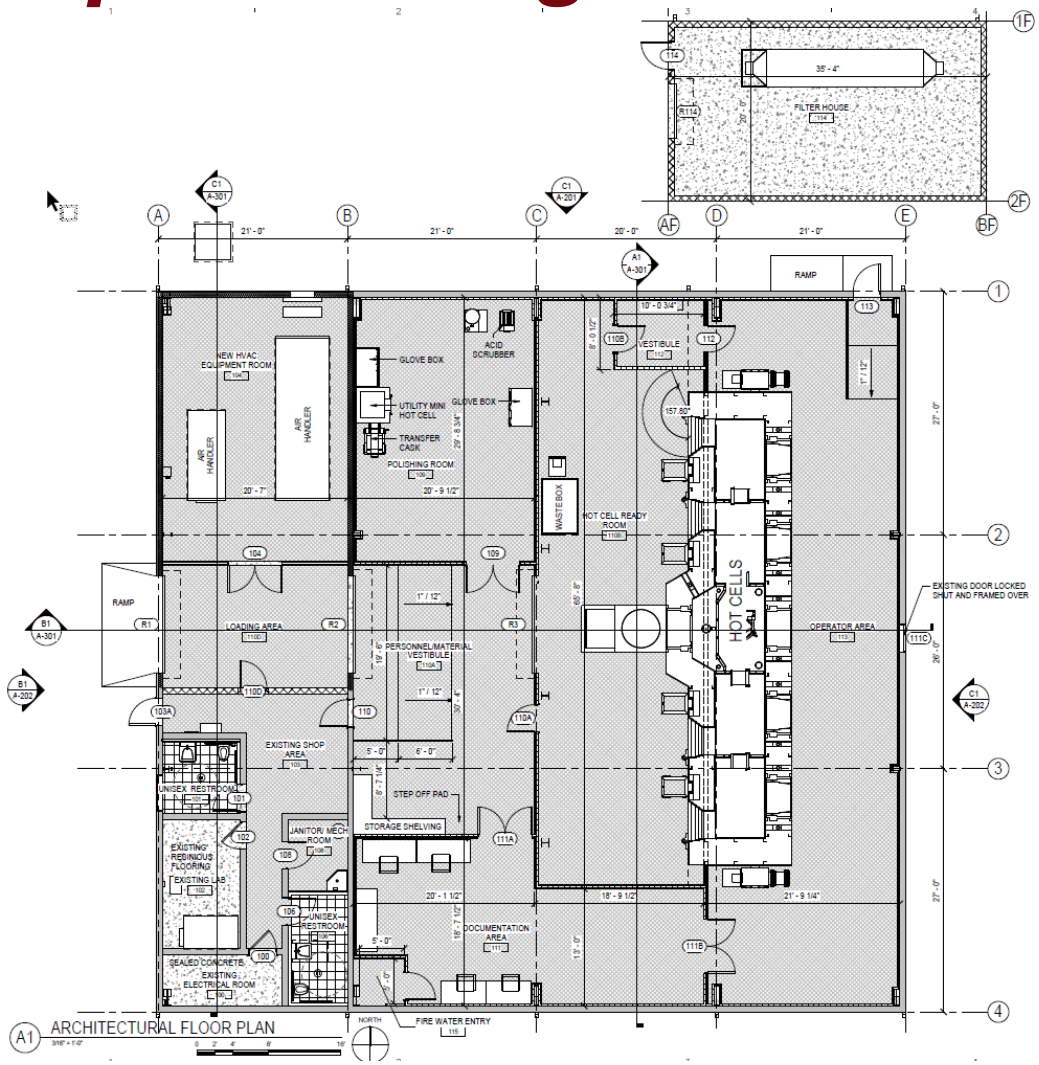
Repurposing Former HC3 Facility - Bldg. 870





- Waste Management Facility (Mixed Waste Building) is no longer needed due to significant reductions in the amount of this waste stream being created.
- This facility was designed as a Haz Cat-3 facility and has a number of bays and a lab allowing for hot cell installation.

Preconceptual design



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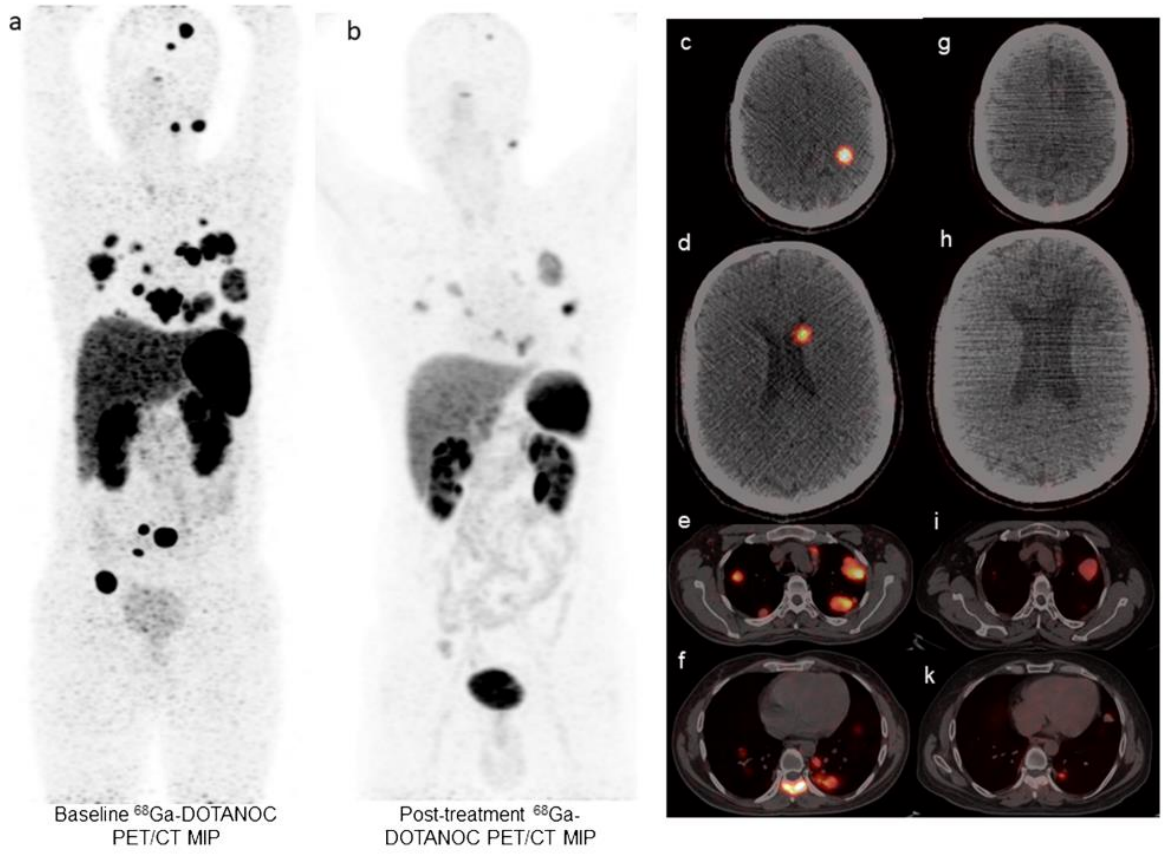
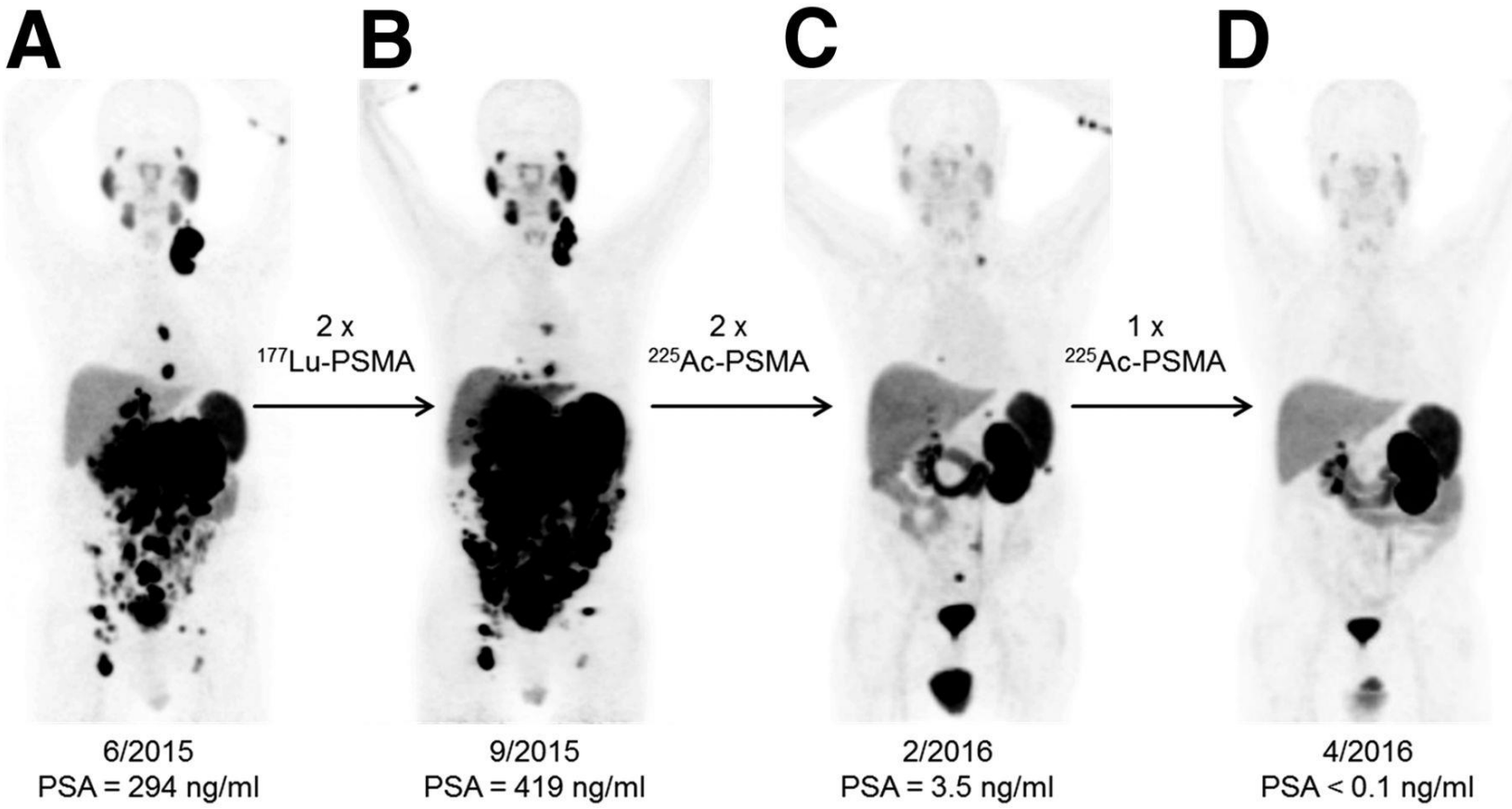
Efficacy and safety of ^{225}Ac-DOTATATE targeted alpha therapy in metastatic paragangliomas: a pilot study



European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:1595–1606

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

JNM The Journal of NUCLEAR MEDICINE

Questions?