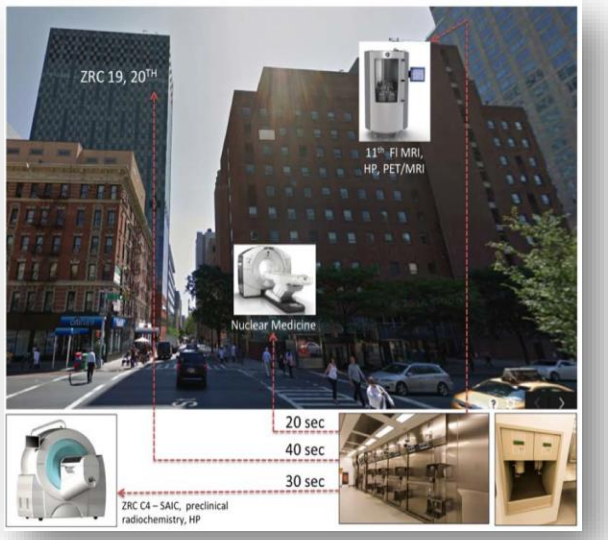
Memorial Sloan Kettering
Cancer Center
RMIP Core

Experience With Novel Radionuclides in Radiopharmacy



November 19th, 2025

Serge K. Lyashchenko, Pharm.D.

Associate Attending, Memorial Hospital, Memorial Sloan Kettering Cancer Center

Associate Professor of Radiochemistry and Radiopharmacy, Weill Cornell Medical College, Cornell University

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

- Radionuclide Availability and Accessibility
- Regulatory Landscape
- Costs
- Infrastructure and Training

Availability and "Accessibility" of Novel Radionuclides 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)

Regulatory Interpretation is Impactful

- $^{225}Ac/^{227}Ac$ CANNOT be used interchangeably with pure ^{225}Ac
  - Impurity percentage grows with time.
  - Molar quantity of ^{227}Ac may exceed ^{225}Ac.
  - Differences in radioactive decay chain may result in differences in dosimetry, safety and efficacy.
  - If ^{232}Th spallation material is used in Phase I/II, it should also be used in Phase III.
- End users need to confirm
  - Radionucidic purity at reference time
  - Chemical purity
  - Identity
- Radioactive waste management will be a problem

		percent radioactivity [%]	
	$t_{1/2}$	$^{227,225}Ac^{\dagger}$	$^{225}Ac^{*}$
Ac-225	9.92 d	93.04	98.82
Ac-227	21.8 y	0.15	$<7.5 \times 10^{-5}$
Ac-226	29.4 h	5.83	<0.01
La-140	1.68 d	2.29	0.01
Ru-106	372 d	<0.04	0.13
Ru-103	39.2 d	0.25	0.72
Sr-85	64.8 d	0.14	0.33
Th-227	18.7 d	<0.04	<0.17
Ra-226	1600 y	<0.01	<0.06
Ra-225	14.9 d	<0.01	<0.05
Ra-224	3.66 d	<0.07	<0.02
Ra-223	11.4 d	<0.04	<0.14
Ce-141	32.5 d	<0.01	<0.03
Ba-140	12.8 d	<0.01	<0.04

Inorg. Chem. 2020, 59, 17, 12156-12165

^{225}Ac Supply Chain Problems Persist

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

^{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]

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

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.

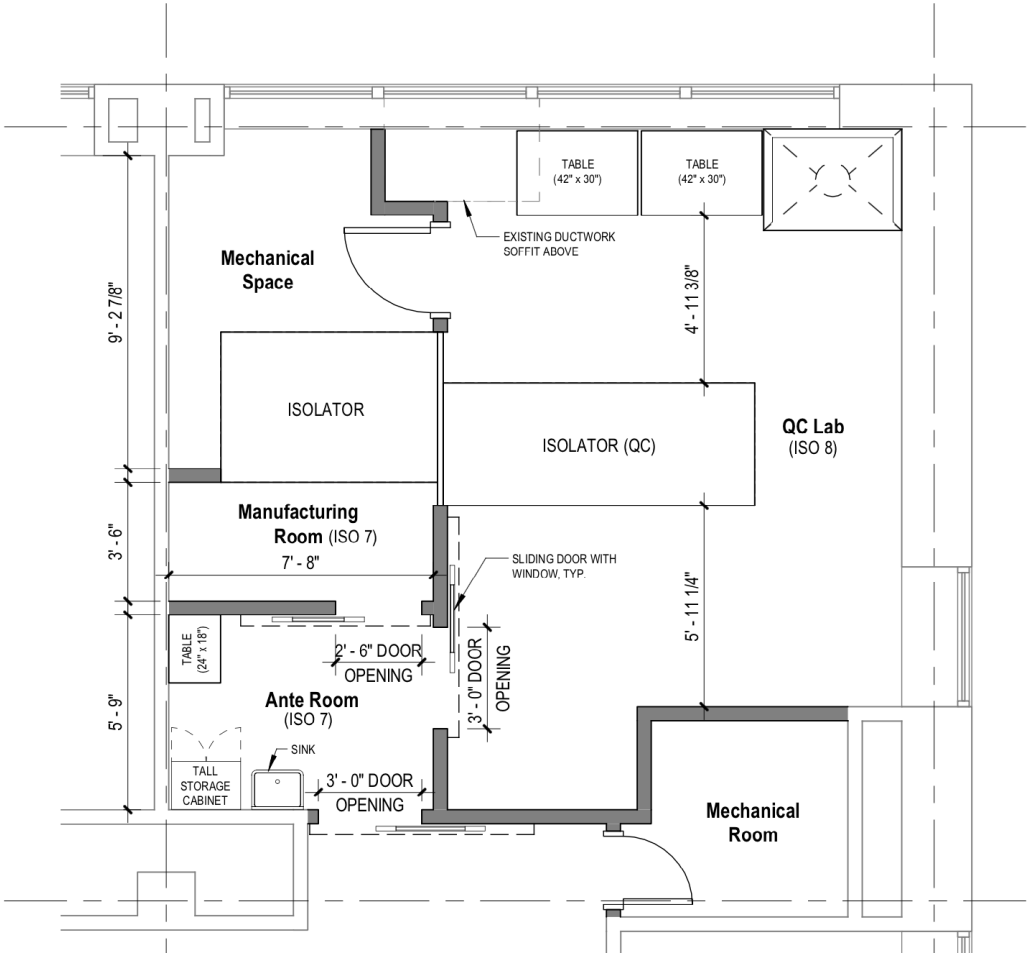
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5565267/pdf/nihms895197.pdf

Michael McDevitt

Memorial Sloan Kettering Cancer Center
RMIP Core

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

Return of ^{225}Ac Clinical Production to MSK



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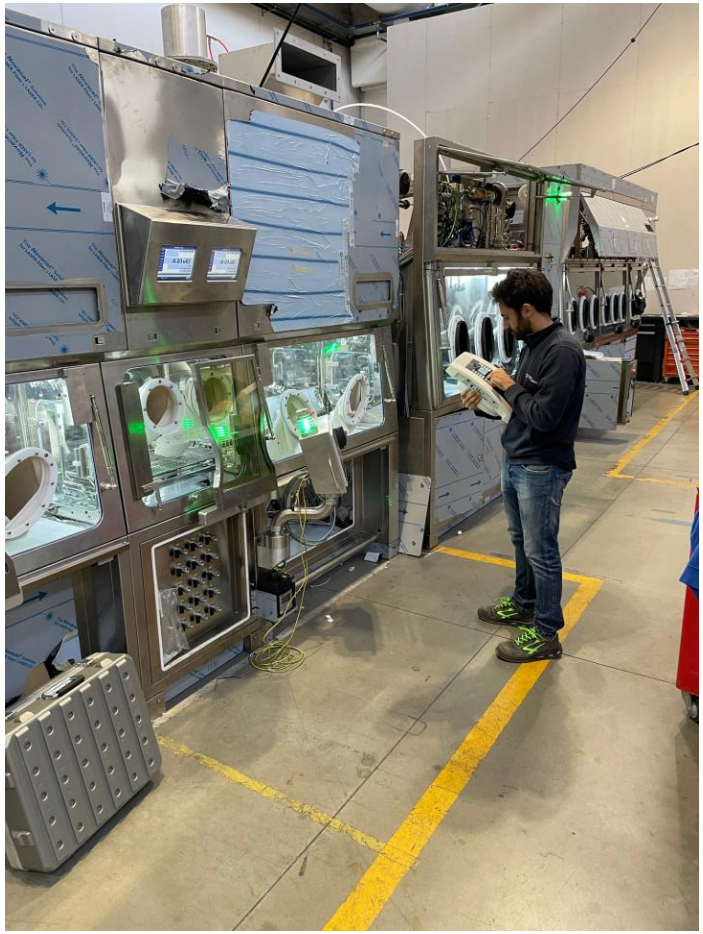
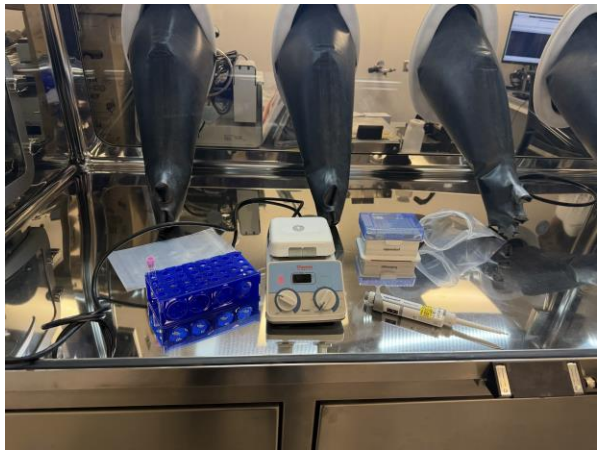
$^{225}Ac/^{211}At$ GMP Production Line



Facility in Final Stages of Construction



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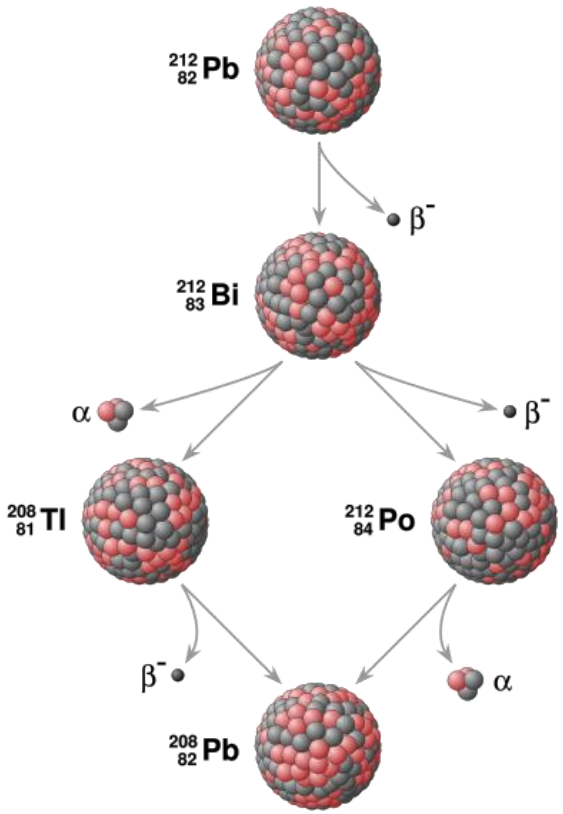
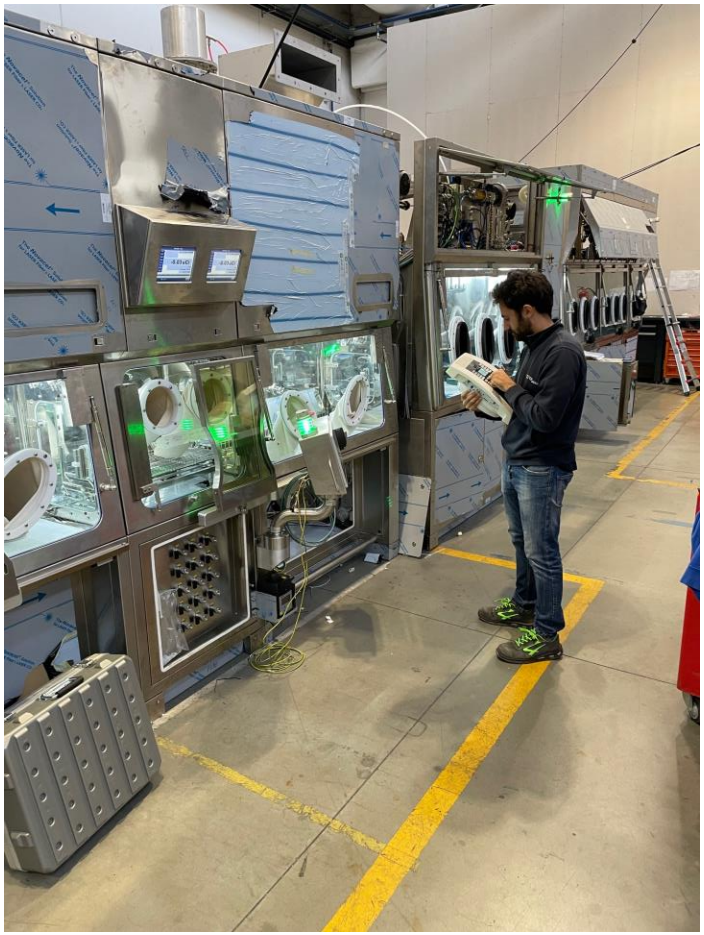
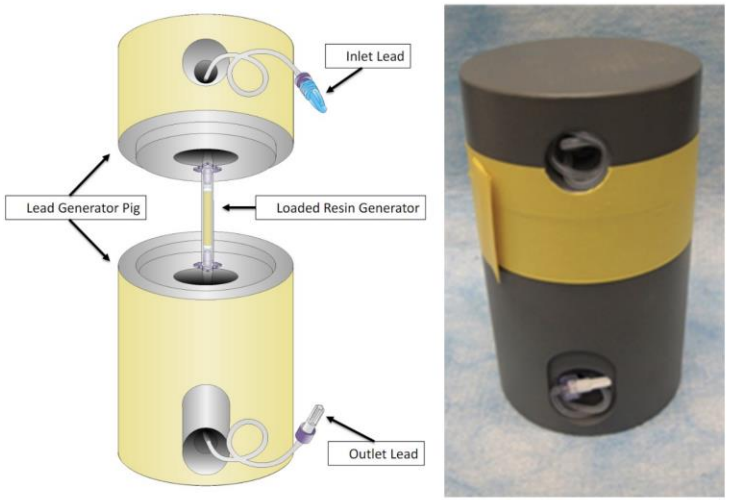
MSK RMIP Core Lead-212 Radiopharmaceutical Production Initiatives



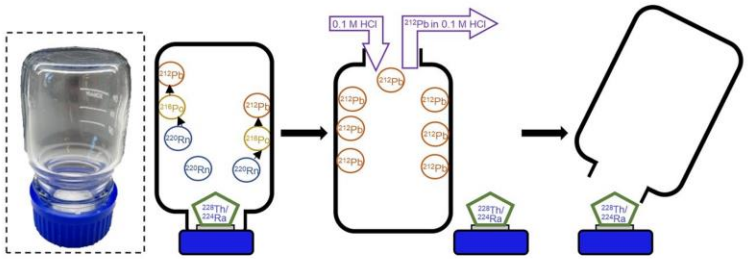
https://commons.wikimedia.org/wiki/File:Thorium_decay_chain_from_lead-212_to_lead-208.svg

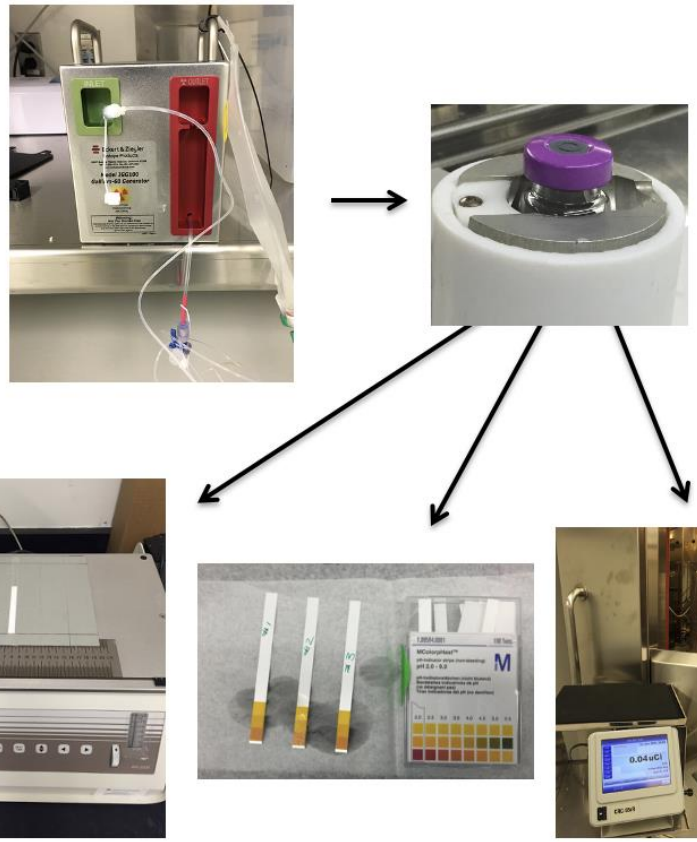


^{212}Pb Current Regulatory Considerations



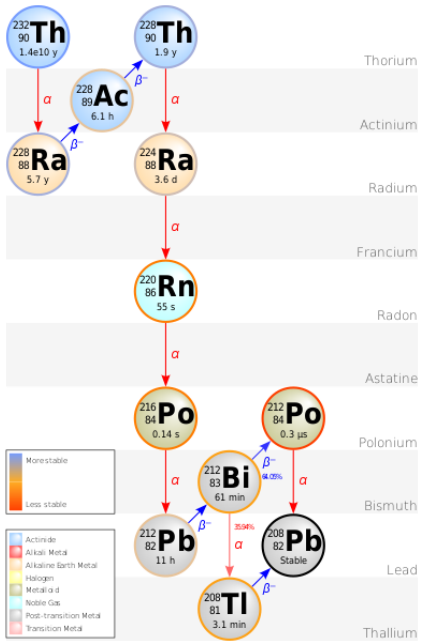
https://www.isotopes.gov





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

"Novel ^{212}Pb Generator" technology developed at MSKCC



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

- Direct Isolation of ^{212}PbCl2 from ^{228}Th
- Current generator capacity tested : 100mCi
  - 80mCi of ^{212}Pb isolated per elution
  - ^{228}Th stock solution in 100mL vials, allowing for multiple generators per hot cell.
- Pending patent submission by MSKCC

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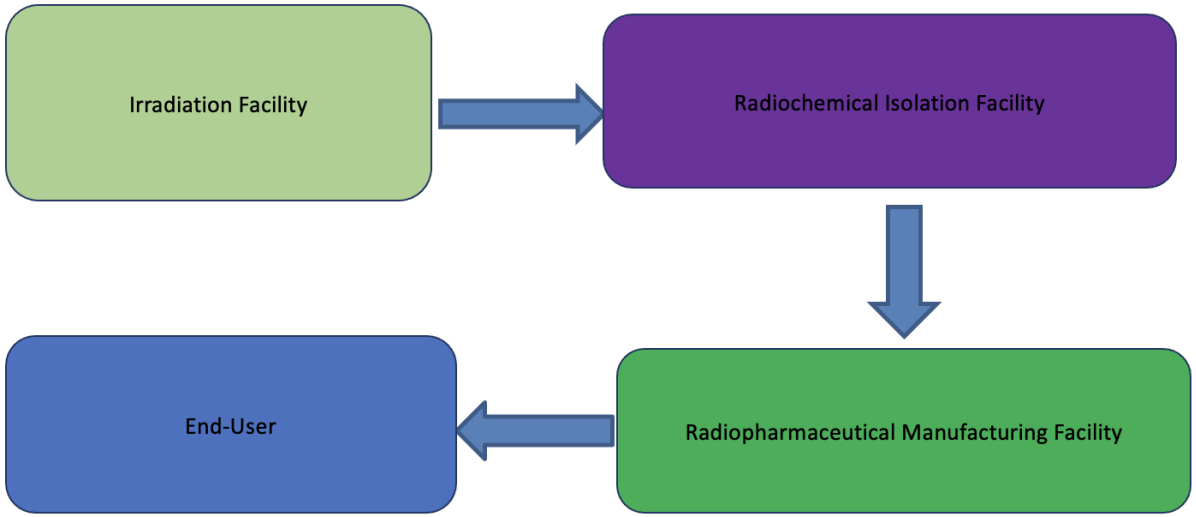
Radioactive Half-Life has Major Impact on Availability, Logistics, and Clinical Care

- ^{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)



IAEA

Mark Bartholomä

Cathy Culter

Memorial Sloan Kettering Cancer Center
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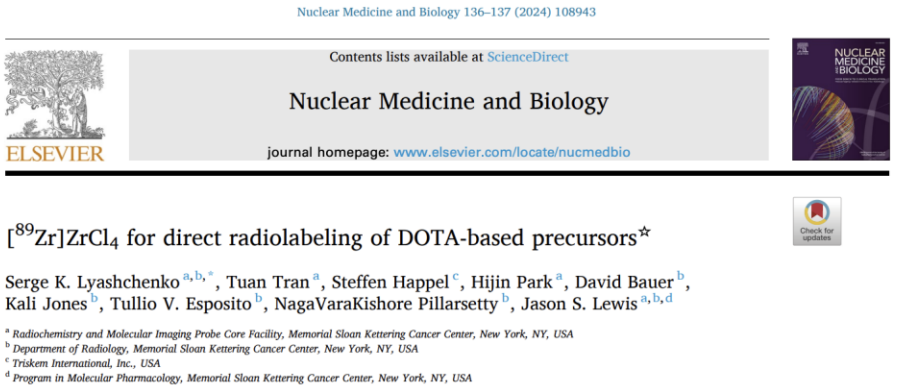
$^{89}ZrCl_4$ as a global PET radiometal of choice?

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

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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]

[a] Radiochemistry and Molecular Imaging Probe Core Facility, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[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

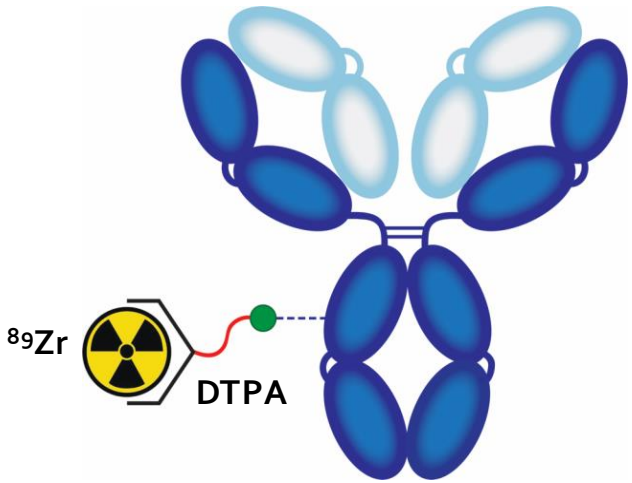
- Industrial quantities of DOTA-PSMA-617 and DOTAGA-PSMA-I&T were quantitatively labeled with ^{89}Zr.
- Certain advantages over ^{68}Ga and ^{64}Cu.

Key Regulatory Considerations:

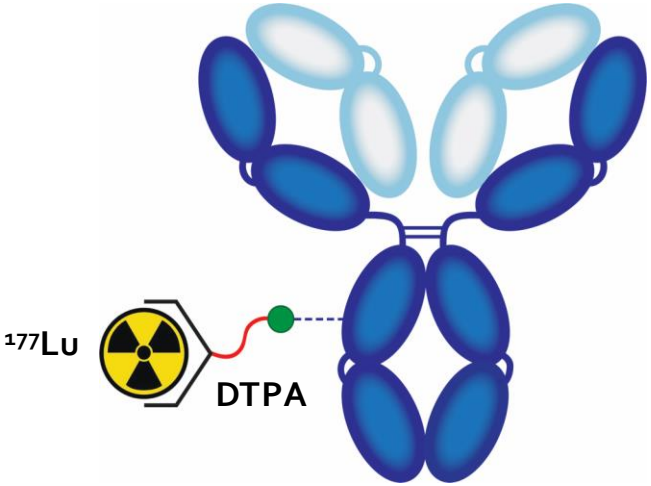
- Radio(chemical) Form and Stability
- Radionuclidic Purity
- Specific Activity
- Trace Metals Content

Clinical Translation of $^{89}Zr/^{177}Lu$-DTPA-mAb's

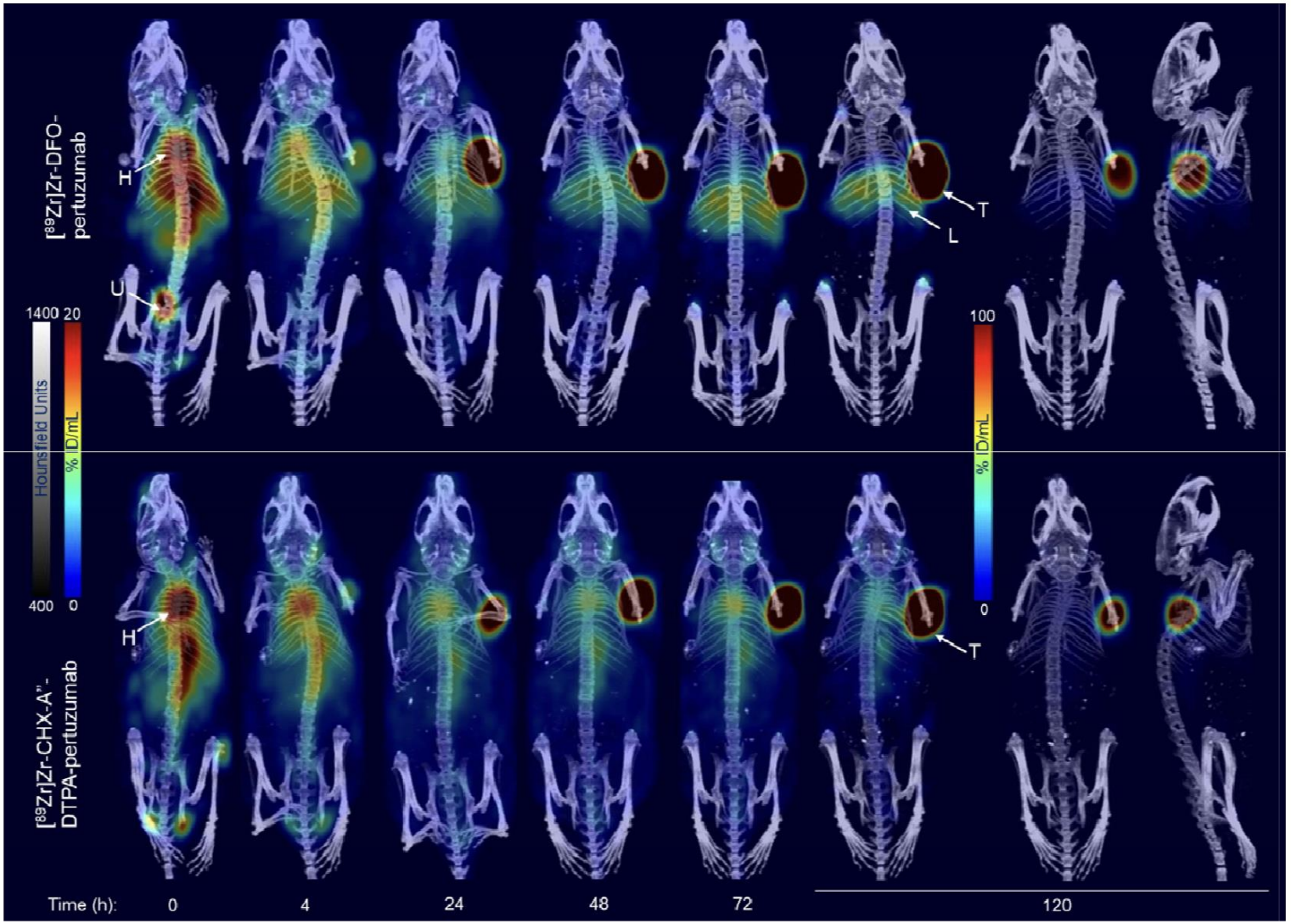
immunoPET imaging



radioimmunotherapy



Clinical Translation of ^{89}Zr-DTPA-Pertuzumab



Lyashchenko et al, JNM, in press.

" In-House Production" Facilitates Early Evaluations in Humans

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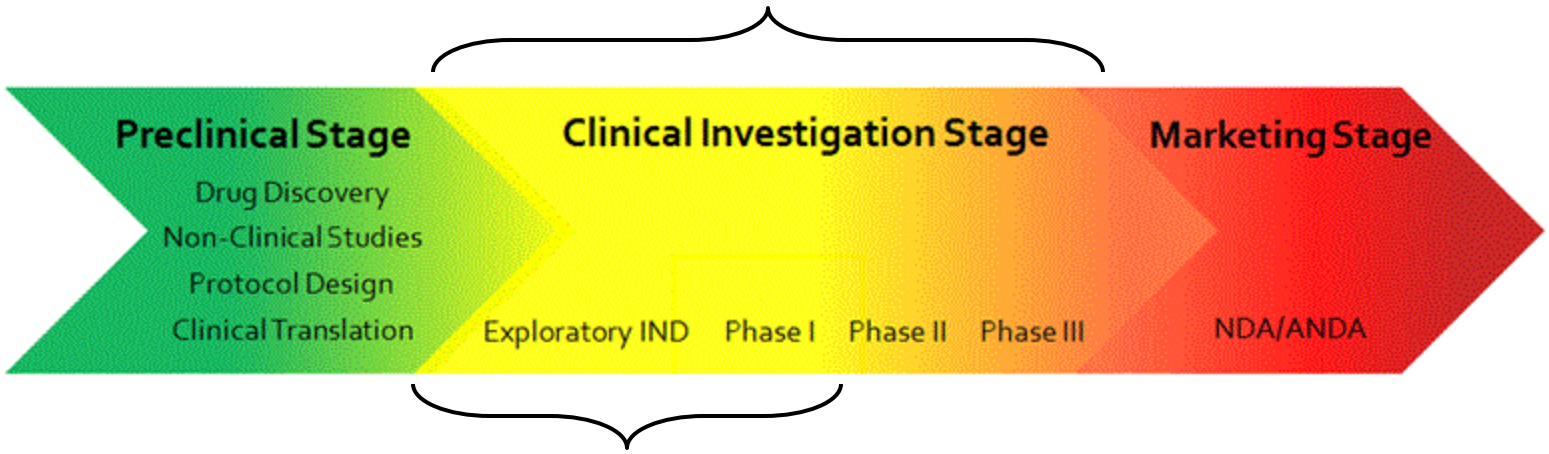
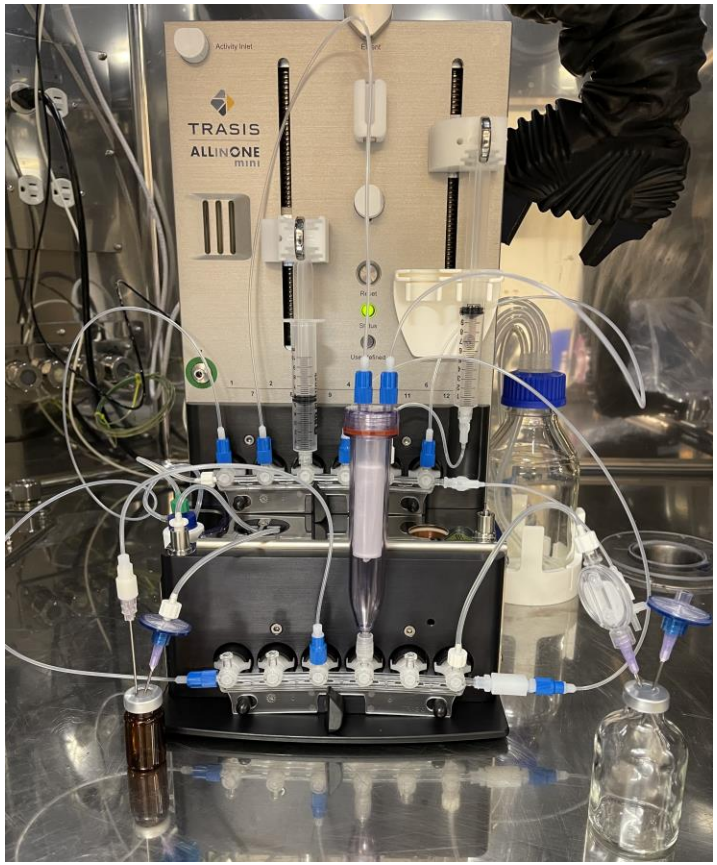
Situation with "In-House Production" in the United States

Emphasis on FDA approval



In-house production is not allowed. Must file an IND application

Operator Safety Considerations And Training



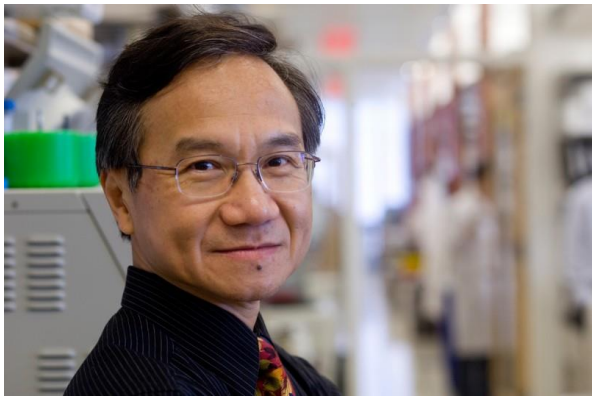
Analytical Equipment Considerations

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

The Importance of Well-Controlled Clinical Trials: Story of ^{131}I-8H9

Phase I Study of Intrathecal Radioimmunotherapy using ^{131}I-8H9 for Central Nervous System/Leptomeningeal Neoplasms

(PI's: Drs. Kim Kramer/Nai-Kong Cheung)



$^{124}I/^{131}I$-8H9 Omburtamab

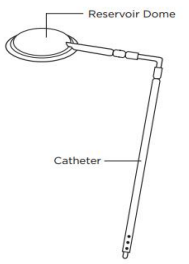


Figure 1: Ommaya reservoir

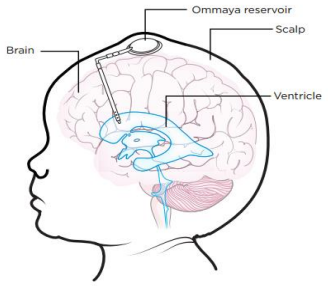
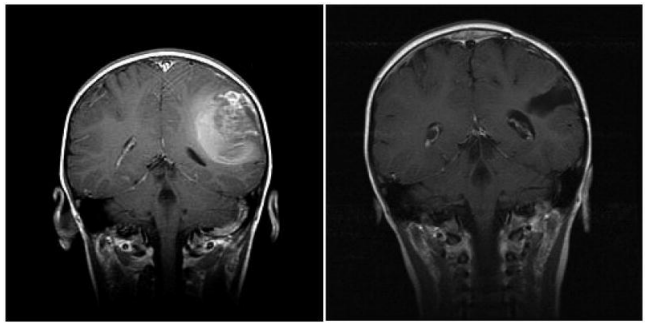
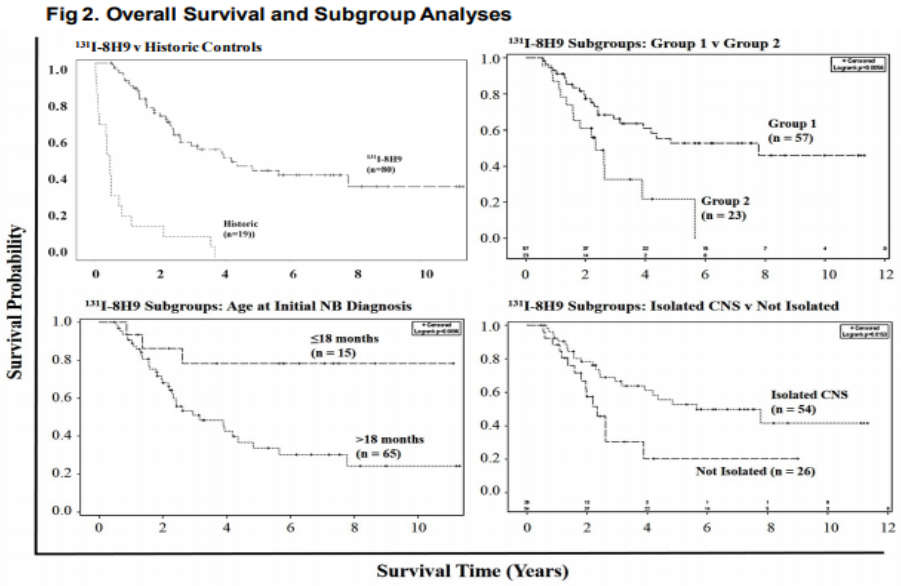


Figure 2: Placement of the Ommaya reservoir



Kramer, et al. J. Neurooncol. 2010 May

- 80 patients treated
- 45% alive at 36 months
- 29% alive at >60 months



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https://www.ymabs.com/application/assets/pdf/asco2017_poster_msk_8h9.pdf

Regulatory Outcome and Lessons Learned…….

- Having a control arm in ultrarare cancer clinical trials presents a unique set of challenges
- Molecular imaging could play a vital role in radiotherapeutic clinical trials
- Our community could benefit from additional education on proper clinical trial design

Pre-^{131}I-Omburtamab Treatment for CNS Relapse

FDA

Time	Suggested Pre-treatment for Study 03-133
Week -12	**Resection** when possible
Week -11	**Irinotecan**
Week -10	**Craniospinal irradiation**
Week -5	**Irinotecan and Temozolomide**
	Carboplatin if systemic disease present
	Stem cell rescue if necessary
Study start	**^{131}I-omburtamab** administration

Source: www.fda.gov

Y-mAbs Therapeutics, Inc.

Y-mAbs Announces Complete Response Letter for Omburtamab Biologics License Application

December 1, 2022

NEW YORK, Dec. 01, 2022 (GLOBE NEWSWIRE) -- Y-mAbs Therapeutics, Inc. (the "Company" or "Y-mAbs") (Nasdaq: YMAB) a commercial-stage biopharmaceutical company focused on the development and commercialization of novel, antibody-based therapeutic products for the treatment of cancer, today announced that the U.S. Food and Drug Administration ("FDA") has issued a complete response letter ("CRL") for the Biologics License Application ("BLA") for the investigational medicine ^{131}I-omburtamab ("omburtamab") for the treatment of CNS/leptomeningeal metastasis from neuroblastoma.

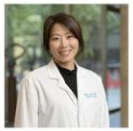
Source: www.ymabs.com

Thank you!

People

Serge K. Lyashchenko
Director

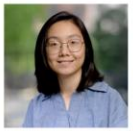
Members



Hijin A. Park
Lead, Nuclear Pharmacist

Tuan Tran
RMIP Core Business Manager

Shake Ahmmed
RMIP Core Radiopharmacist



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Sam Frackowiak
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Kyle Stewart
Cyclotron Engineer

Angelo Valdivia
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Jiong "Lilly" Wu
Research Technician, Sr.

Jason S. Lewis
Scientific Director