MAYO CLINIC

Alpha-PET DoubLET

A Flexible Theragnostic Molecular Platform Technology for Alpha and/or Beta Therapy with PET-based Dosimetry

RPT Interest Group 6-7-23

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Chair, Nuclear Medicine
Associate Director, Mayo Clinic Comprehensive Cancer Center

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Director, Molecular Imaging Research Program

Disclosures

Research Funding

Novartis, Pfizer, MedTrace, Clarity, Clovis, Perspective, GE

Consulting

Pfizer, Novartis, Curium, Blue Earth, AstraZeneca, Siemens, Z-Alpha, Lantheus, GE

Intellectual Property

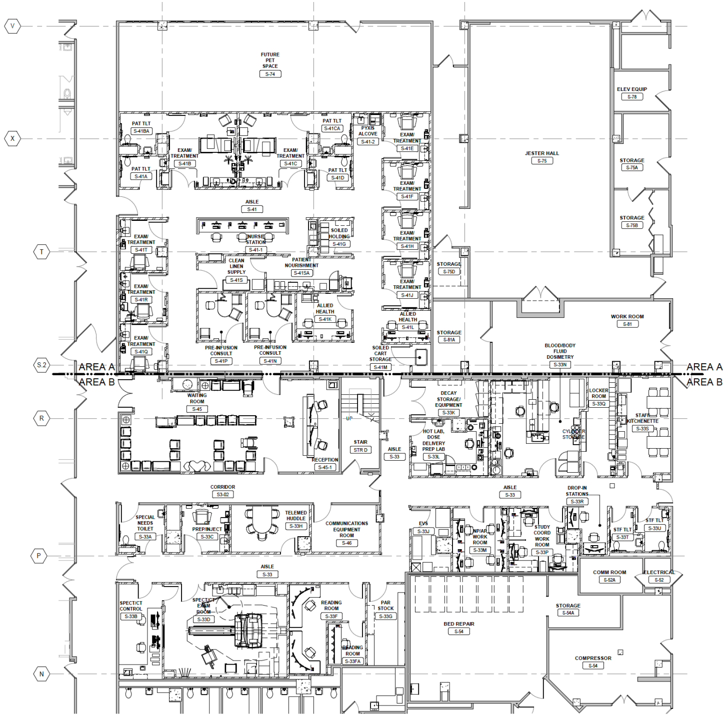
Mayo and I hold patents pending on radionuclide theranostic technologies

Mayo and I have know-how agreements for technology development with Perspective, MedTrace and Nucleus

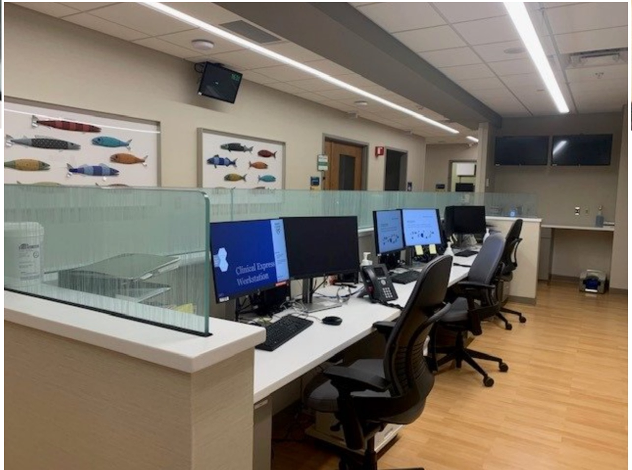
Positions

Chief Scientific Officer, Nuclear RadioPharma

Mayo Clinic Opens New and Largest Radiopharmaceutical Theranostic Center



Nuclear Medicine Therapy Center



Nuclear Medicine Therapy Center

Mayo Clinic's New Dedicated Theranostic Center

- 9 new outpatient dedicated theranostic rooms
  - 2 with beds and dedicated bathrooms
  - 7 with chairs and shared patient bathrooms
- *10 Therapy/Uptake rooms* (Research Center)*
- *4 Inpatient therapy rooms* (Hematology Floor)*
- 2 Consultation rooms
- Teleconference room
- Decay storage space
- Hot lab for drug preparation
- Blood and body fluid lab
- Central nursing station (x6 seats)
- Study coordinator workspace (x6)
- Dedicated waiting room
- Nurse practitioner workspace (x4)
- Allied heath staff workspace
- GE StarGuide SPECT/CT
- *Veriton SPECT/CT* (Clinical Nuc Med floor)*
- Reading room with 3 PACS
- Locker room
- Break room
- Visiting provider drop-in room/computers
- Pneumatic tube station for radiopharmaceutical delivery

* Different floor, but in the same building

Kern Center/Leadership Program

- Tuba Kendi, MD
- Geoff Johnson, MD, PhD
- Annie Packard, MD
- Jason Young, MD

- Brooke Gentzler, MBA, CNMT





Physician Team

- Tuba Kendi, MD (Chair Therapy Operations)
- Corrie Bach, MD
- Mike Bold, MD
- Jolanta Durski, MD
- Eric Ehman, MD
- Ajit Goenka, MD
- Derek Johnson, MD
- Geoff Johnson, MD, PhD
- Brendan Lunn, MD
- Patrick Navin, MB, BCh, BAO
- Annie Packard, MD
- Hiroaki Takahashi, MD, PhD
- Matt Thorpe, MD, PhD
- Greg Wiseman, MD

Multi-Disciplinary Leaders

- A Oliver Sartor, MD
  - Med Onc
- Eugene Kwon, MD
  - Urology
- Kenny Merrell, MD
  - Rad Onc
- Thor Halfdanarson, MD
  - Med Onc
- Tim Hobday, MD
  - Med Onc
- Brad Stish, MD
  - Rad Onc






Mayo as a key partner for phase 0,I,II,III and beyond

- Leading academic center
- Radiopharmaceutical Comprehensive Therapy Center of Excellence
  - This is the highest level of certification
  - New designation established by the Society of Nuclear Medicine and Molecular Imaging (SNMMI)
- Fully integrated multidisciplinary clinical and research teams
- Large practice
  - >20 theranostic cancer trials active at Mayo
  - 23 therapy rooms
  - >4,000 Lu doses given
- Top notch infrastructure
  - Cutting edge scanners, new theranostic center, Nuclear Medicine practice, PET radiochemistry, compounding nuclear pharmacy and research facilities embedded in cancer hospital

Alpha and Beta Therapies are Fundamentally Different

- **Electron**
- Small
  - Low LET
- 2-12 mm: 1,000’s cell diameters
  - Crossfire killing
- Single DNA breaks
  - Secondary cancer
  - Hypoxic defenses

- **Helium atom**
- Big
  - High LET
- 2-3 cell diameters
  - Precise targeting
- Double DNA breaks
  - Kill tiny tumors
  - Overcome resistance
  - PSMA negative cells?
  - Bystander Killing

Problem Statement

- How can we differentiate the effects of Beta and Alpha emission in the body?

- Answer
  - Mayo’s Alpha-PET DoubLET technology
  - Key academic partner(s)
  - Imaging
  - Novel Readouts

BACKGROUND

- Alpha radionuclide therapy (α-therapy) is emerging as a promising targeted radionuclide therapy to treat and potentially cure cancer

- Advantages
  - More powerful
  - More precise
  - Road to cure

- Disadvantages
  - α-therapy can't create images well
  - Lack perfect theranostic pairs with PET
    - Select lead compounds

Patient Selection
PSMA PET

Problem Statement

- Desired reality
  - High-quality PET imaging ideal for precise biodistribution of alpha-emitting radionuclide therapies
  - Perfect theranostic pairs are needed
- Current reality
  - Alpha-emitting radiopharmaceuticals cannot be imaged well
    - poor quality imaging
    - inordinately long time to image
    - cannot be imaged over a required dosimetry timeframe
    - cannot see smaller tumors
  - Different radiopharmaceuticals are used for imaging and therapy that have significantly different biodistribution, creating inaccurate data

Alpha-PET

- We propose to resolve these issues and more by using a new Mayo Alpha-PET platform technology

- The platform will allow for…
    - Flexibility in laboratory experiments
    - Expediting selection of lead compounds
    - Expediting clinical trials
    - De-risking drug development
    - Accurate patient selection
    - Monitoring of therapeutic benefit during therapy cycles
    - Accurate calculation of radiation exposure to organs and tumors
    - Enhancing clinical workflows

Alpha-PET

- To our knowledge, Alpha-PET is the first and only technology that allows a researcher to choose
  - Alpha
  - Beta
  - Alpha+Beta
  - Titration of doses
  - Perfectly matched biodistribution

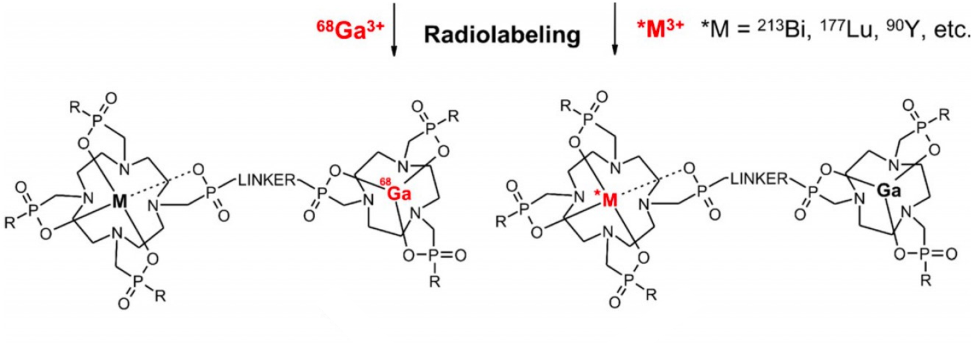
Alpha-PET

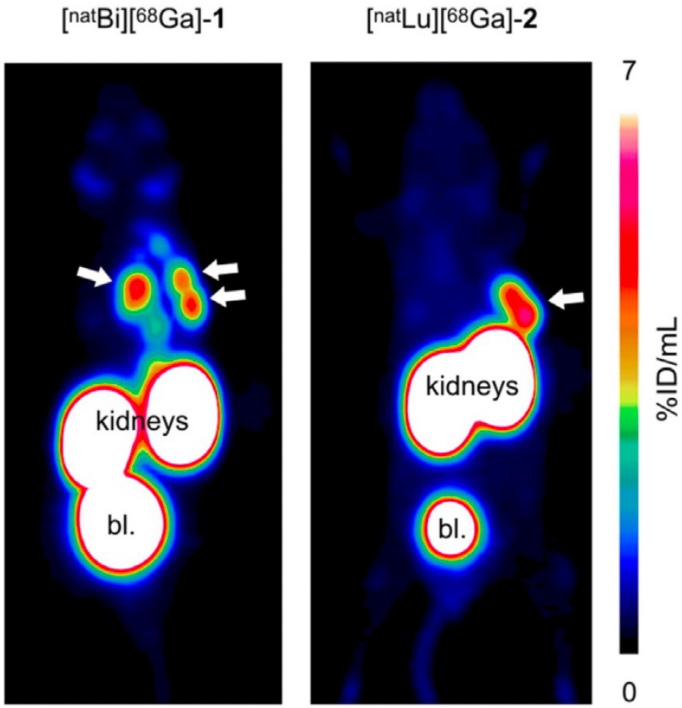
- To our knowledge, Alpha-PET is the first and only technology that allows a researcher to choose
  - Alpha
  - Beta
  - Alpha+Beta
  - Titration of doses
  - Perfectly matched biodistribution

  - Can image with PET
  - Calculate Dosimetry

Double/Multi Chelator Model

- Dual Chelator Concept
  - Johannes Notni lab
  - ^{68}Ga and ^{213}Bi
  - PET imaging of distribution

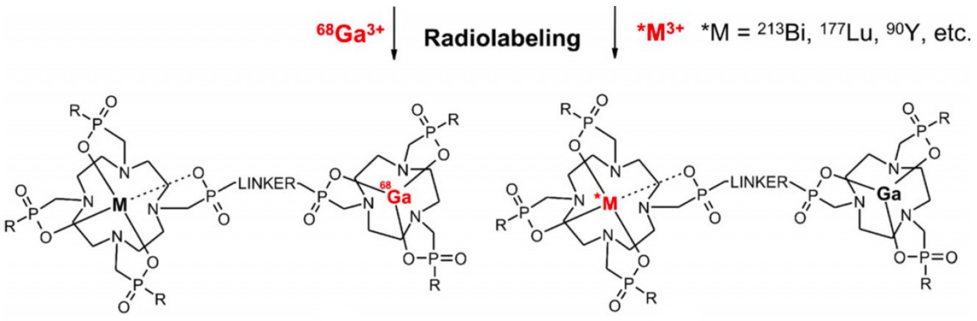


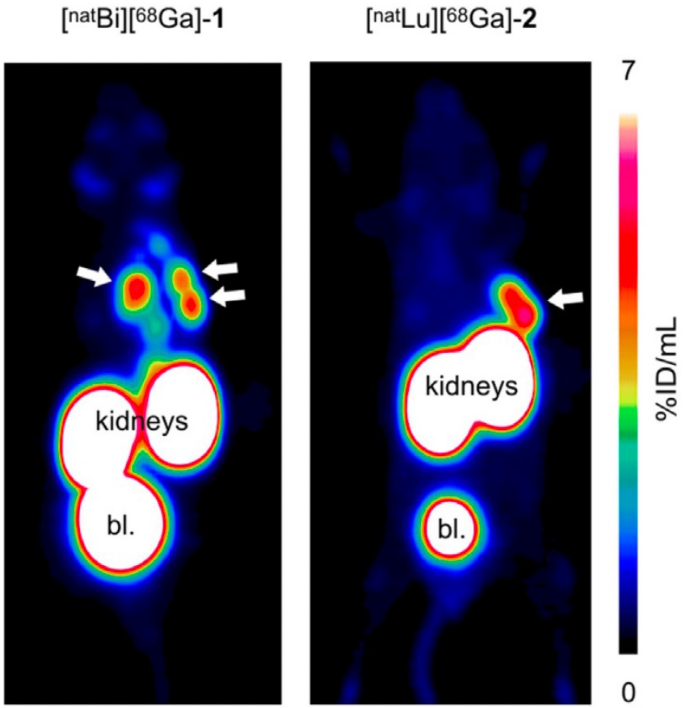


Wurzer et al 2016

Double/Multi Chelator Model

- Issues
  - 1-hour T1/2
    - Supply Chain
  - Efficacy?
    - Clearance
  - Beta therapy option
    - Non-identical biodistribution

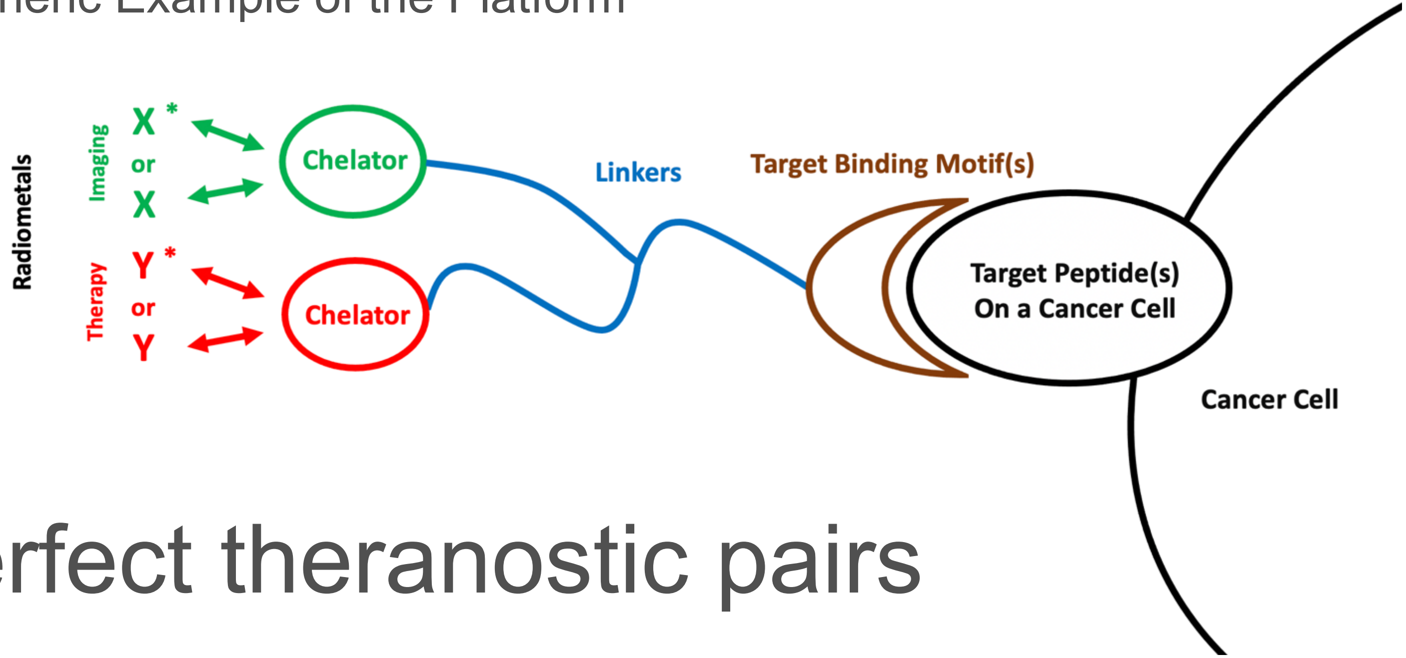




Wurzer et al 2016

Alpha-PET TECHNOLOGY

Generic Example of the Platform



Perfect theranostic pairs

Patents-Pending

Alpha-PET TECHNOLOGY Example

63Cu – Stable
64Cu – Positron & Beta

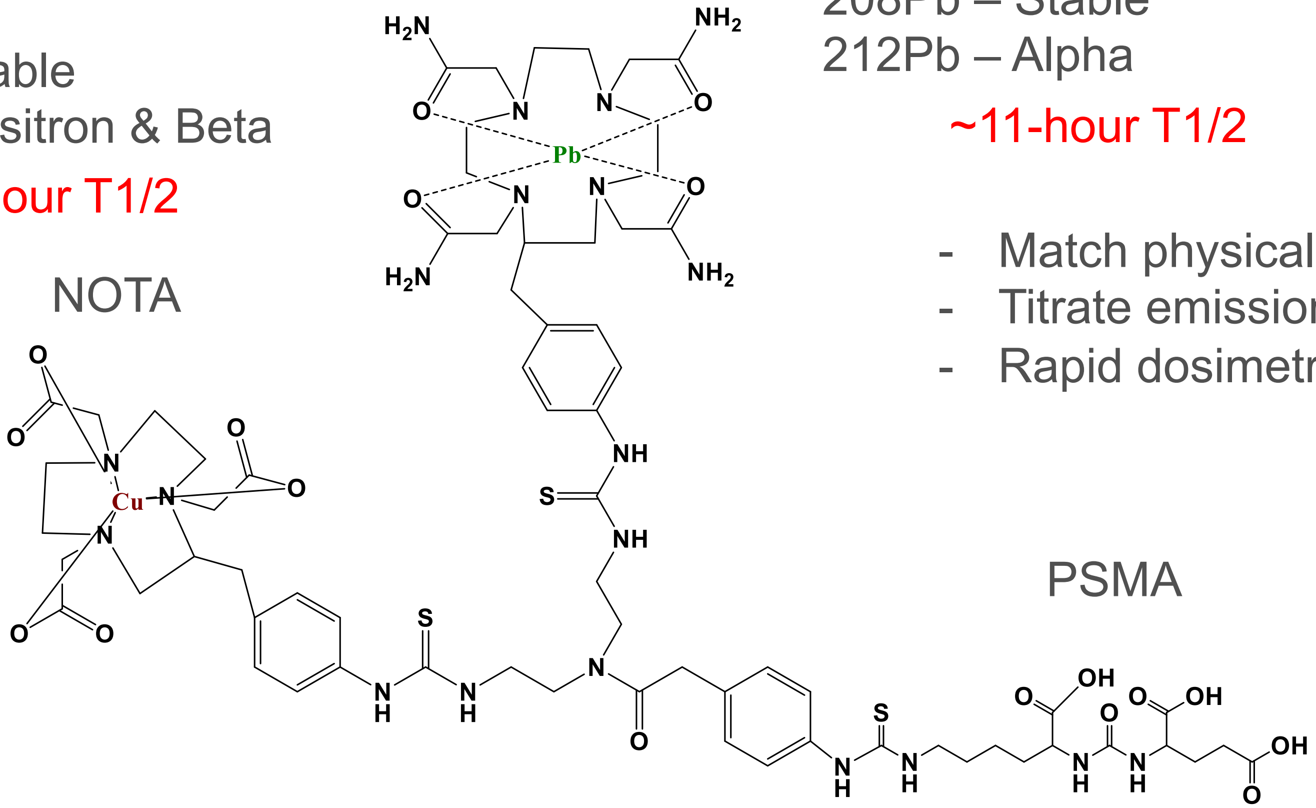
~12-hour T1/2

208Pb – Stable
212Pb – Alpha

~11-hour T1/2

TCMC

NOTA

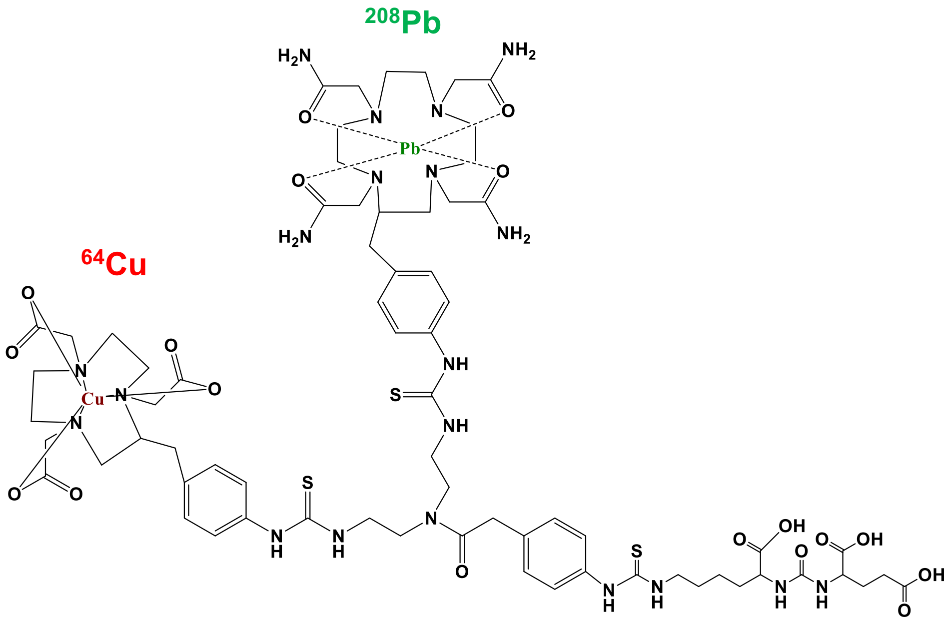


PSMA

- Match physical half-life
- Titrate emissions
- Rapid dosimetry

Patents-Pending

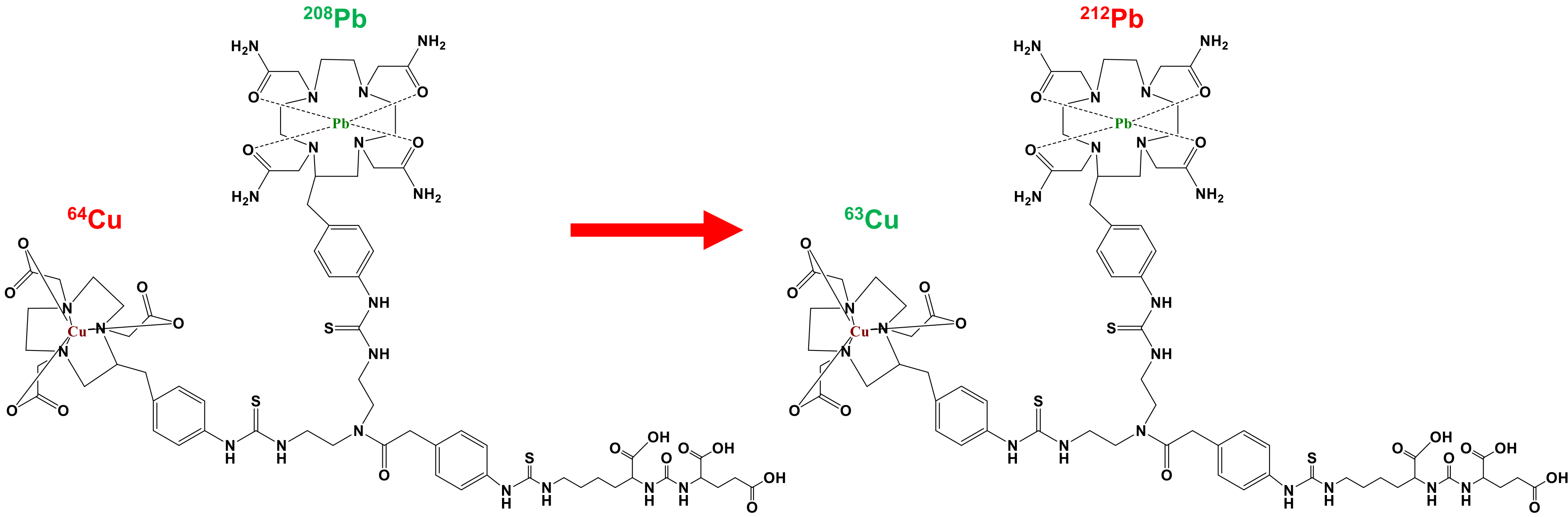
Alpha-PET TECHNOLOGY Example



3-5 mCi for PET Imaging

Patents-Pending

Alpha-PET TECHNOLOGY Example



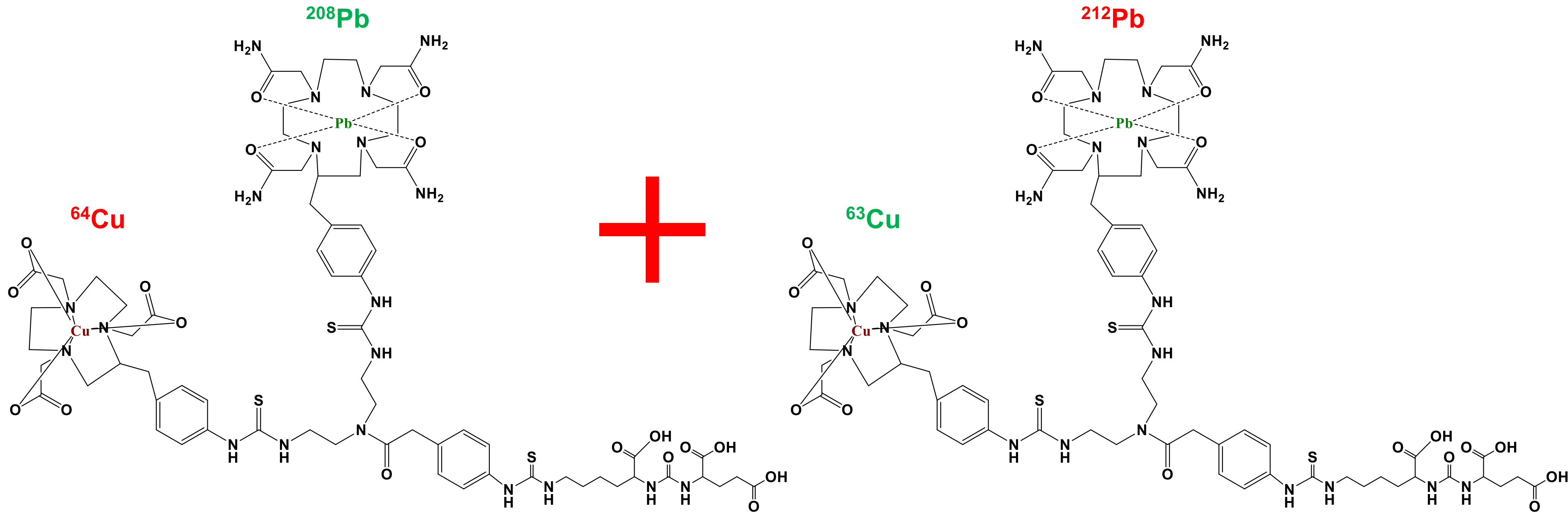
3-5 mCi for PET Imaging

Alpha Therapy

Patents-Pending

Alpha-PET TECHNOLOGY Example

Allows for Alpha and Beta therapy: **Alpha-PET DoubLET**



100-400 mCi for PET Dosimetry, Staging, Therapy-Monitoring

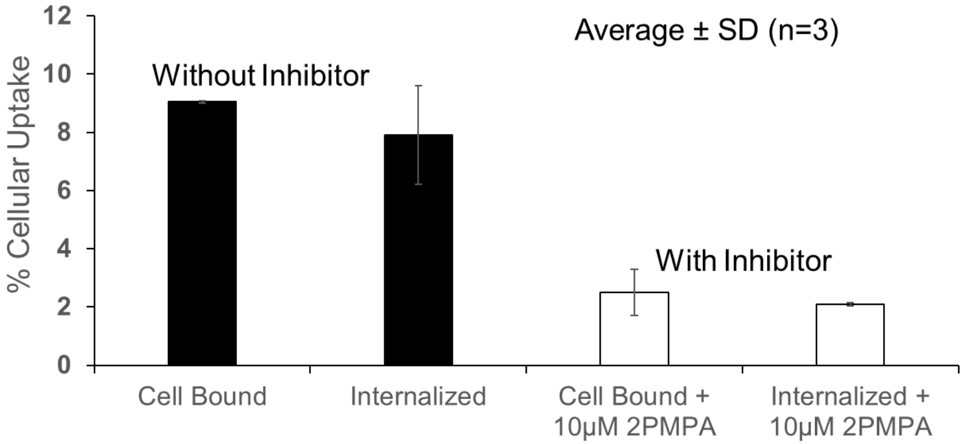
Alpha Therapy

Patents-Pending

Alpha-PET TECHNOLOGY

- Binding of 64Cu Alpha-PET PSMA to cancer cells is PSMA specific

- PSMA expressing cell lines (LNCaP cells).
- Both binds to and is internalized by LNCaP cells, as confirmed in competition experiments.

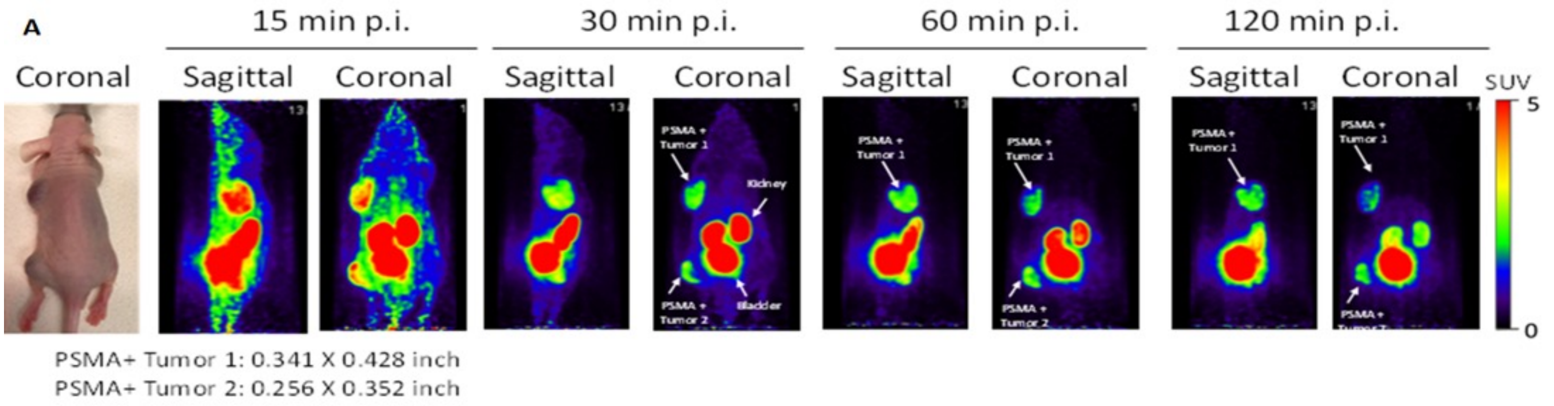


Patents-Pending

Alpha-PET TECHNOLOGY

- We can image tumors with 64Cu Alpha-PET PSMA

- In-vivo micro-PET imaging confirms cancer cell binding in a LNCaP mouse tumor model, as well as effective renal clearance.

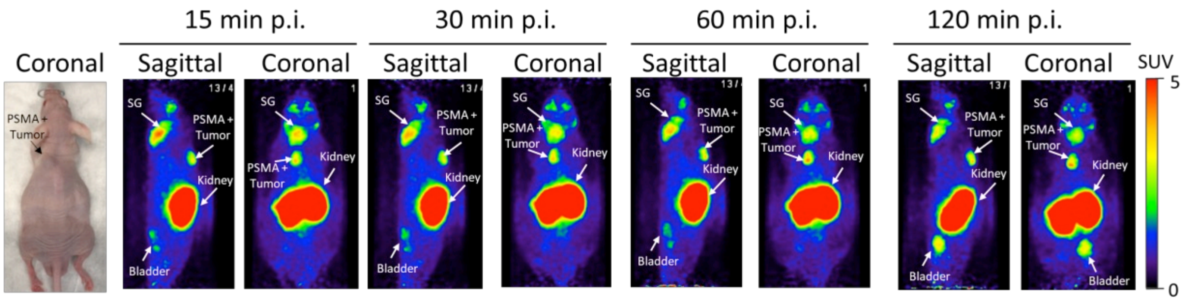


Patents-Pending

Alpha-PET TECHNOLOGY

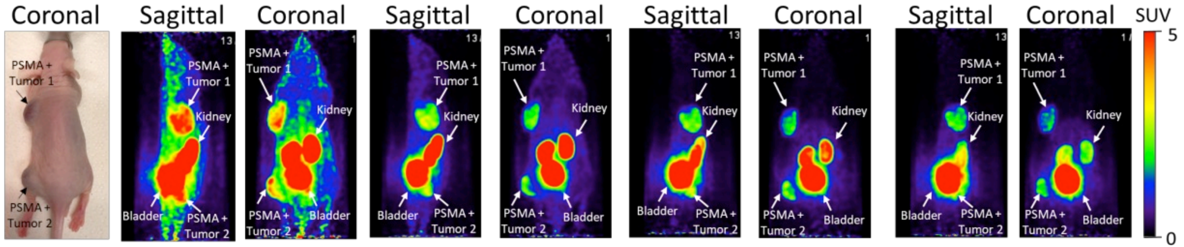
Comparison of uptake of [^{68}Ga]Ga-PSMA and [^{64}Cu]Cu-NSN24901 in LNCaP tumor athymic nude mice

[^{68}Ga]Ga-PSMA



PSMA+ Tumor: 0.26 X 0.29 inch; SG = Salivary Gland

[^{64}Cu]Cu-NSN24901

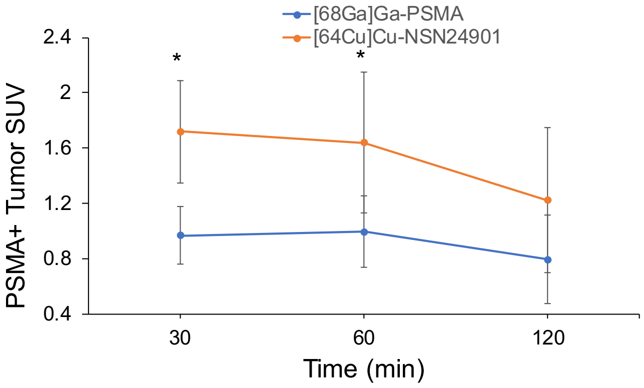


PSMA+ Tumor 1: 0.34 X 0.43 inch; PSMA+ Tumor 2: 0.26 X 0.35 inch

Patents-Pending

Alpha-PET TECHNOLOGY

Comparison of uptake of $[^{68}Ga]$Ga-PSMA and $[^{64}Cu]$Cu-NSN24901 in tumor, kidney and salivary gland of LNCaP tumor athymic nude mice



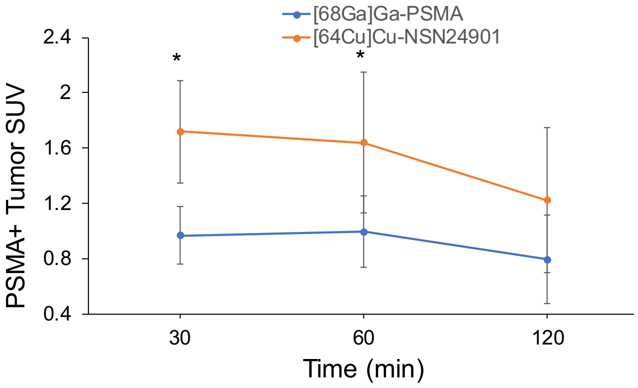
*$p < 0.05$ $[^{64}Cu]$Cu-NSN24901 Vs $[^{68}Ga]$Ga-PSMA

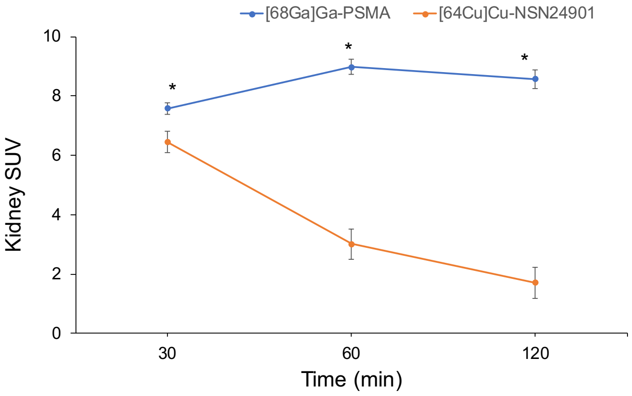
Q?: Does the double Chelator Cause an issue?
A: Not in this case example

Patents-Pending

Alpha-PET TECHNOLOGY

Comparison of uptake of [^{68}Ga]Ga-PSMA and [^{64}Cu]Cu-NSN24901 in tumor, kidney and salivary gland of LNCaP tumor athymic nude mice



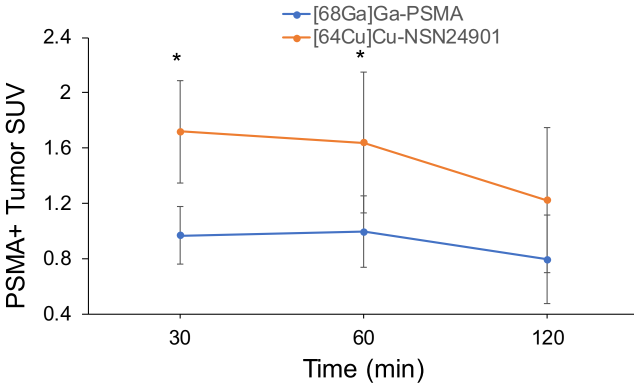


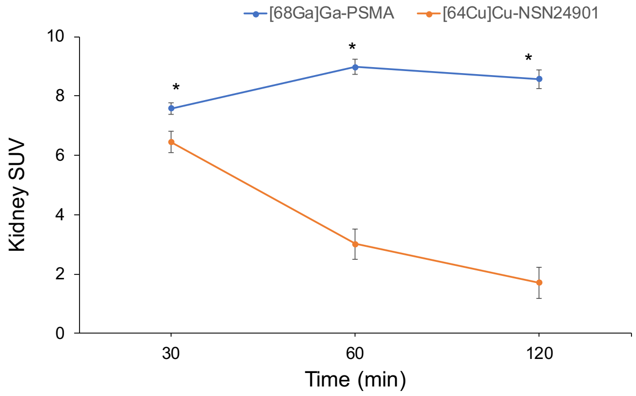
*$p < 0.05$ [^{64}Cu]Cu-NSN24901
Vs [^{68}Ga]Ga-PSMA

Patents-Pending

Alpha-PET TECHNOLOGY

Comparison of uptake of [^{68}Ga]Ga-PSMA and [^{64}Cu]Cu-NSN24901 in tumor, kidney and salivary gland of LNCaP tumor athymic nude mice





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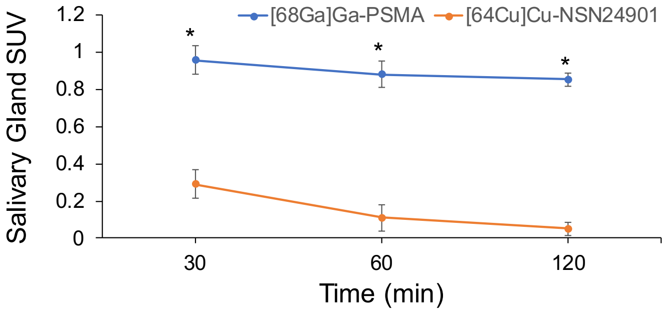
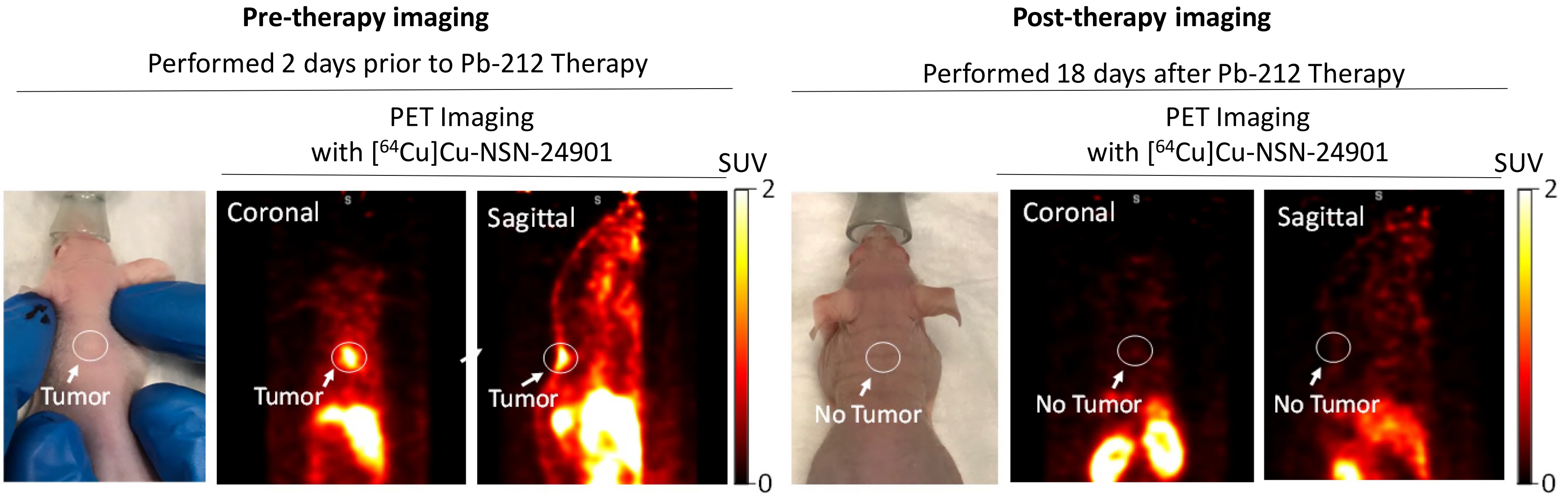


Patents-Pending

Alpha-PET TECHNOLOGY

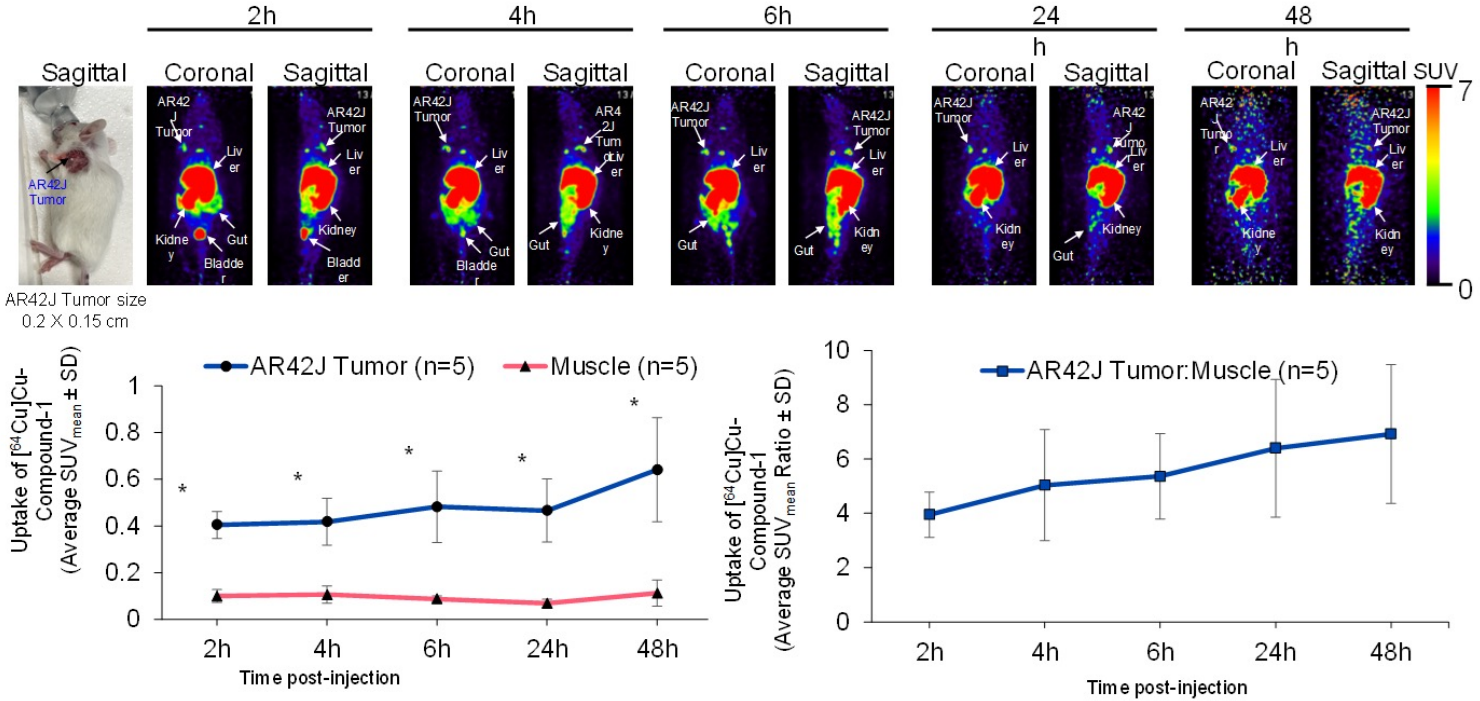
- We can kill tumors with 212Pb Alpha-PET PSMA and mice survive
- Treatment of prostate cancer xenograft with ^{212}Pb loaded construct reduced tumor size 38% in 3 days and complete response after 9 days



Patents-Pending

Alpha-PET TECHNOLOGY

- We can image tumors with Alpha-PET DOTATATE



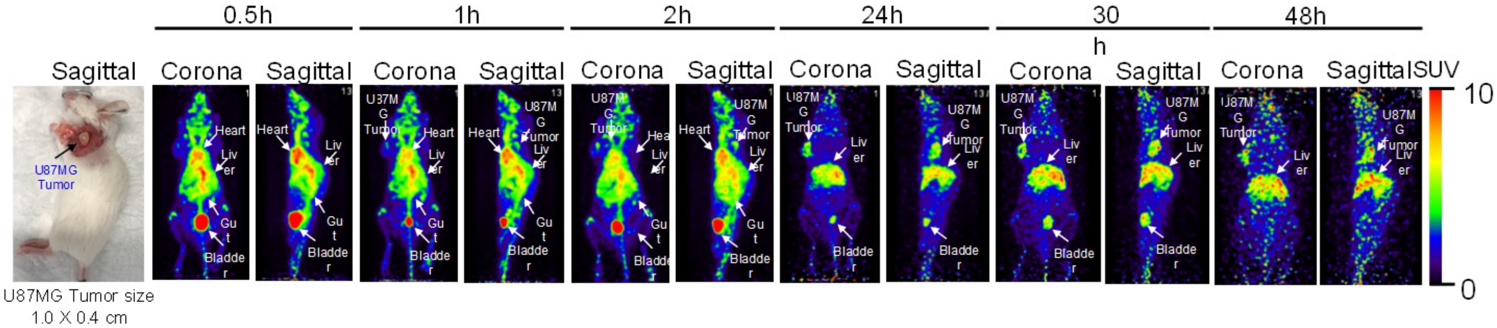
*p < 0.05 AR42J Tumor vs Muscle

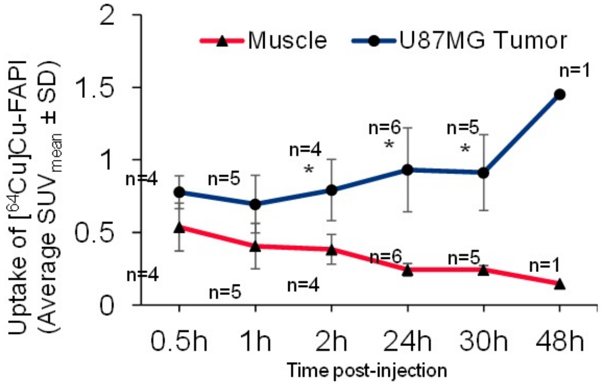
SUV_{mean} calculated by PET image analysis

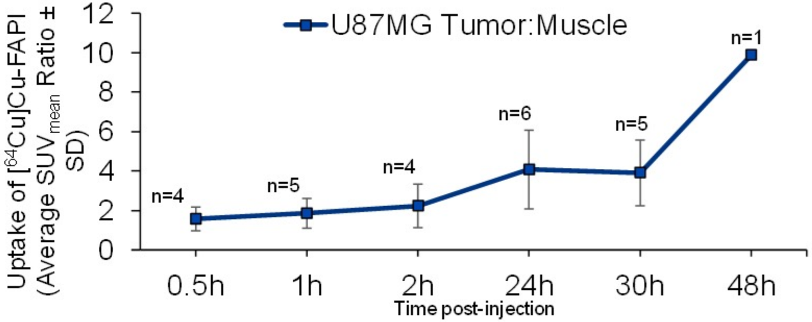
Patents-Pending

Alpha-PET TECHNOLOGY

- We can image tumors with Alpha-PET FAPI







*$p < 0.05$ U87MGTumor vs Muscle

Patents-Pending

Alpha-PET DoubLET TECHNOLOGY

Nuclide	Emission	Imaging	Use
64Cu	Beta+ Beta-	PET	Patient selection, Biodistribution, Dosimetry (tumor/organ), Beta Therapy

Alpha-PET DoubLET TECHNOLOGY

Nu

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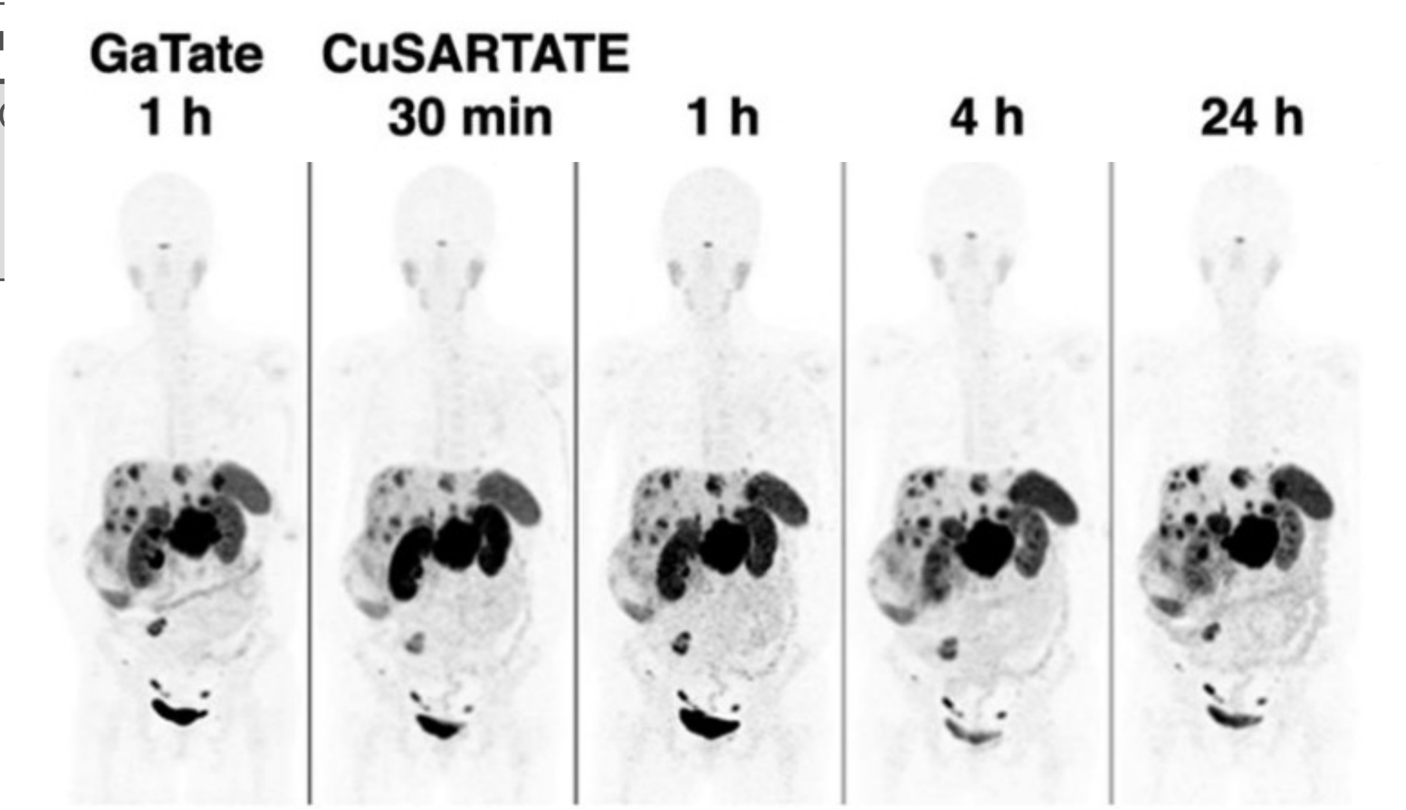
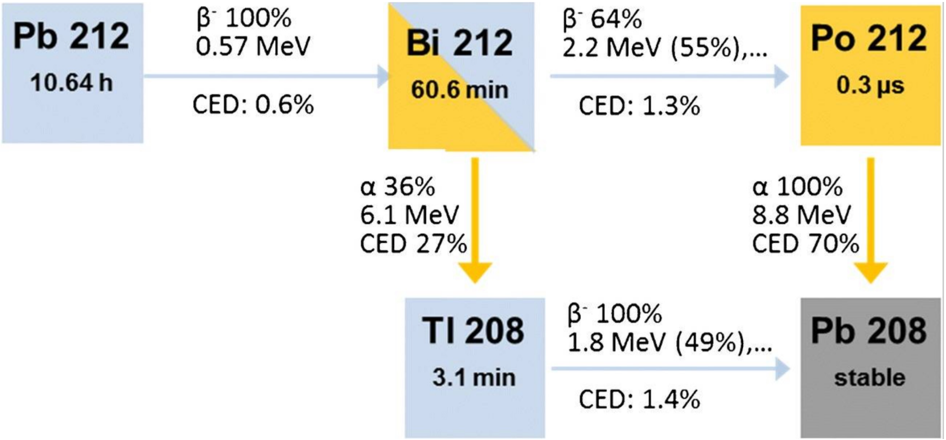


Hicks et al 2019

Alpha-PET DoubLET TECHNOLOGY

Nuclide	Emission	Imaging	Use
64Cu	Beta+ Beta-	PET	Patient selection, Biodistribution, Dosimetry (tumor/organ), Beta Therapy
212Pb	Alpha*	NA	Alpha Therapy



* Decay is one Beta- with recoil daughter 212Bi emitting one Alpha. Also Gamma.

Alpha-PET DoubLET TECHNOLOGY

Nuclide	Emission	Imaging	Use
64Cu	Beta+ Beta-	PET	Patient selection, Biodistribution, Dosimetry (tumor/organ), Beta Therapy
212Pb	Alpha*	NA	Alpha Therapy
212Pb, 64Cu	Alpha*, Beta+, Beta-	PET	DoubLET therapy, Therapy monitoring

- Alpha-PET DoubLET
  - Structurally Identical
  - Matched Biodistribution
  - Matched T1/2

Patents-Pending

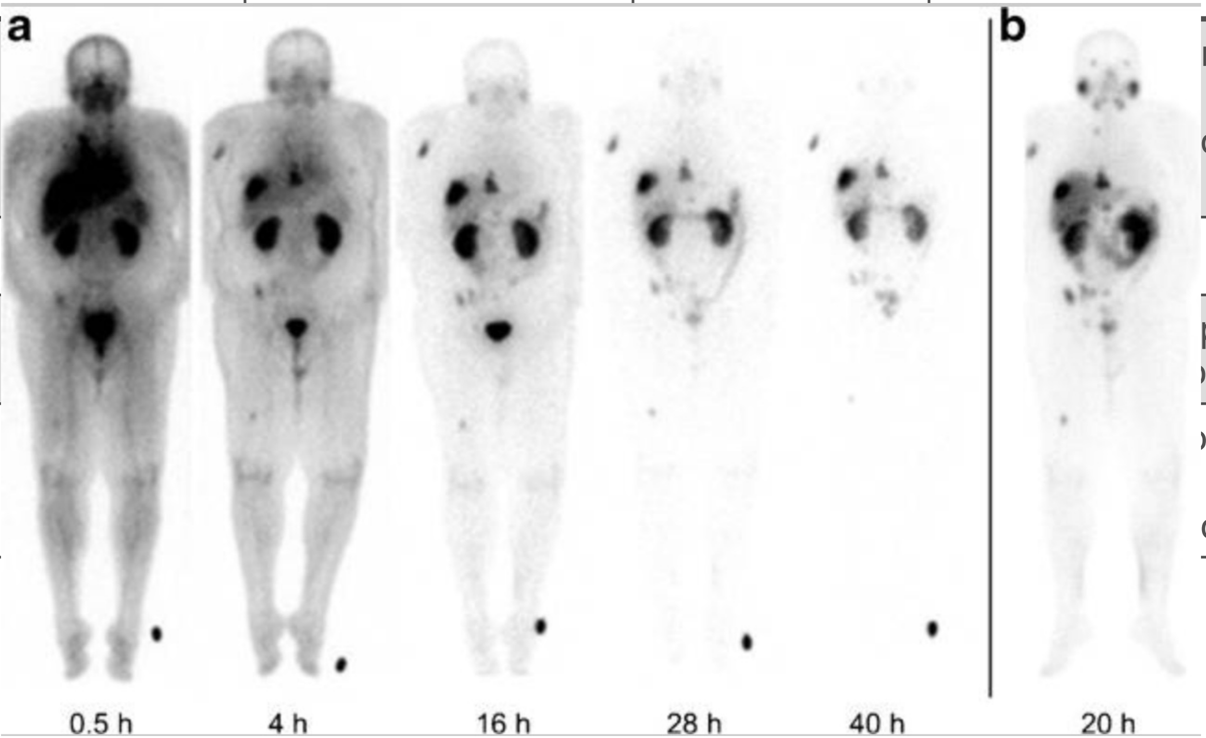
Alpha-PET DoubLET TECHNOLOGY

Nuclide	Emission	Imaging	Use
64Cu	Beta+ Beta-	PET	Patient selection, Biodistribution, Dosimetry (tumor/organ), Beta Therapy
212Pb	Alpha*	NA	Alpha Therapy
212Pb, 64Cu	Alpha*, Beta+, Beta-	PET	DoubLET therapy, Therapy monitoring
203Pb	Gamma	SPECT	Patient Selection, Biodistribution, Dosimetry (tumor/organ)

Mengshi et al 2020

Alpha-PET DoubLET TECHNOLOGY

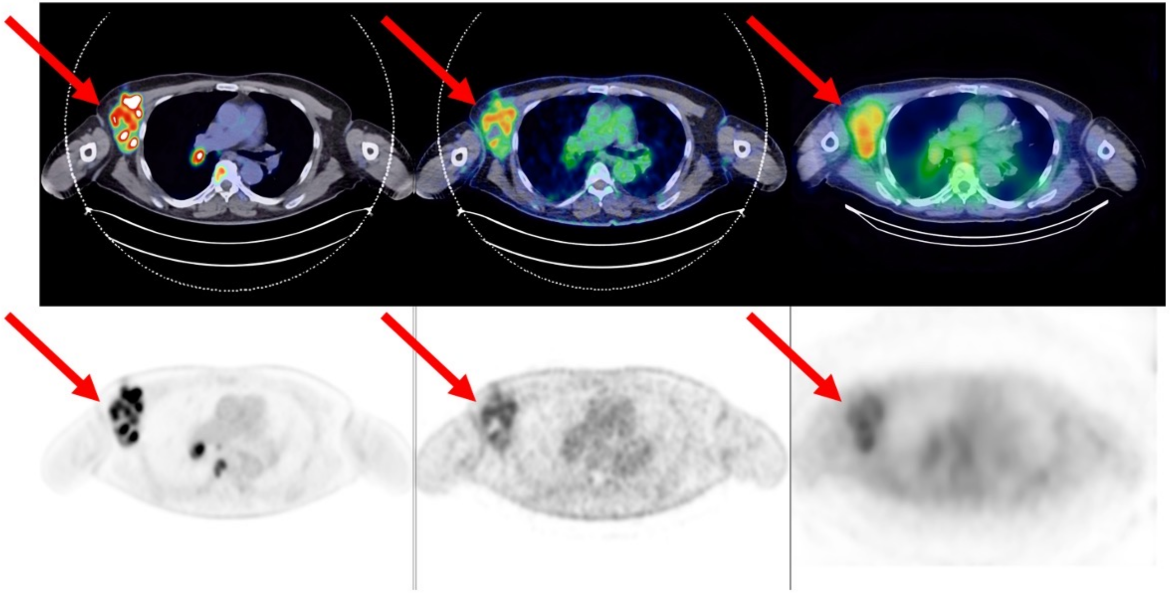
Nuclide	Emission	Imaging	Use
64Cu			n, or/organ),
212Pb			
212Pb,			py, ring
203Pb			n, or/organ)



Carlos dos Santos et al 2019

Alpha-PET DoubLET TECHNOLOGY

Nuclide	Emission	Imaging	Use
64Cu			organ),
212Pb			
212Pb, 64			g
203Pb			organ)



FDG PET/CT, 1Hr   68Ga-VMT02 PET/CT, 3Hr   203Pb-VMT01 SPECT/CT 24hr

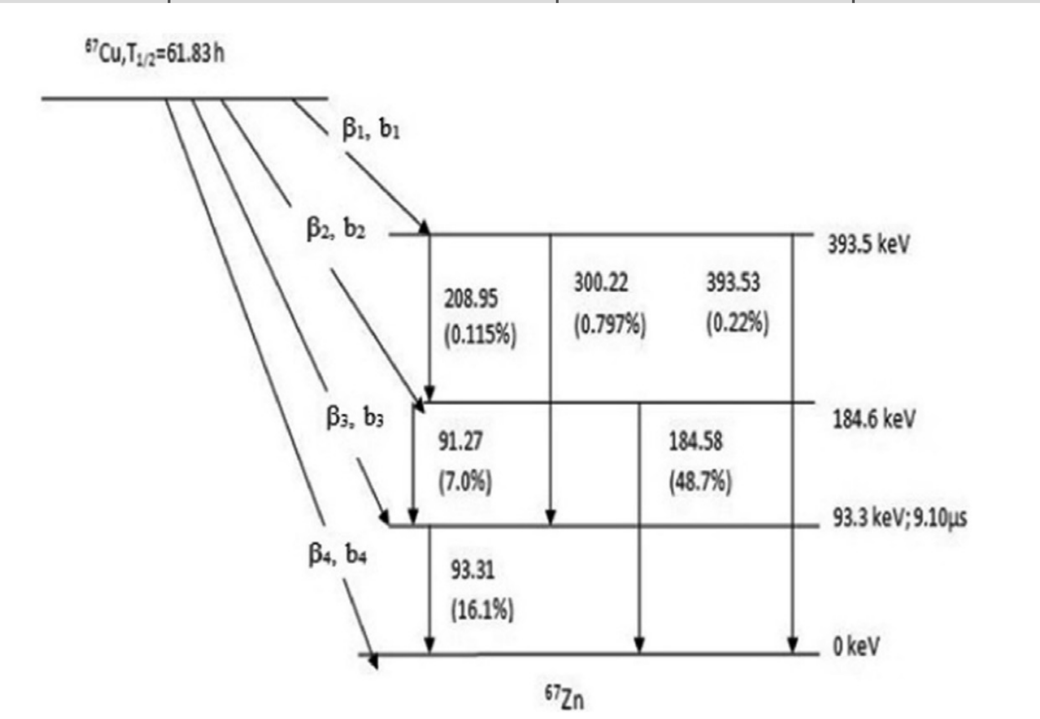
Alpha-PET DoubLET TECHNOLOGY

Nuclide	Emission	Imaging	Use
64Cu	Beta+ Beta-	PET	Patient selection, Biodistribution, Dosimetry (tumor/organ), Beta Therapy
212Pb	Alpha*	NA	Alpha Therapy
212Pb, 64Cu	Alpha*, Beta+, Beta-	PET	**DoubLET therapy**, Therapy monitoring
203Pb	Gamma	SPECT	Patient Selection, Biodistribution, Dosimetry (tumor/organ)
67Cu	Beta+, Gamma	SPECT	Biodistribution, Dosimetry (tumor/organ)

Cullinane et al 2020

Alpha-PET DoubLET TECHNOLOGY

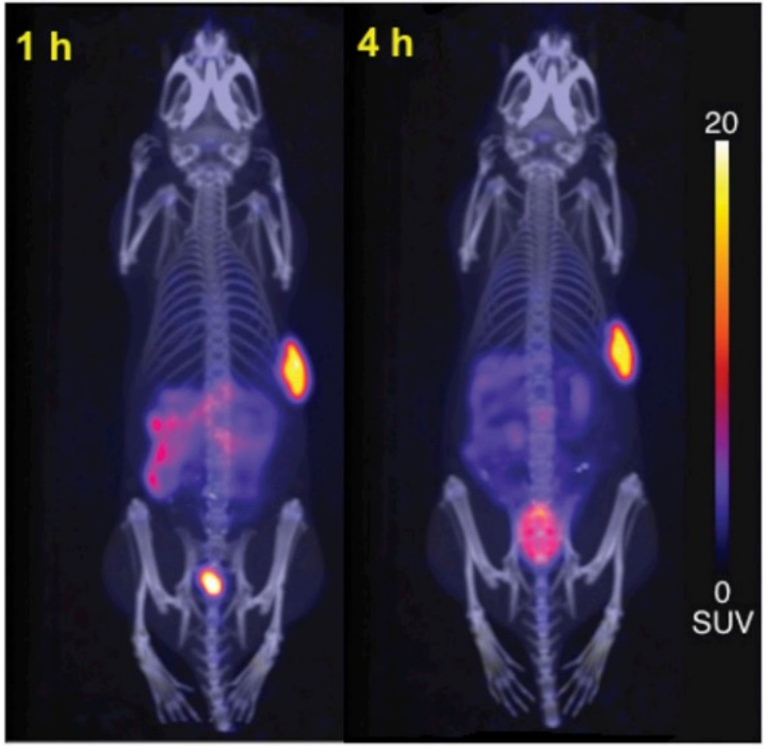
Nuclide	Emission	Imaging	Use
64Cu			lection, ition, (tumor/organ), apy
212Pb			rapy
212Pb, 64C			**therapy**, ionitoring
203Pb			election, ition, (tumor/organ)
67Cu			ition, (tumor/organ)



Sahagia et al 2018

Alpha-PET DoubLET TECHNOLOGY

Nuclide	Emission	Imaging	Use
64Cu			ient selection, distribution, simetry (tumor/organ), a Therapy
212Pb			ha Therapy
212Pb, 64Cu			**ubLET therapy**, erapy monitoring
203Pb			ient Selection, distribution, simetry (tumor/organ)
67Cu			distribution, simetry (tumor/organ)



Cullinane et al 2020

Alpha-PET DoubLET TECHNOLOGY

Nuclide	Emission	Imaging	Use
64Cu	Beta+ Beta-	PET	Patient selection, Biodistribution, Dosimetry (tumor/organ), Beta Therapy
212Pb	Alpha*	NA	Alpha Therapy
212Pb, 64Cu	Alpha*, Beta+, Beta-	PET	**DoubLET therapy**, Therapy monitoring
203Pb	Gamma	SPECT	Patient Selection, Biodistribution, Dosimetry (tumor/organ)
67Cu	Beta+, Gamma	SPECT	Biodistribution, Dosimetry (tumor/organ)
61Cu	Beta+	PET	Patient Selection, Biodistribution, Dosimetry (tumor/organ)

Fonseca et al 2022

 |

Alpha-PET DoubLET TECHNOLOGY

Nuclide	Emission	Physical T1/2	Use
64Cu	Beta+ Beta-	12hr	Patient selection, Biodistribution, Dosimetry (tumor/organ), Beta Therapy
212Pb	Alpha*	11hr**	Alpha Therapy
212Pb, 64Cu	Alpha*, Beta+, Beta-	11hr/12hr	**DoubLET therapy**, Therapy monitoring
203Pb	Gamma	52hr	Patient Selection, Biodistribution, Dosimetry (tumor/organ)
67Cu	Beta+, Gamma	62hr	Biodistribution, Dosimetry (tumor/organ)
61Cu	Beta+	3.3hr	Patient Selection, Biodistribution, Dosimetry (tumor/organ)

** Double decay

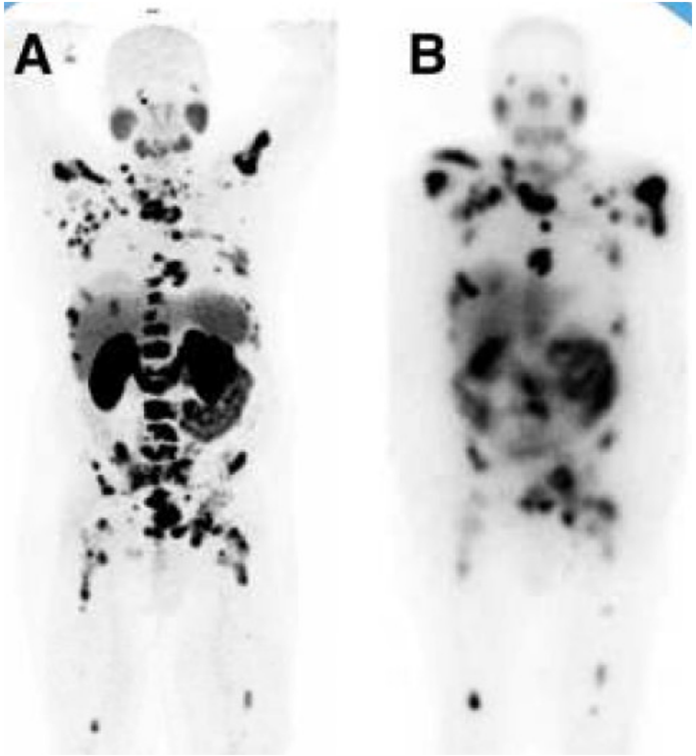
How do we “Read out” Alpha vs Beta vs Alpha+Beta?

- Outcome
  - Survival
  - Toxicity
- Imaging Response/PFS
  - Conventional (CT, MRI)
  - PET, SPECT
- Blood tests
  - ctDNA
  - Tumor “Secretome”
    - Extracellular Vesicles (EVs)

BACKGROUND

- Beta radionuclide therapy (β-therapy) is established technology.

68Ga PSMA-11
PET/CT
Before
Therapy



177Lu-PSMA-617
Planar
After
Therapy

Qualitative only
2D like a bone scan

Rahba et al, JNM 2016

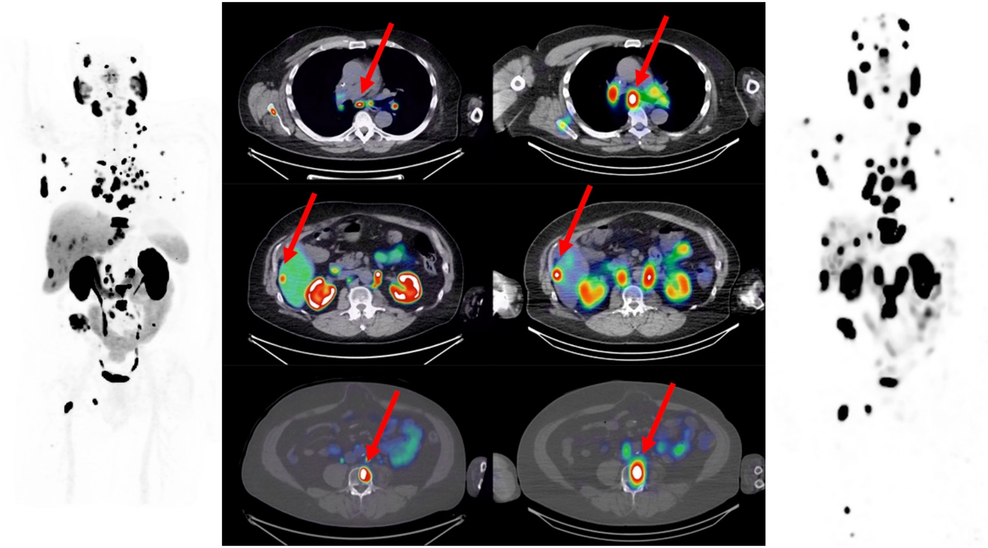
BACKGROUND

- Beta radionuclide therapy (β-therapy) is established technology.

68Ga PSMA-11
PET/CT
Before
Therapy

PSMA PET/CT
Patient Selection

PSMA SPECT/CT
Therapy Monitoring



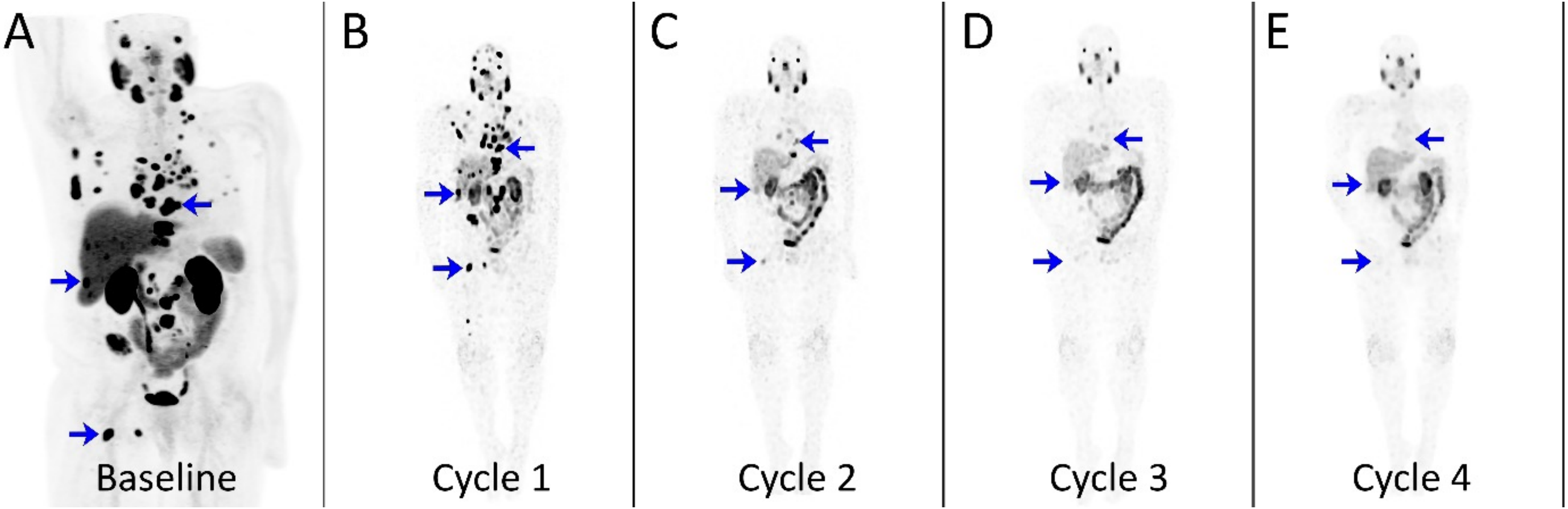
177Lu-PSMA-617
SPECT/CT
After
Therapy

Quantitative
3D "like" a PET scan

Performed pre-therapy
Shows tumors express PSMA
Patient is eligible for therapy

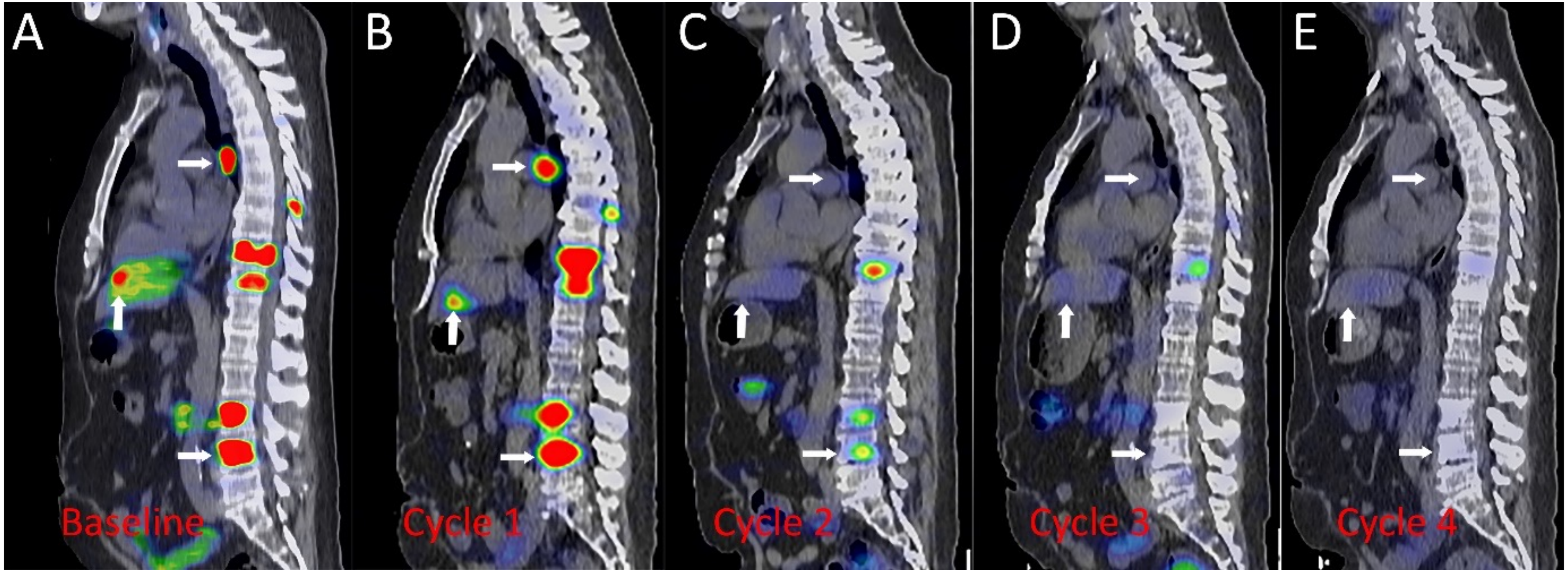
Performed post-therapy
Is a scan of the therapy itself
Shows therapy successfully targeted tumors

177Lu-PSMA-617 Therapy Monitoring



In press

177Lu-PSMA-617 Therapy Monitoring



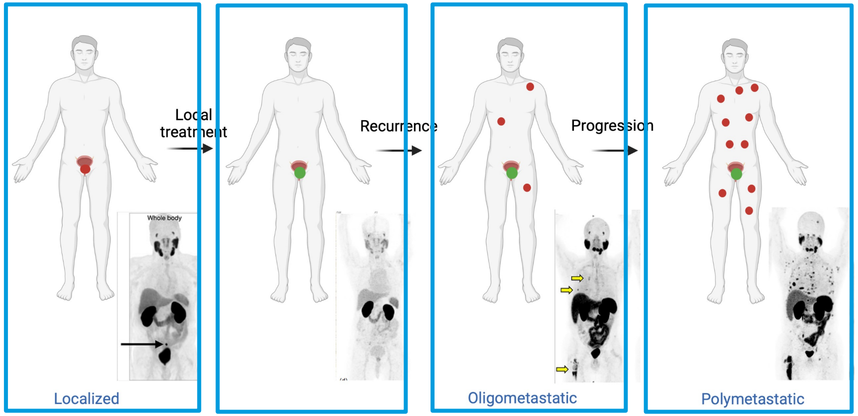
Patient Selection
PSMA PET/CT

Therapy-Monitoring
SPECT PET/CT

In press

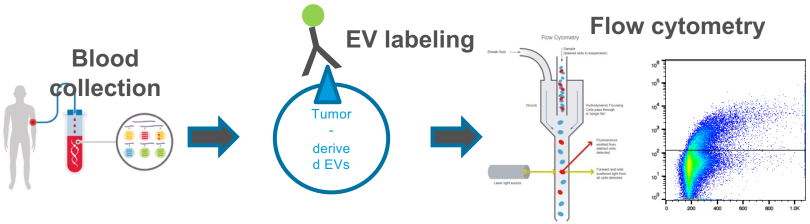
Circulating tumor-derived EVs reflect disease burden

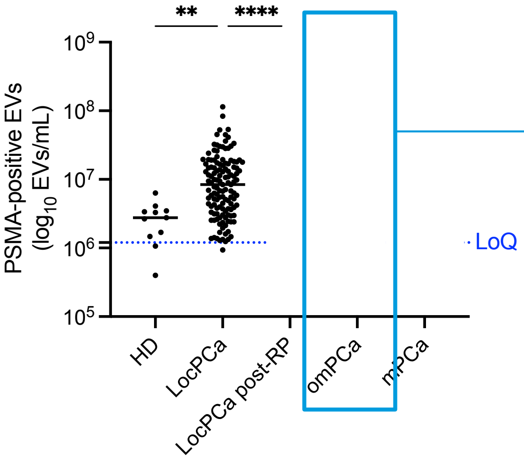
Prostate Cancer

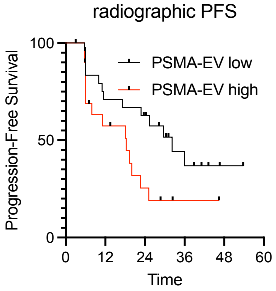


Fabrice Lucien, PhD

Sean Park, MD, PhD







Hazard Ratio : 0.5 (95% CI: 0.2-1.1), p=0.04
Median rPFS: 18.3 months (high) vs 32.2 months (low)

Kim Y et al, Nanoscale 2022
Lucien F et al, IJROBP 2022

PSMA expression in tumor-derived EVs reflect tumor expression

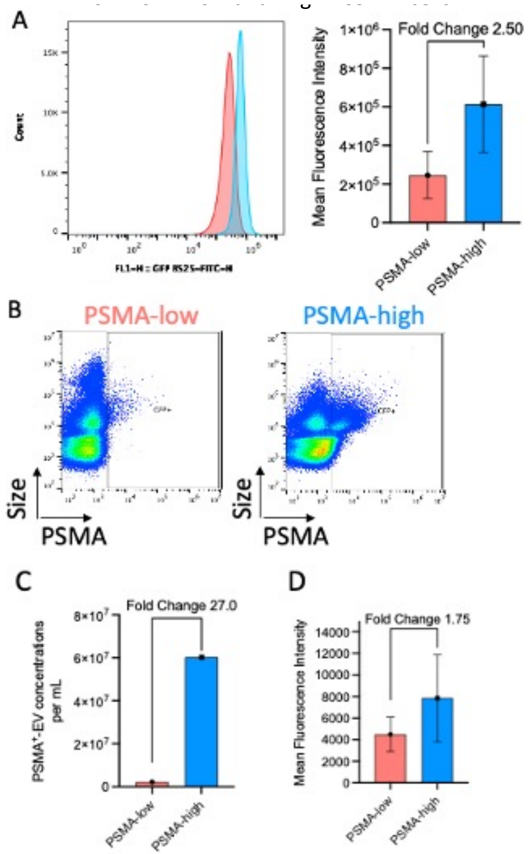


Figure 6:

A) Cellular PSMA expression in PSMA-low and PSMA-high PC3-PIP cells (positive for PSMA)

B) Scatterplots showing PSMA expression in EVs from PSMA-low and high PC3-PIP cells

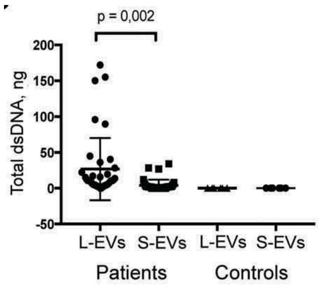
C) Concentrations of PSMA-positive EVs from PSMA-low and -high PC3-PIP cells

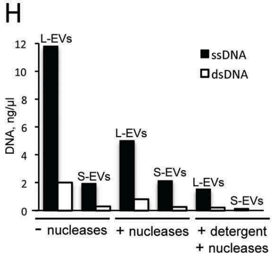
D) EV PSMA expression of PSMA-positive EVs from PSMA-low and -high PC3-PIP cells

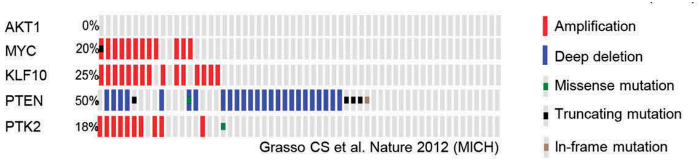
Tumor-derived EVs are enriched in disease-specific cargo

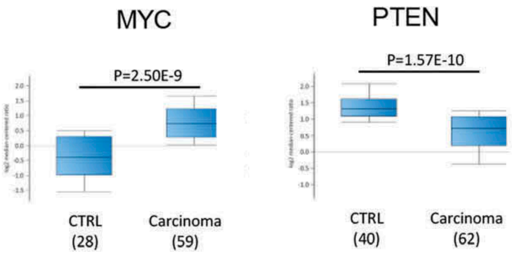
- RNA fusion transcripts (e.g TMPRSS2-ERG)
- Mutations (e.g AR-V7 – Joncas MH, Lucien F et al, Prostate 2019)
- DNA alterations (e.g mutations, copy number variant)

Metastatic Prostate Cancer









Vagner T et al, JEV, 2018

Opportunities for radiopharmaceuticals

- Comparative analysis of the EV cargo (DNA, RNA, proteins) in prostate cancer cells treated with alpha vs beta-emitters *in vitro* for discovery of markers of response/resistance
- Response/resistance signatures can be tested using patient plasma
- Circulating levels of PSMA-positive EVs and PSMA expression on EVs as baseline predictor of response to alpha-emitters and for monitoring response. (Ongoing work with PSMA-617)
- Immunocompetent mouse models of prostate cancer to characterize immunogenic cell death with alpha and beta-emitters

Alpha-PET

- To our knowledge, Alpha-PET is the first and only technology that allows a researcher to choose
  - Alpha
  - Beta
  - Alpha+Beta
  - Titration of doses
  - Perfectly matched biodistribution

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  - Can image with PET
  - Calculate Dosimetry

How do we "Read out" Alpha vs Beta vs Alpha+Beta?

- Outcome
  - Survival
  - Toxicity
- Imaging Response/PFS
  - Conventional (CT, MRI)
  - PET, SPECT
- Blood tests
  - ctDNA
  - Tumor "Secretome"
    - Extracellular Vesicles (EVs)

MAYO CLINIC

Alpha-PET DoubLET

A Flexible Theragnostic Molecular Platform Technology for Alpha and/or Beta Therapy with PET-based Dosimetry

RPT Interest Group 6-7-23

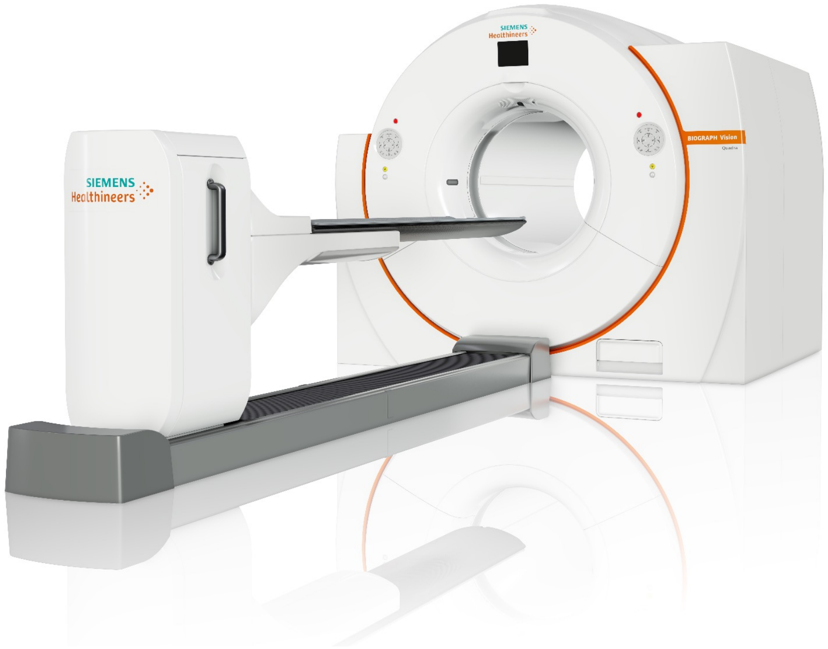
Geoffrey B Johnson, MD, Ph.D
Chair, Nuclear Medicine
Associate Director, Mayo Clinic
Comprehensive Cancer Center

Mukesh K Pandey, Ph.D, FRSC
Director, Molecular Imaging Research Program

First Installation in North America at Mayo Clinic Siemens Quadra Long-Bore PET/CT

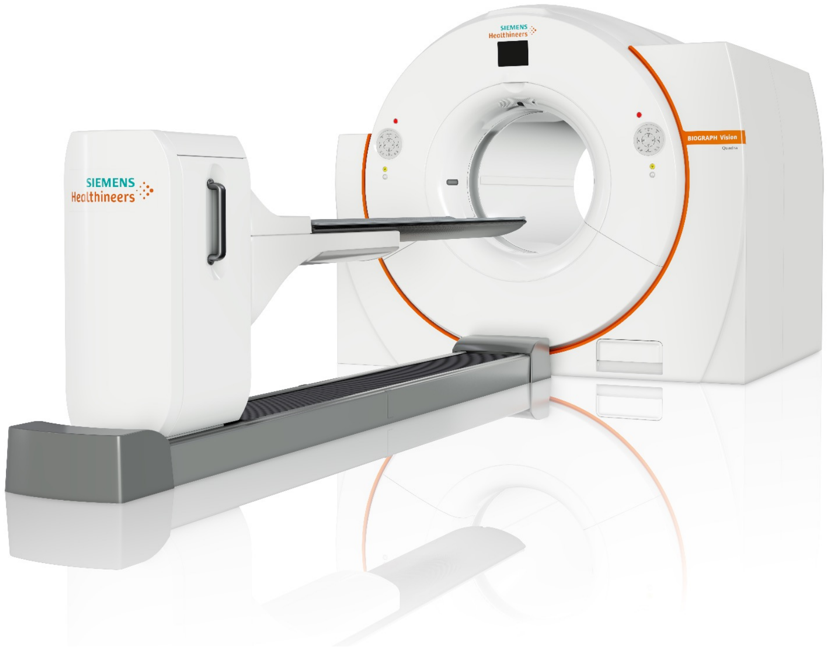
- Installation September 2022
- 4 x length (Long-bore)
- 10 x sensitivity*
  - Quality
  - Speed
  - Reduce Radiation

*Compared to our current best scanner



First Installation in North America at Mayo Clinic Siemens Quadra Long-Bore PET/CT

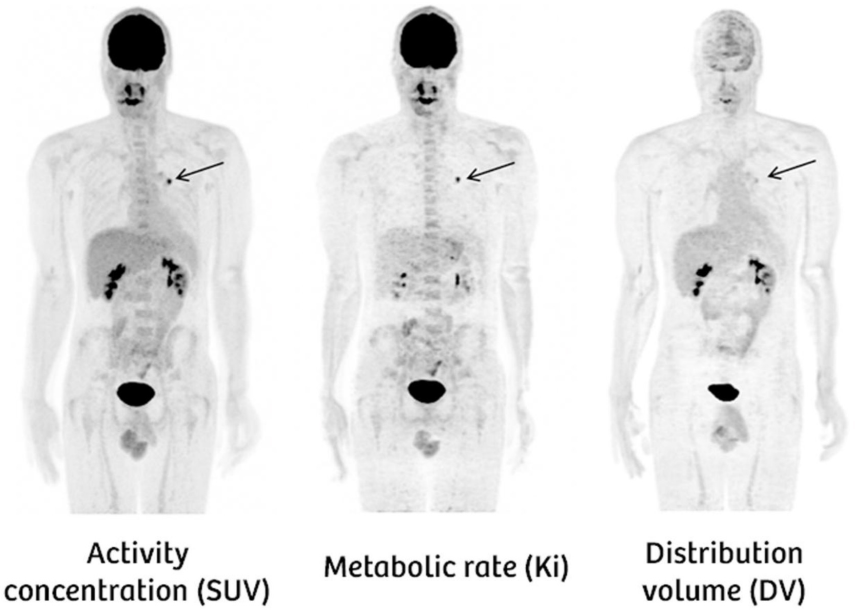
- Dynamic full coverage scanning allows for:
  - Multiple tracer simultaneous imaging
    - CRISMA Technology
  - Compartment modeling to remove unbound tracer from the image
    - More accurate for predicting outcome?
- Rapidly test new imaging and therapy radiopharmaceuticals



Compartment modeling for Alpha Dosimetry?

- Remove/decrease background blood pool activity

Brad Kemp, PhD



P3-MT100 (Medtrace, DK)

- Production of [O-15] Water
- Integrated synthesis and dose administration system
- Clean air environment
- Fully lead shielded
- Consumable sterile components
- Connected to cyclotron approx. 250 ft distance

- RAPID-WATER phase 3 clinical trial

Stage One: Nucleus RadioPharma 2 Discovery Square, Rochester Site

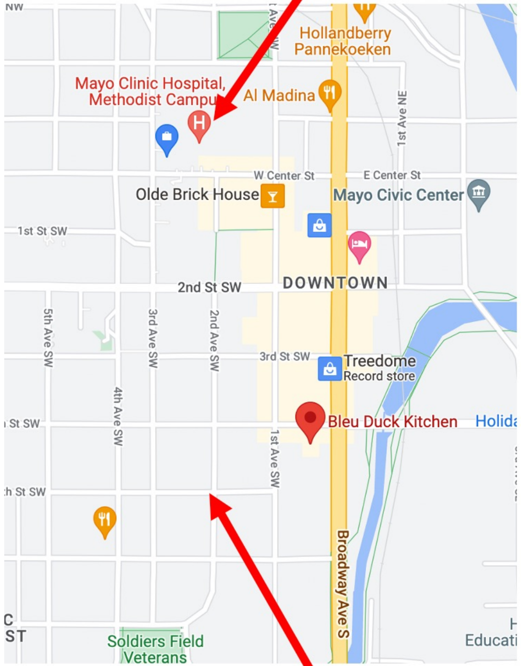
Nucleus RadioPharma

Mayo/Nuclear Medicine Therapy Center

Office Space 2nd Floor

Production Facilities Main Floor

~10,000 sq ft



2 Discovery Square Angle of view in image

Alpha-PET TECHNOLOGY

Better for radiopharmaceuticals with longer biologic half-life, slower binding, and/or slower clearance (such as antibodies)

Nuclide	Emission	Imaging	Use
89Zr	Beta+	PET	Patient/RLT selection
225Ac	Alpha	NA	Therapy
89Zr, 225Ac	Alpha, Beta+	PET	Therapy Therapy monitoring

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