Memorial Sloan Kettering
Cancer Center
RMIP Core

Establishing Radiopharmaceutical Production – Considerations

October 30th, 2025

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Disclosures

Serge K. Lyashchenko declares that he:

- Is a consultant to, and has equity in, Evergreen Theragnostics, Inc.
- Is consultant to Solve Tx, Inc.
- Is a consultant to, has equity in, and is on the Board of Managers at Juniper Radiopharma, LLC.

Factors impacting global radiopharmaceutical supply

- Medical radionuclide availability and accessibility
  - Regional geography
- Radiopharmaceutical regulatory landscape
  - In-house production
  - Interplay between health and nuclear energy regulators
- Insufficient professional training
- High costs

Availability and "Accessibility" of Radionuclide Remains a Challenge

Diagnostic (PET)

- ^{89}Zr (78.4hours)
- ^{124}I (100.4 hours)
- ^{72}As (26 hours)
- ^{152}Tb (17.5 hours)
- ^{76}Br (16.2 hours)
- ^{86}Y (14.74 hours)
- ^{43}Sc (3.89hours)
- ^{44}Sc (3.97 hours)
- ^{45}Ti (3.05hours)

Therapeutic

- Beta
  - ^{131}I (8.02 days)
  - ^{177}Lu (6.65 days)
  - ^{67}Cu (2.57days)
  - ^{47}Sc (3.35days)
  - ^{161}Tb (6.95 days)
- Alpha
  - ^{225}Ac (9.95days)
  - ^{213}Bi (45.6minutes)
  - ^{212}B (60 min)
  - ^{211}At (7.21hours)
  - ^{227}Th (18.7 days)

Currently, the ^{225}Ac supply chain problems persist

PHARMA

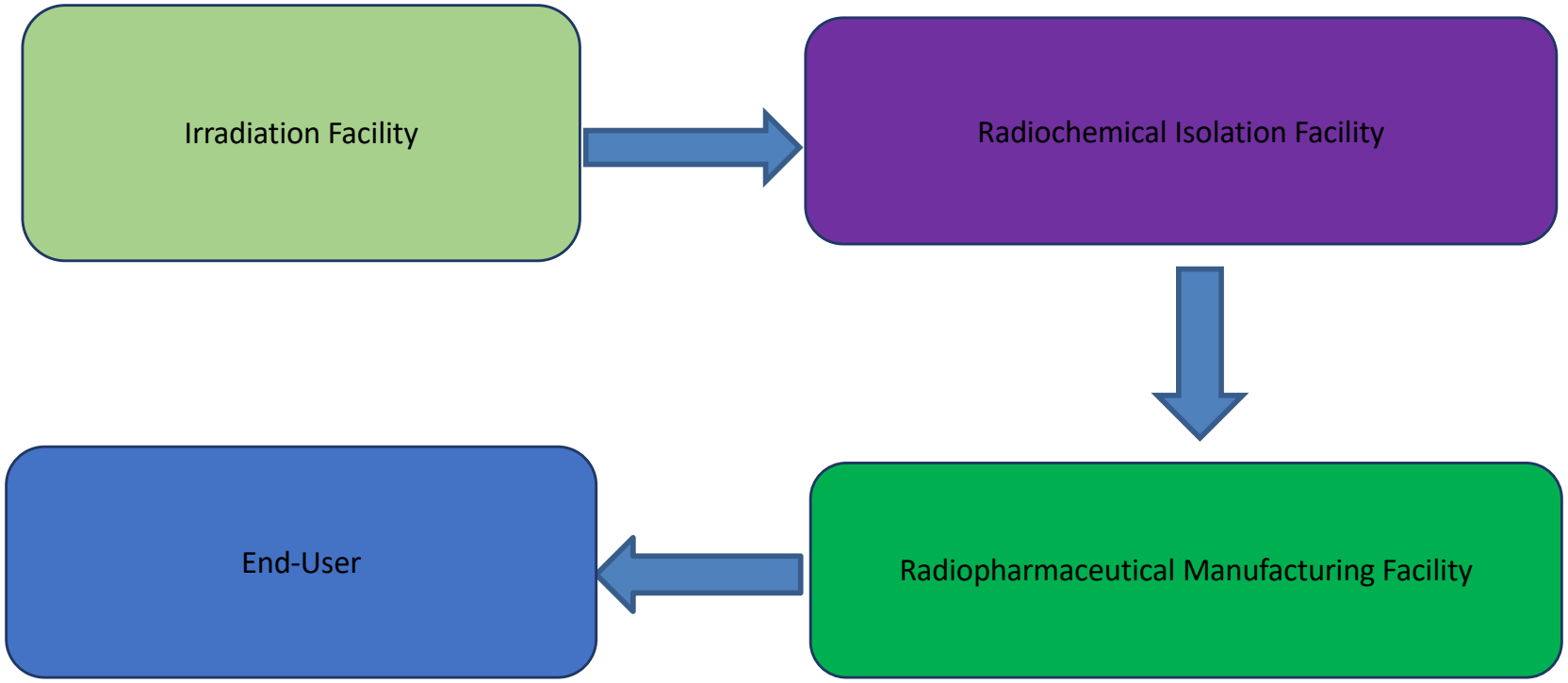
Bristol Myers' RayzeBio halts radiotherapy trial enrollment after isotope runs scarce

By **Fraiser Kansteiner** · Jun 3, 2024 3:38pm

Bristol Myers Squibb | RayzeBio | radiotherapy | radiopharmaceuticals

https://www.fiercepharma.com/pharma/bms-and-rayzebio-halt-radiotherapy-trial-enrollment-after-isotope-runs-scarce

Radioactive Half-Life has Major Impact on Radionuclide Availability



$^{89}ZrCl_4$ as a global PET radiometal of choice?

Considerations

- Ability to be incorporated into well-established chelators
- Half-life and distribution potential
- Overcoming regional regulatory restrictions
- **Availability of enriched target material**
- **It is cheap!**

Nuclear Medicine and Biology 136–137 (2024) 108943

Contents lists available at ScienceDirect

Nuclear Medicine and Biology

journal homepage: www.elsevier.com/locate/nucmedbio

[^{89}Zr]$ZrCl_4$ for direct radiolabeling of DOTA-based precursors☆

Serge K. Lyashchenko [a,b,*], Tuan Tran [a], Steffen Happel [c], Hijin Park [a], David Bauer [b], Kali Jones [b], Tullio V. Esposito [b], NagaVaraKishore Pillarsetty [b], Jason S. Lewis [a,b,d]

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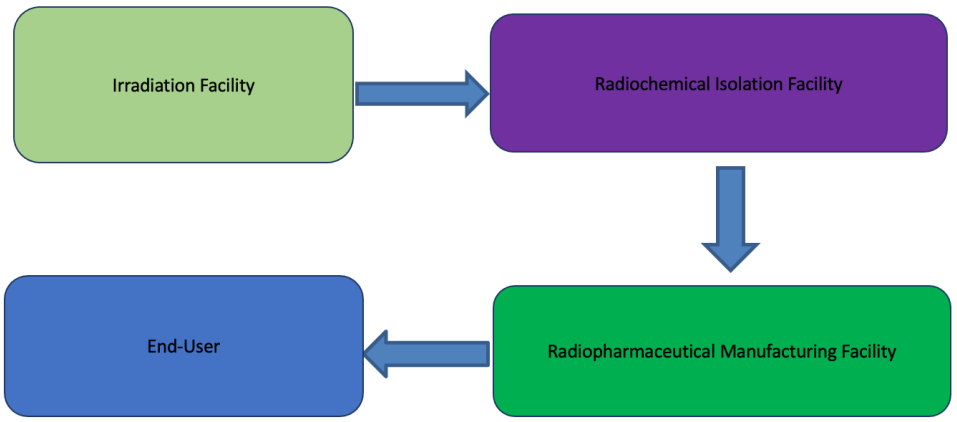
[b] Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[c] Triskem International, Inc., USA
[d] Program in Molecular Pharmacology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

- Industrial quantities of DOTA-PSMA-617 and DOTAGA-PSMA-I&T were quantitatively labeled with ^{89}Zr.
- Certain advantages over ^{68}Ga and ^{64}Cu.



Dr. Mark Bartholomä, PhD.

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Regulatory landscape does impact patient access to radiopharmaceuticals

- Balance between demonstration of quality, safety and efficacy, and enabling patient access
- Impact on cost and speed of development
- Interplay between health and nuclear energy regulators

Concept of " In-House Production"

What is it?

- A regulatory mechanism that allows for local production of radiopharmaceuticals for human use based on the order from a medical doctor for a specific patient.

Considerations and Implications

- **Emphasis on improved patient access**
  - In geographically remote areas
  - To agents with clinical data obtained in other regions of the world
  - **When the benefit outweighs the risk, based risk assessment conducted by a medical doctor**
- Radiopharmaceutical could include:
  - Novel compound
  - Investigational agent with some clinical data
  - An analogue of a drug with marketing authorization
- Fewer applied production process controls equates to smaller overall costs
- Production normally conducted by "above technician level" trained individuals
- Often requires intimate collaboration between the producer and the regulator
- **Less emphasis from regulators for producer to eventually obtain marketing authorization**

Dr. Marina Bicalho Silveira, PhD, CDTN, Brazil

Dr. Anderson Montai, PhD, Anvisa, Brazil

Professor Andrew Scott, MD, Austin Hospital, Australia

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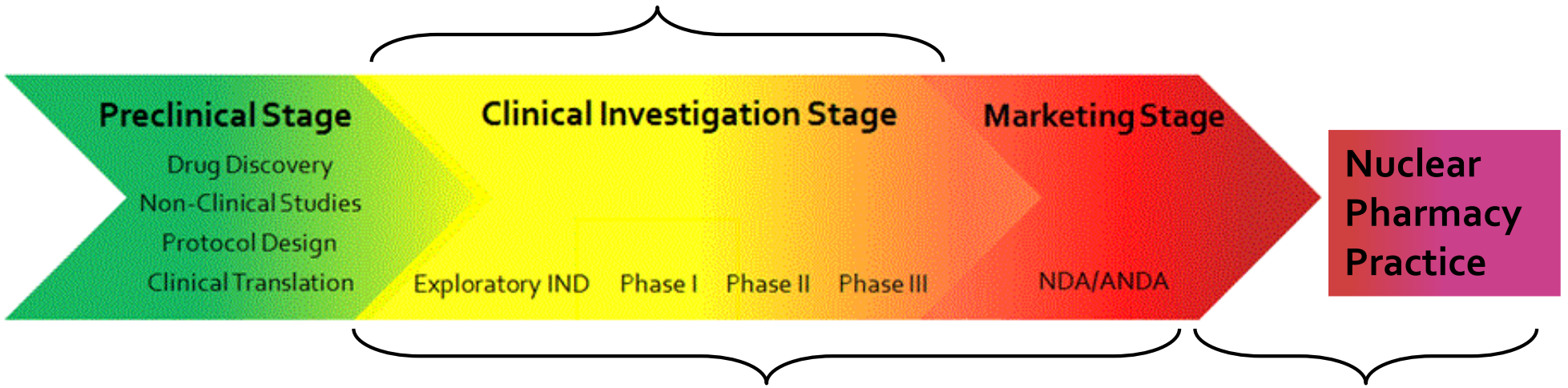
Situation with "In-House Production" in the United States

Emphasis on FDA approval, yet treating patients with investigational agents may be possible on a limited basis under "expanded access IND".



Cannot make "copies" of FDA approved drugs.

Can make "copies" during shortage of FDA approved RP's.

What happens when there is a shortage of approved radiopharmaceutical?

MANUFACTURING

Novartis halts Pluvicto new patient starts, struggles with radiotherapy's supply amid manufacturing expansion

By Angus Liu • Feb 28, 2023 03:29pm

https://www.fiercepharma.com/manufacturing/novartis-halts-pluvicto-new-patient-starts-struggles-radiotherapy-supply-amid

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Lutetium Lu 177 Vipivotide Tetraxetan (Pluvicto) Injection
Status: Currently in Shortage
»Date first posted: 03/07/2023
»Therapeutic Categories: Oncology

https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages

The ^{177}Lu-PSMA-617 (Pluvicto) Supply Problem Will Be Solved by Competition

Johannes Czernin and Jeremie Calais
Ahmanson Translational Theranostics Division, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, California

An editorial in this issue of *The Journal of Nuclear Medicine* by the theranostics teams of Dana–Farber Cancer Institute and Brigham and Women's Hospital addresses ongoing challenges with the rollout of ^{177}Lu-PSMA-617 (^{177}Lu-vipivotide tetraxetan; Pluvicto [Novartis]) (*1*). The authors highlight several major problems: insufficient and slow supply remains a daunting problem for patients, their families, caregivers, and treating physicians. Most alarmingly, 5% of the authors' patients died while waiting for treatment, as this can be delayed by 2 mo or even longer (*1*). These observations match our own experience. The authors point to additional consequences, including long intervals between pretreatment prostate-specific membrane antigen (PSMA) PET/CT scans and therapy rendering patient stratification and treatment monitoring unreliable (*1*).

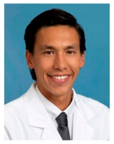
The U.S. Food and Drug Administration approved the new-drug application for Pluvicto 9 mo ago. The Centers for Medicare and Medicaid Services has reimbursed for it since October 2022. Novartis halted production of Pluvicto in Ivrea, Italy, and Milburn, New Jersey, in May 2022 and resumed production and delivery at the Ivrea site in June 2022. Yet, Pluvicto availability has remained a significant problem because only one of the two previous sites is currently operational for Pluvicto production.

Drugs are usually considered a failure if they do not meet revenue and profit expectations, which is one suggested reason for the market withdrawal of the CD20 antibody ^{131}I-tositumomab (Bexxar; GlaxoSmithKline) (*2*). But commercialization starts with suc-

NCT04689828) (*5*). This, and several ongoing investigator- or industry-initiated late-stage randomized clinical trials, place PSMA-targeted therapies at various stages of prostate cancer, suggesting that indications will broaden and demand will increase dramatically.

What are the solutions? Novartis added a new production site at Purdue Research Park near Indianapolis, and it is hoped that this and the Milburn site will be fully operational later this year. Novartis needs to create further backup solutions to guarantee a drug supply for new patients whose waiting times are unacceptable and for those who are already undergoing treatment and are waiting for the subsequent therapy cycles. Competition will certainly contribute to solving the supply problem. Several compounds are undergoing testing in phase 3 clinical trials, including SPLASH (NCT0464752, POINT Biopharma/Lantheus) and ECLIPSE (NCT05204927, Curium), and are likely

Johannes Czernin



Jeremie Calais

Czernin et al J Nucl Med. 2023 Mar;64(3):343

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” In-house production” during shortage- considerations

- Compounding vs patient expanded access IND
- Registration as a state nuclear pharmacy vs submitting an IND
- Access to required raw materials
- Legal repercussions
- Billing and reimbursement mechanisms
- Degree of manufacturing applied controls
- Patents
- **Communication with the FDA is a good idea**

MSKCC PETtrace 880 Installation

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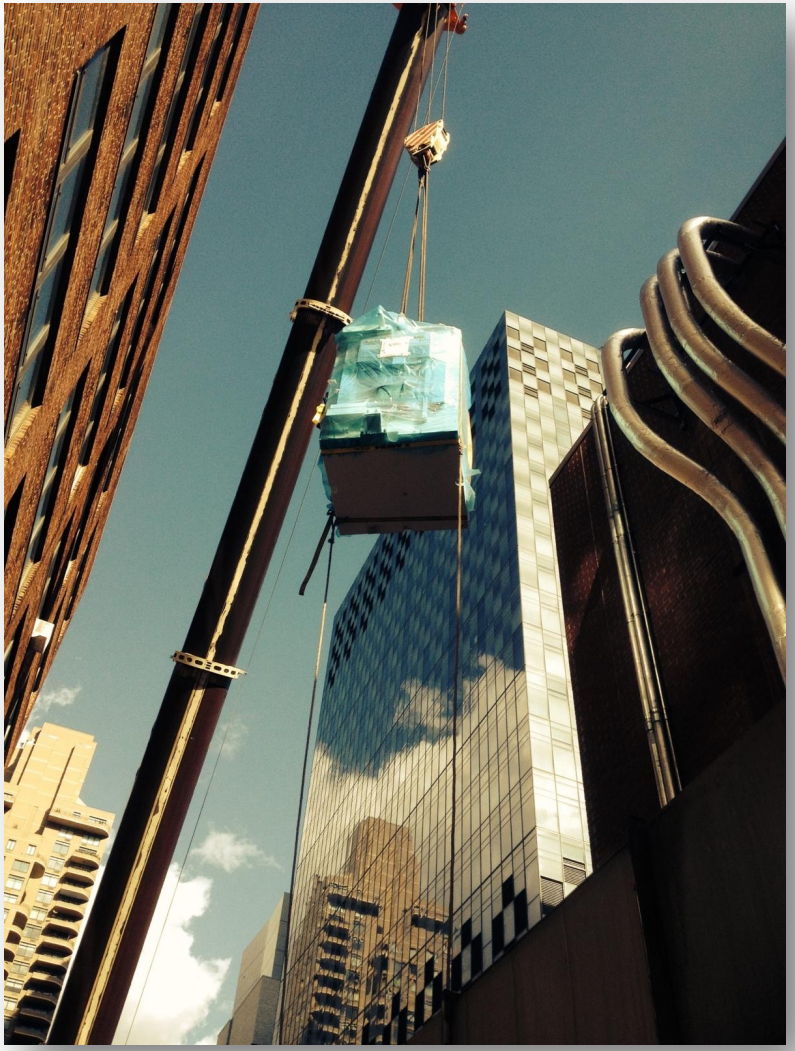
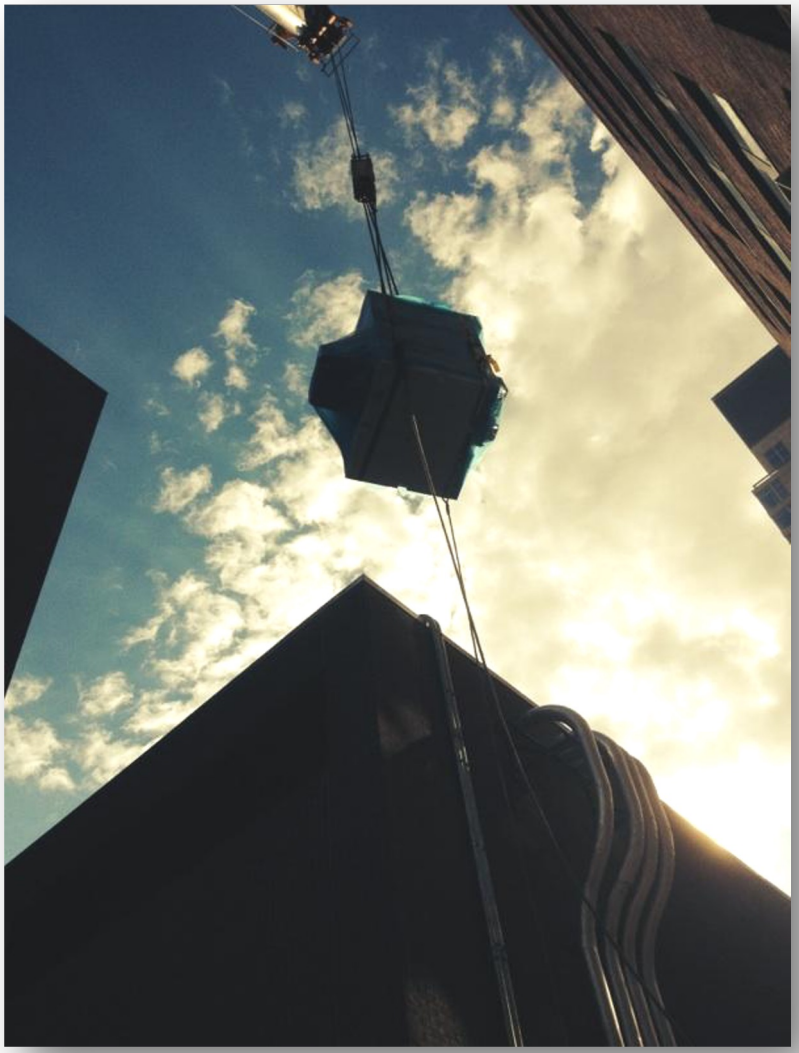
MSKCC PETtrace 880 Installation





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MSKCC PETtrace 880 Installation

MSKCC PETtrace 880 Installation

MSK GE PETtrace 880 Cyclotron

Radiopharmaceutical Production Program Implementation

- Understanding
- Planning
- Executing

First Step- Define Operational Structure

- Regulatory Structure
- Purpose
  - Academic vs. Commercial
- Stage of drug development
- Clinical indication
  - Diagnostic PET vs. Therapeutic
- Facility and equipment capabilities
- Staffing
- Long term goals and commitments
- Risk assessment

Plan Your Process

- What drug quality related data is available?
  - Diagnostic Radiopharmaceuticals
  - Therapeutic Pharmaceutics
- What available technical resources may be relevant?
  - USP <800> Hazardous Drugs – Handling in the Healthcare Setting
  - USP<825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging

Facility Design Key Considerations

- Once HVAC is built out, changes become cost prohibitive
- User Requirements Specifications
  - Cleanroom specs
  - Hot Cell Design
  - Room Layout
  - Custom equipment
  - Safety features

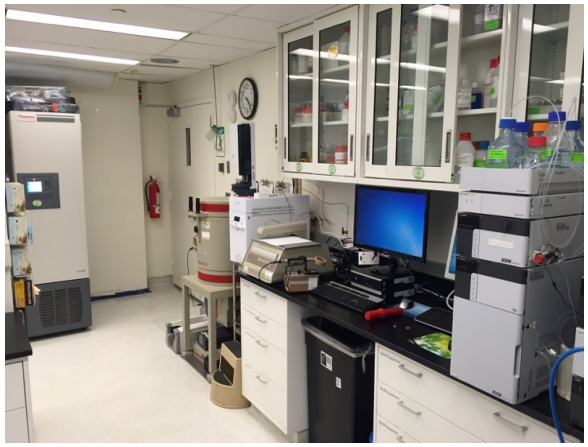
Planning – URS generation

- Secondary Engineering Controls
  - Pressure differentials
  - Air classifications
  - Waste management
  - Ergonomics
  - Size
  - Redundancies
  - Equipment layout

Hot Cell Equipment for Phase I/II

1. Pre-clinical development
2. Chemistry optimization
3. Relatively smaller radioactivity
4. Process flexibility

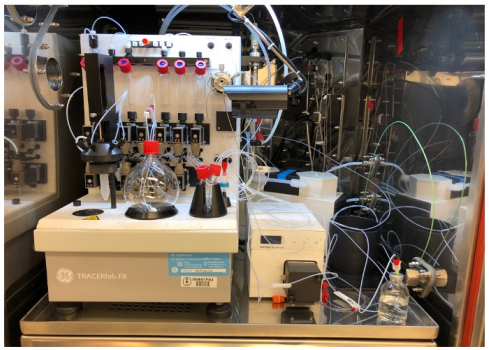
Hot Cell Equipment for Phase III and Beyond

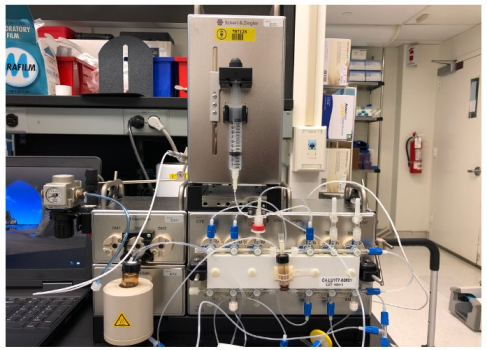


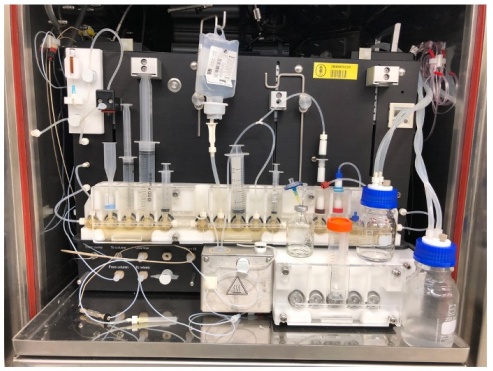
- Completely automated production lines
- Established process with limited flexibility
- Large amounts of radioactive waste
- Increased manufacturing controls

Radiopharmaceutical Synthesizer Considerations

- Planned use
- Synthesis complexity
- User rights
- Reliability
- Customer support
- Disposables availability







Operator Safety Considerations

Analytical Equipment Considerations

- Cost
- Planned frequency of use
- Reliability and customer support
- Operational software - user friendliness and regulatory compliance
- Preventative maintenance availability
- Number of units needed

Good People – Key Factor

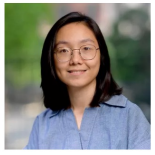
People

Serge K. Lyashchenko
Director

Members

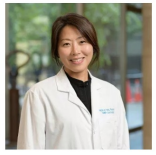
Jason S. Lewis
Scientific Director

Shake Ahmmed
RMIP Core Radiopharmacist



Stephanie Cheung
RMIP Core Radiopharmacist

Sam Frackowiak
Manager, RMIP Core Manufacturing



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Radiopharmacy Tech I

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RMIP Core Systems Specialist

Tricia Taylor
RMIP Core Project Manager

Tuan Tran
Manager, RMIP Core Manufacturing

Angelo Valdivia
Sr. Radiopharmacy Technician

Jiong "Lilly" Wu

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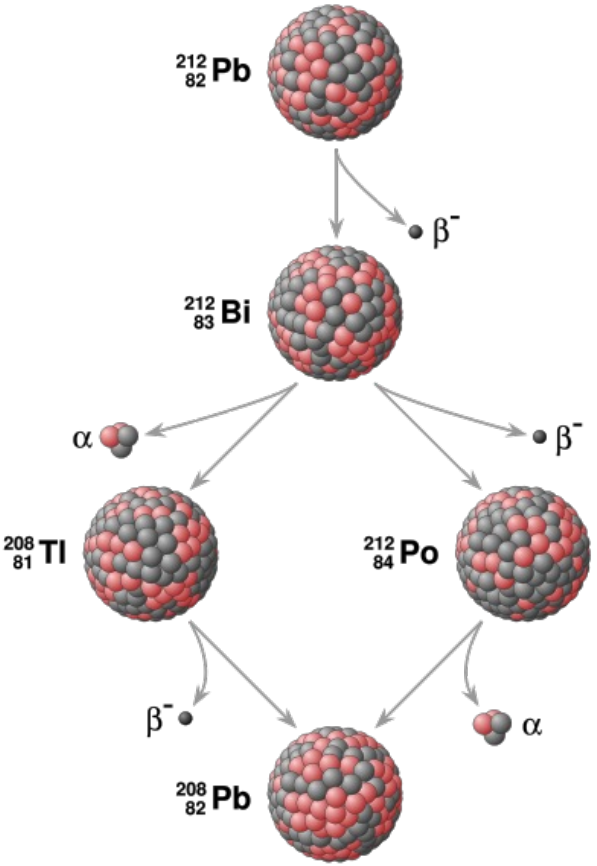
Staffing Considerations

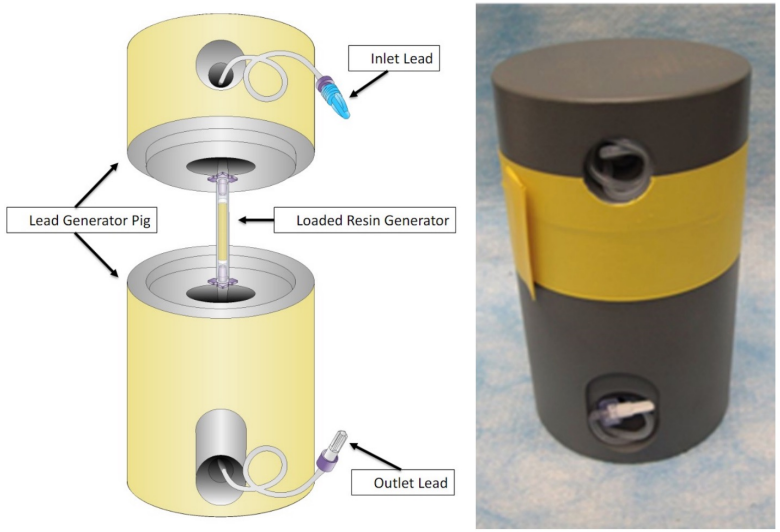
- One of the most critical components of radiopharmaceutical production program
- Designated responsibilities and common goals
- Individualized approach and professional growth is a must
- Degree of staffing must be balanced against current and planned operational needs
- Time vs. money
- GMP compliance is very expensive
  - Increased staffing and documentation are a must when the investigational drug is progressing through development

MSK RMIP Core Alpha Radiopharmaceutical Production Initiatives

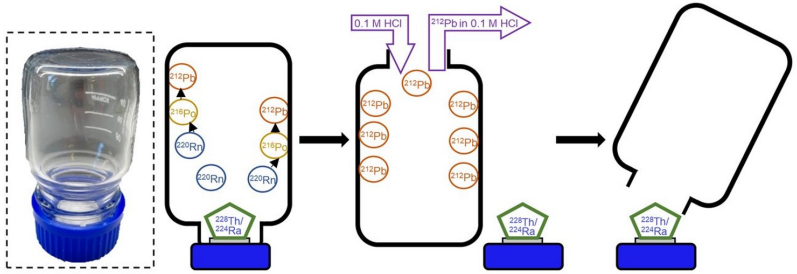


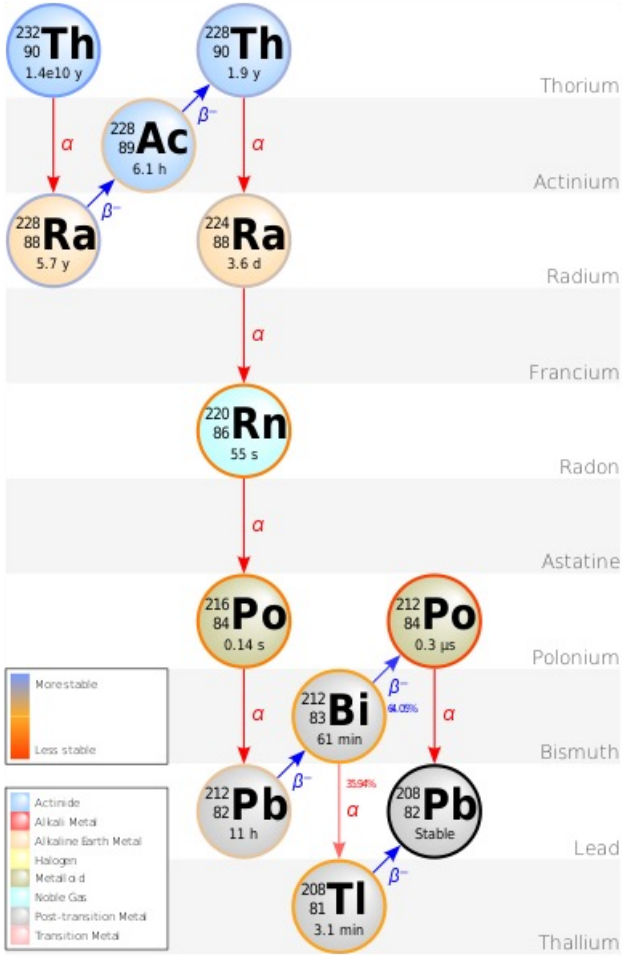
https://commons.wikimedia.org/wiki/File:Thorium_decay_chain_from_lead-212_to_lead-208.svg

^{212}Pb Current Availability: Portable Generators



https://www.isotopes.gov

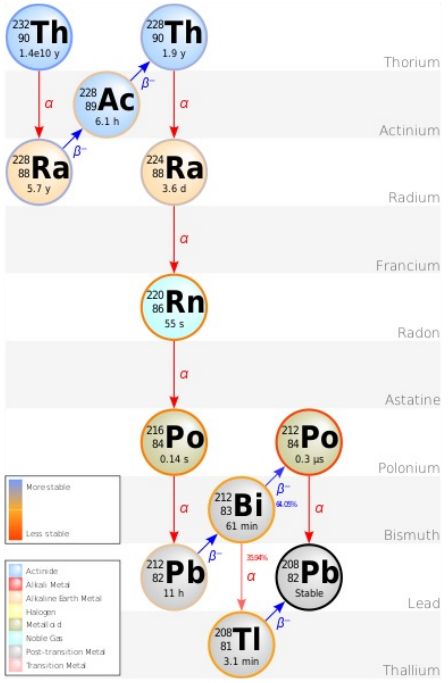




https://commons.wikimedia.org/wiki/File:Decay_Chain_of_Thorium-232.svg

Ruth Gong Li et al. J Nucl Med 2023;64:173-176

MSK RMIP Core's Own ^{212}Pb "Generator"



https://commons.wikimedia.org/wiki/File:Decay_Chain_of_Thorium-232.svg

- Method based on lead-trapping resins
- Current generator capacity: ~45mCi
- Currently available to MSK non-clinical investigators
- FIH studies planned for second half of 2026

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Tuan Tran

David Bauer

^{225}Ac Radiopharmaceutical Production at MSK: Historical Context

ELSEVIER

Applied Radiation and Isotopes
Volume 57, Issue 6, December 2002, Pages 841-847

Design and synthesis of ^{225}Ac radioimmunopharmaceuticals

Michael R. McDevitt [a], Dangshe Ma [a], Jim Simon [b], R.Keith Frank [b], David A. Scheinberg [a 1]

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CURRENT

Meeting Abstract: 2011 ASCO Annual Meeting I
FREE ACCESS | Leukemia, Myelodysplasia, and Transplantation | May 20, 2011

Phase I trial of the targeted alpha-particle nano-generator actinium-225 (^{225}Ac-lintuzumab) (anti-CD33; HuM195) in acute myeloid leukemia (AML).

Authors: J. G. Jurcic, T. L. Rosenblat, M. R. McDevitt, N. Pandit-Taskar, J. A. Carrasquillo, S. M. Chanel, C. Ryan, M. G. Frattini, D. Cicic, S. M. Larson, and D. A. Scheinberg | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 29, Number 15_suppl • https://doi.org/10.1200/jco.2011.29.15_suppl.6516

https://ascopubs.org/doi/10.1200/jco.2011.29.15_suppl.6516

HHS Public Access
Author manuscript
Curr Radiopharm. Author manuscript; available in PMC 2017 August 21.

Published in final edited form as:
Curr Radiopharm. 2011 October ; 4(4): 306–320.

Actinium-225 in targeted alpha-particle therapeutic applications

David A. Scheinberg, M.D., Ph.D.[1] and **Michael R. McDevit, Ph.D.**[2,*]

[1]Department of Molecular Pharmacology and Chemistry, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065

[2]Departments of Medicine and Radiology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065

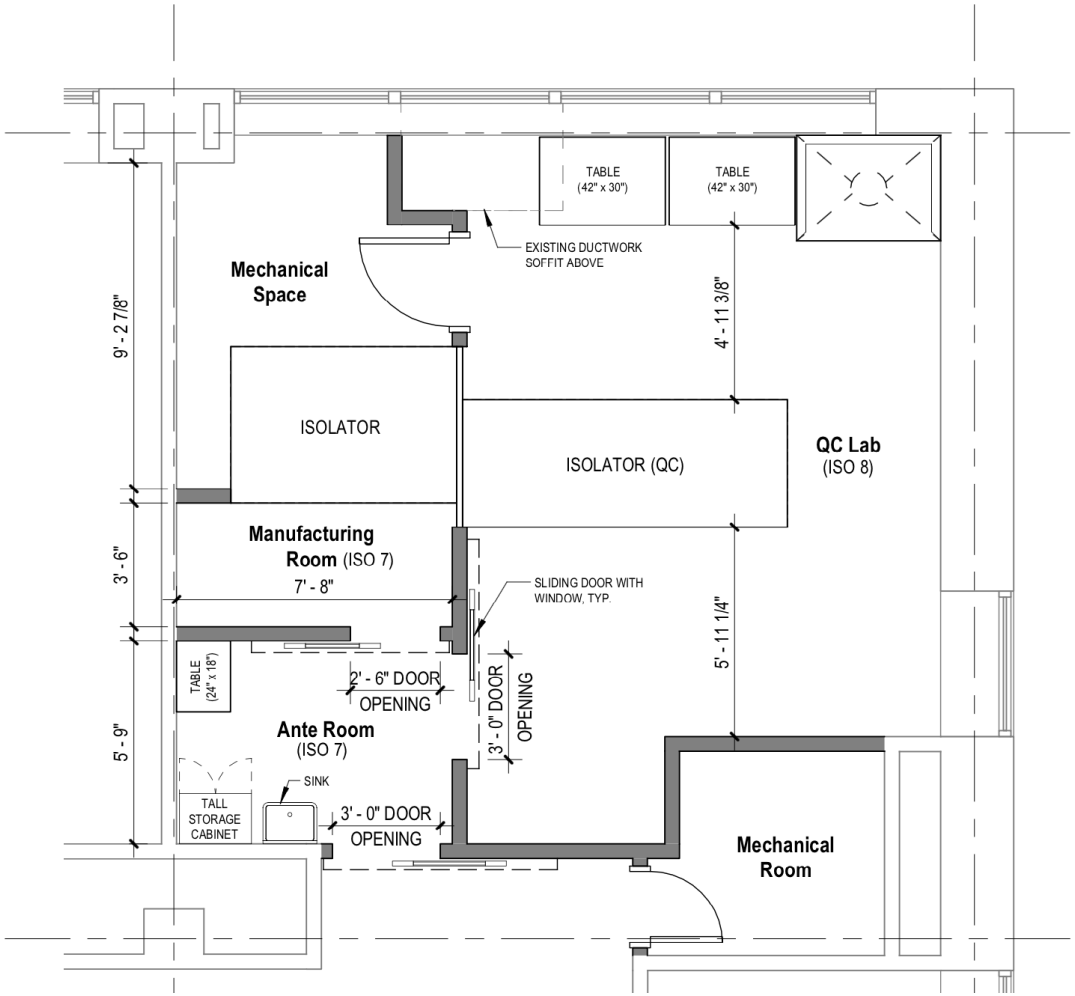
Abstract

Alpha particle-emitting isotopes are being investigated in radioimmunotherapeutic applications because of their unparalleled cytotoxicity when targeted to cancer and their relative lack of toxicity towards untargeted normal tissue. Actinium-225 has been developed into potent targeting drug constructs and is in clinical use against acute myelogenous leukemia. The key properties of the alpha particles generated by ^{225}Ac are the following: i) limited range in tissue of a few cell diameters; ii) high linear energy transfer leading to dense radiation damage along each alpha track; iii) a 10 day half-life; and iv) four net alpha particles emitted per decay. Targeting ^{225}Ac-drug constructs have potential in the treatment of cancer.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5565267/pdf/nihms895197.pdf

https://www.sciencedirect.com/science/article/abs/pii/S0969804302001677?via%3Dihub

Return of ^{225}Ac Clinical Production to MSK



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Facility in Final Stages of Construction

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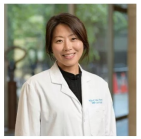
Summary and Conclusion

- Establishing a radiopharmaceutical production program is both challenging very rewarding process
- Funding is critical
  - Cost should not be the only determinant
- Only the end user knows exactly what the end user needs
  - Planning is critical
  - End user is ultimately responsible
- In an academic clinical investigation setting, clinical demand is absolutely essential.

People

Serge K. Lyashchenko
Director

Members



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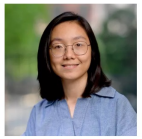

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RMIP Core Systems Specialist

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Cyclotron Engineer

Angelo Valdivia
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Jiong "Lilly" Wu
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Jason S. Lewis
Scientific Director

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