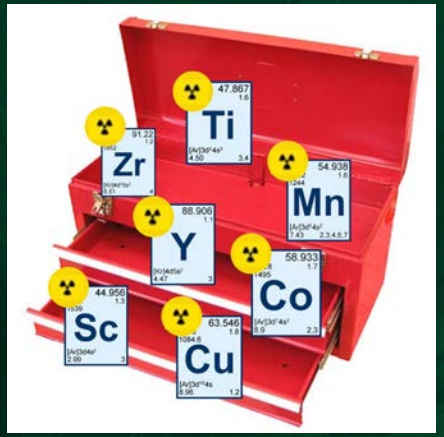


Expanding the radioisotope toolbox for nuclear medicine

Suzanne Lapi
Professor of Radiology and Chemistry
Experimental Therapeutics Program Co-Leader
O'Neal Comprehensive Cancer Center
Director, UAB Cyclotron Facility

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Knowledge that will change your world

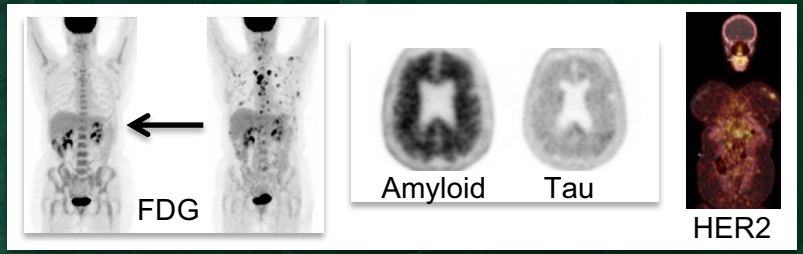
University of Alabama at Birmingham

- Located in Birmingham, AL
- The UAB Cyclotron Facility and Advanced Imaging Facility are located in the center of the medical complex at the O'Neal Comprehensive Cancer Center. Medical and main campus are contiguous.
  - Walk from Chemistry to Cyclotron etc

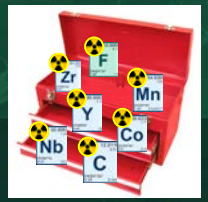
Fun facts timeline:

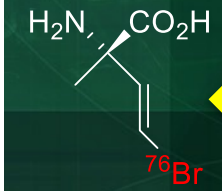
- The TR24 cyclotron was installed in April of 2013 and facilities were completed in July of 2014.
- The first patient dose was injected in January of 2016.
- The UAB cyclotron facility now holds >15 active INDs

Bidirectional Translational Molecular Imaging Program at UAB



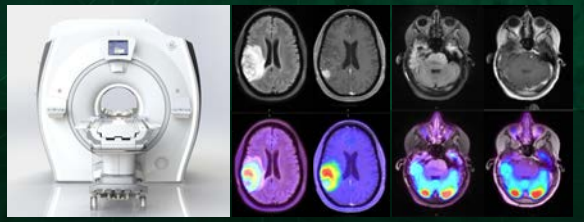
Clinical trials with molecular imaging and therapeutics





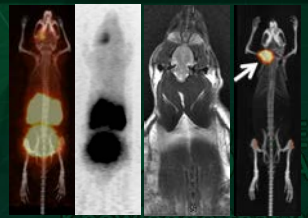
Isotope production and MI agent development

UAB Cyclotron Facility



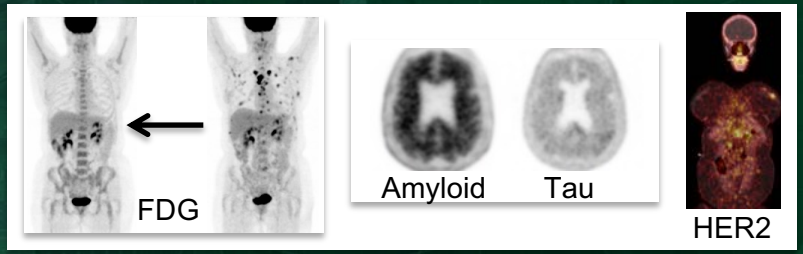
PET/CT and PET/MRI in AIF

In vitro testing



Small animal imaging

Bidirectional Translational Molecular Imaging Program at UAB



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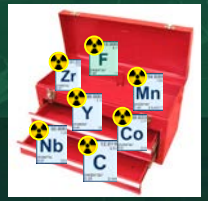
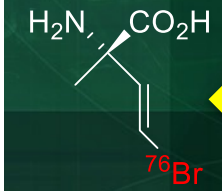
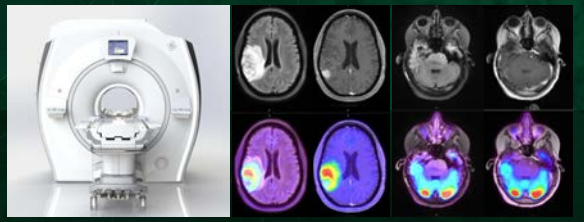




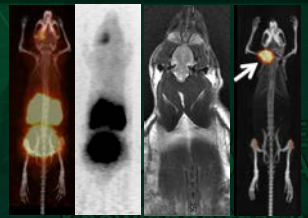
Isotope production and MI agent development

UAB Cyclotron Facility



PET/CT and PET/MRI in AIF

In vitro testing



Small animal imaging

The Cyclotron Facility and the AIF support clinical services as well as clinical and basic science research in the UAB community

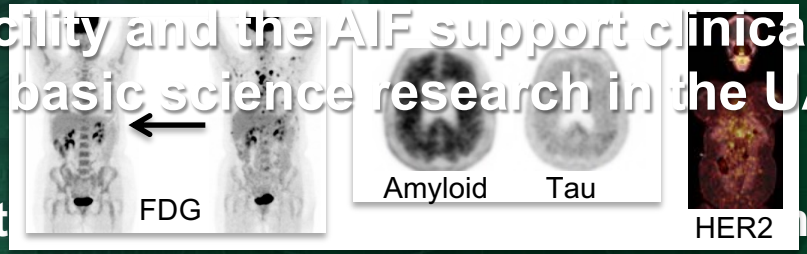
Translational Molecular Imaging Program at UAB

Radiation Oncology

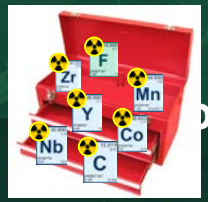
Children's of Alabama

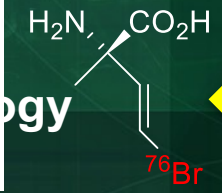
Oncology

Oncology clinical trials with molecular imaging and therapeutics



Biomedical engineering

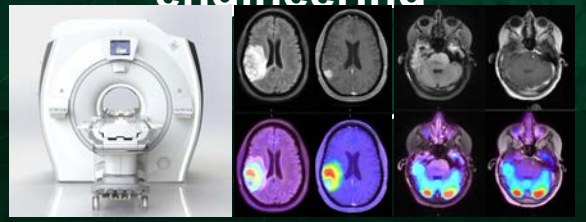




Isotope production and MI agent development

Neuroscience

UAB Cyclotron Facility



PET/CT and PET/MRI in AIF

Rheumatology

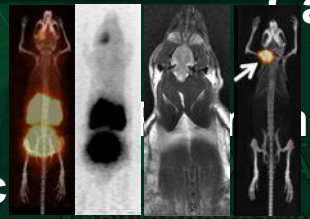
Neurosurgery

Cardiology

Psychology

In vitro testing

Southern Research Institute

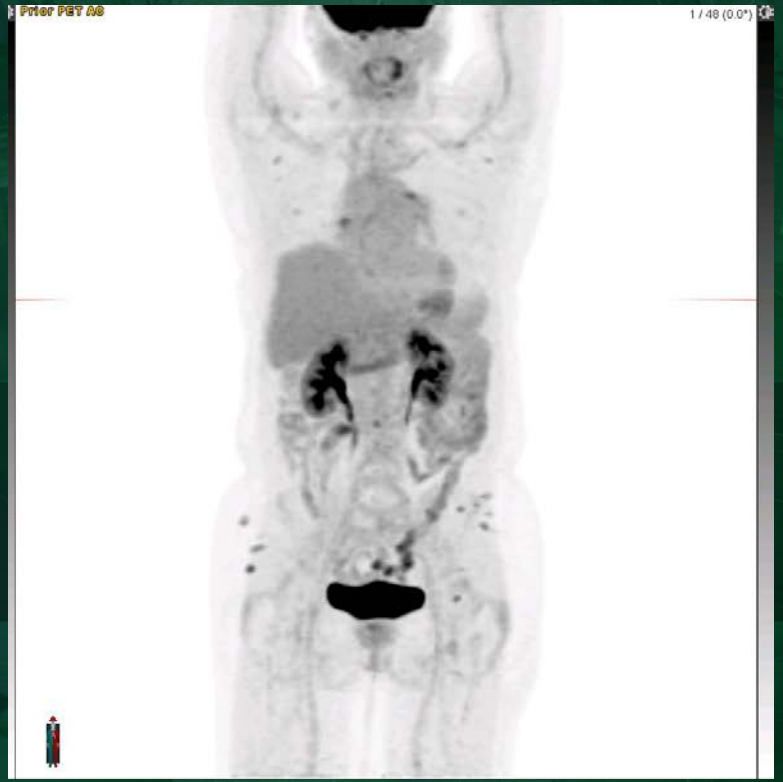


Small animal imaging

Why develop new imaging agents?

- Imaging more than detection of disease:
  - Oncology
  - Neurology
  - Cardiology
- Imaging can provide more information: detection, cell proliferation, amyloid burden, receptor status, oxygenation, microenvironment, immune cell infiltration……
- Prediction of treatment response.

Expanding the Toolbox of Imaging Agents



[^{18}F]FDG

[^{68}Ga]DOTATATE)

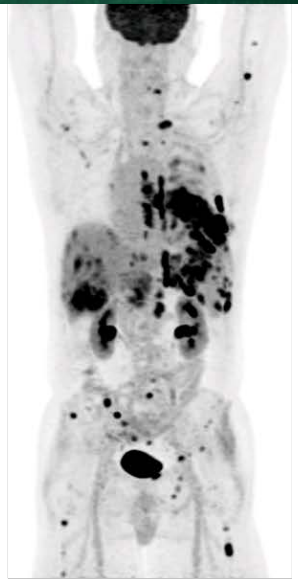
Status of Active Radiotracers for Human Use at UAB

Radiopharmaceutical	Use	Status
[^{18}F]FLT	Proliferation	IND approved
[^{13}N]NH_3	Cardiac blood flow	IND approved, ANDA submitted
[^{68}Ga]DOTATATE	SSTR status	FDA approved
[^{18}F]FMISO	Hypoxia	IND approved
[^{89}Zr]Trastuzumab	HER2 status (breast cancer)	IND approved
[^{18}F]FET	Amino acid transport	IND approved
[^{11}C]PiB	Amyloid	IND approved
[^{18}F]DPA-714	TSPO (neuroinflammation)	IND approved
[^{68}Ga]PSMA-11	PSMA status (prostate cancer)	IND approved
[^{89}Zr]Panitumumab	EGFR status (colon cancer)	IND approved
[^{18}F]AV1451	Tau protein	IND approved
[^{68}Ga]GZP*	Granzyme B (Immune Activation)	IND approved
[^{11}C]Acetate	Cardiac Metabolism	IND approved
[^{89}Zr]Oxine/White Blood Cells*	WBC tracking	IND approved
[^{18}F]MeFAMP*	Cancer metabolism	Chemistry initiated
[^{15}O]H_2O	Blood flow	Chemistry initiated
[^{11}C]UCB-J	Synaptic Vesicle Glycoprotein 2A (SV2A)	Chemistry initiated

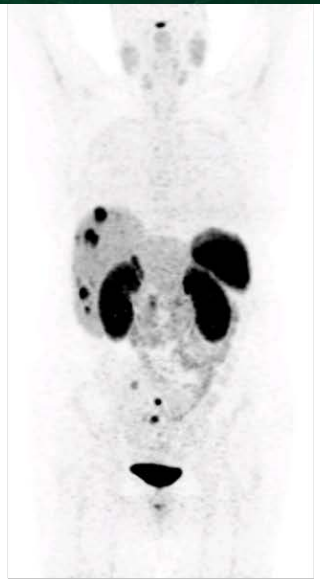
*First in human compound

Whole body PET tracers in use at UAB for oncology

Bone turnover
in skeletal metastases
[^{18}F]fluoride



Glucose metabolism
in many cancers
[^{18}F]FDG

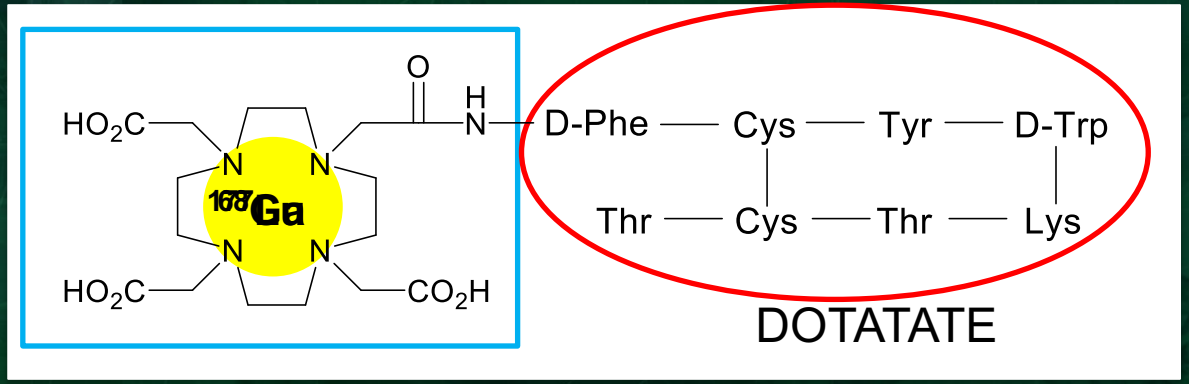


Somatostatin receptors
in neuroendocrine cancers
[^{68}Ga]DOTATATE

Amino acid transport
in prostate cancer
[^{18}F]fluciclovine

HER2 as a target for
therapy in breast cancer
[^{89}Zr]trastuzumab

Theranostics and radionuclide therapy for cancer



- Some radiopharmaceuticals can be labeled for imaging and for therapy: **theranostic approach**

- Radionuclide therapies can succeed after other therapies fail.

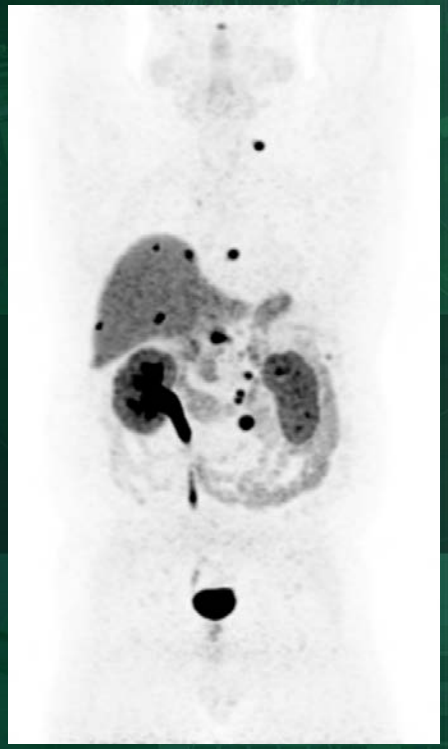
- Imaging often guides therapy by demonstrating the entire tumor burden expresses the therapeutic target

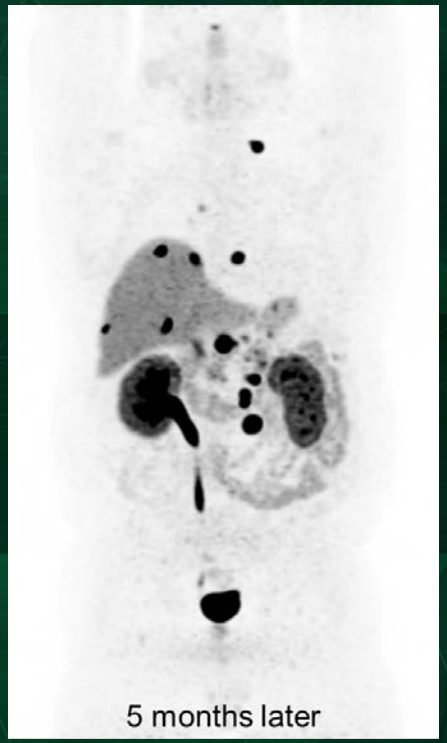
[^{68}Ga]DOTATATE for imaging; [^{177}Lu]DOTATATE for therapy (NETTER-1)

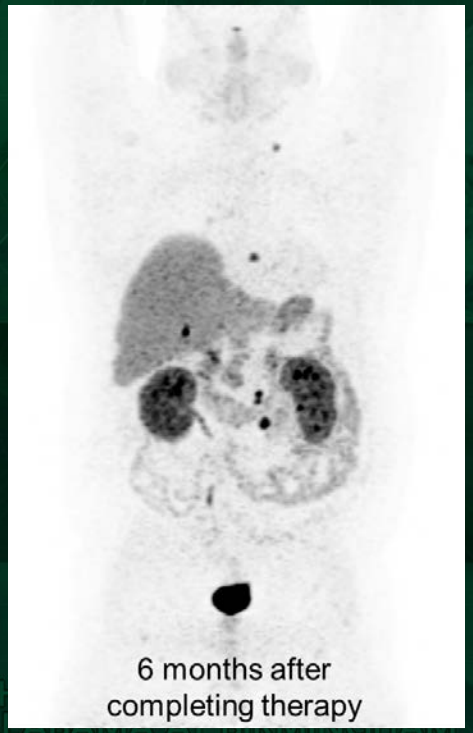
[^{68}Ga]DOTATATE

[^{177}Lu]DOTATATE

[^{68}Ga]DOTATATE imaging for disease progression and response to [^{177}Lu]DOTATATE

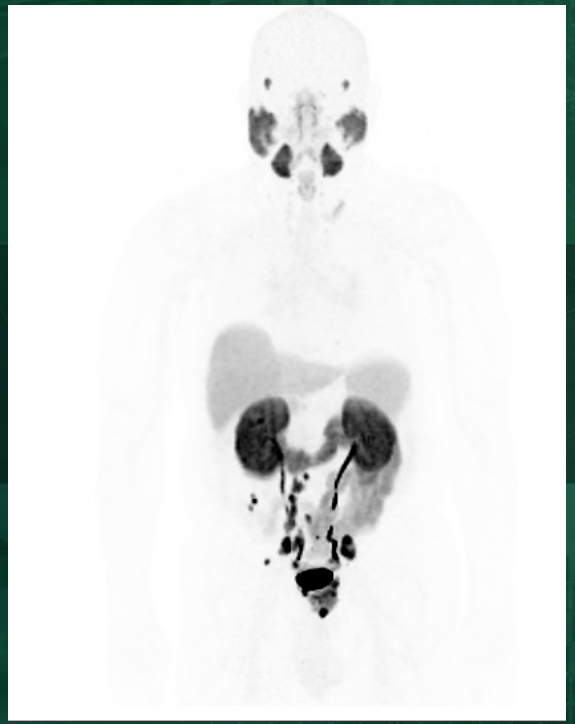


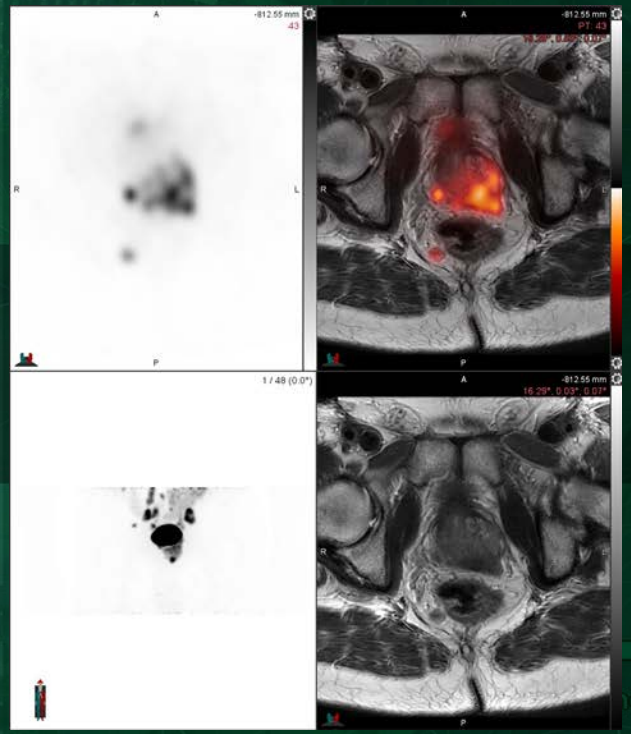




PSMA imaging with [^{68}Ga]PSMA-11

[^{68}Ga]PSMA-11 for initial staging of prostate cancer





DRUGS & TARGETS

Pylarify receives FDA approval as first and only commercially available PSMA PET imaging agent for prostate cancer

May 28, 2021 | Vol.47 No.21

FDA has approved Pylarify, an F 18-labeled prostate-specific membrane antigen targeted positron emission tomography imaging agent to identify suspected metastasis or recurrence of prostate cancer.

Pylarify is sponsored by Lantheus Holdings Inc.

Pylarify is the first and only commercially available approved PSMA PET imaging agent for prostate cancer. The product will be immediately available in parts of the mid-Atlantic and southern regions and availability is expected to rapidly expand over the next six months with broad availability across the U.S. anticipated by year end.

Identification of suspected metastatic disease in men considering initial definitive therapy is important to optimize treatment planning and to avoid futile interventions.

Of men with localized prostate cancer who undergo initial curative intent/management, up to 50% may experience recurrence of their disease within ten years of treatment.

Recurrent disease is often detected by a rise in serum prostate-specific antigen (PSA) levels; however, conventional imaging, especially at low PSA levels, is not able to identify the location and extent of the disease in the majority of cases.

Pylarify was developed to target PSMA, a protein that is overexpressed on the surface of more than 90% of primary and metastatic prostate cancer cells. Pylarify binds to the target, enabling the reader of the PET scan to detect and locate the disease.

Cyclotron production of F 18 offers high batch capacity and high image resolution, and F 18's 110-minute half-life allows for wide geographic distribution.

DOWNLOAD THE

TABLE OF CONTEN

May 28, 2021

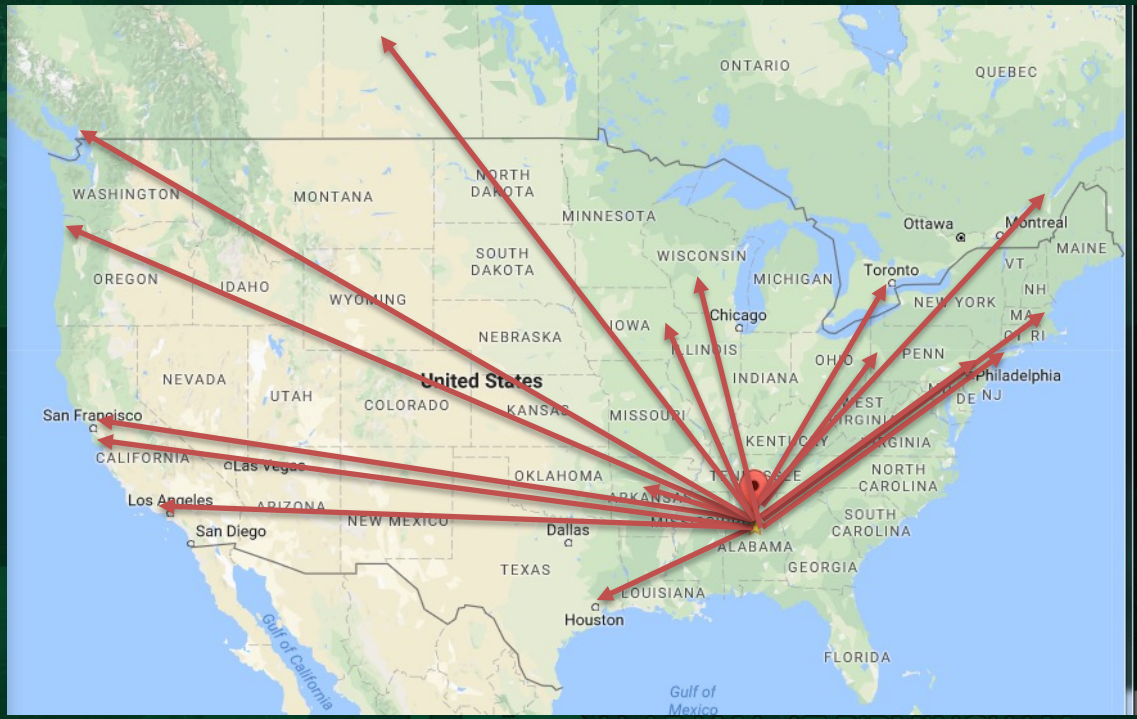
Expanding the tookbox: Radioisotopes (beyond ^{18}F, ^{11}C, ^{13}N, ^{15}O, ^{68}Ga)

Isotope	Half-Life	Target Material	Status
$^{43,47}Sc$	3.9 h	$^{Nat/Enr}Ti$	Chemistry development
^{45}Ti	3.1 h	^{Nat}Sc	Chemistry development
^{48}V	16 d	^{Nat}Ti	Chemistry development
^{52}Mn	5.6 d	$^{Nat/52}Cr$	Routine production for preclinical use
^{55}Co	17.5 h	^{58}Ni	Routine production for preclinical use
^{64}Cu	12.7 h	^{64}Ni	Routine production for preclinical and human use
^{89}Zr	3.27 d	^{89}Y	Routine production for preclinical and human use

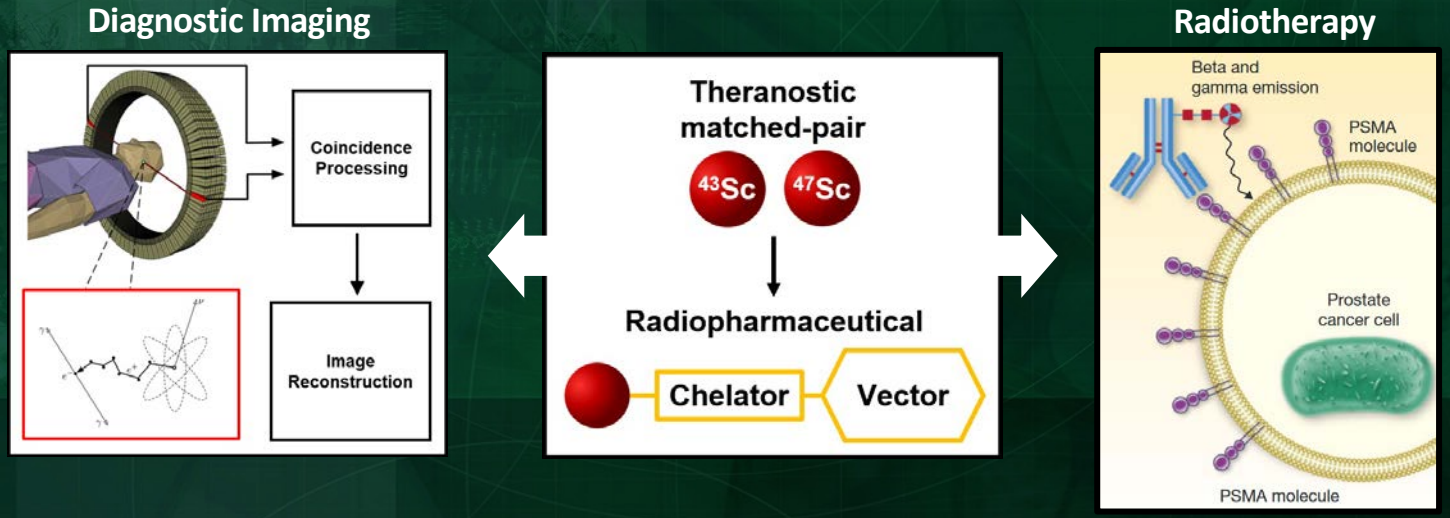
UAB Cyclotron Facility : A Nationwide Resource

Multi-state pharmacist, pharmacy and manufacturing licenses to allow dispensing and distribution of radiopharmaceuticals into adjoining states.

DOT certified shipping containers and internal training to distribute ^{89}Zr and other isotopes to other research facilities throughout the country and internationally.



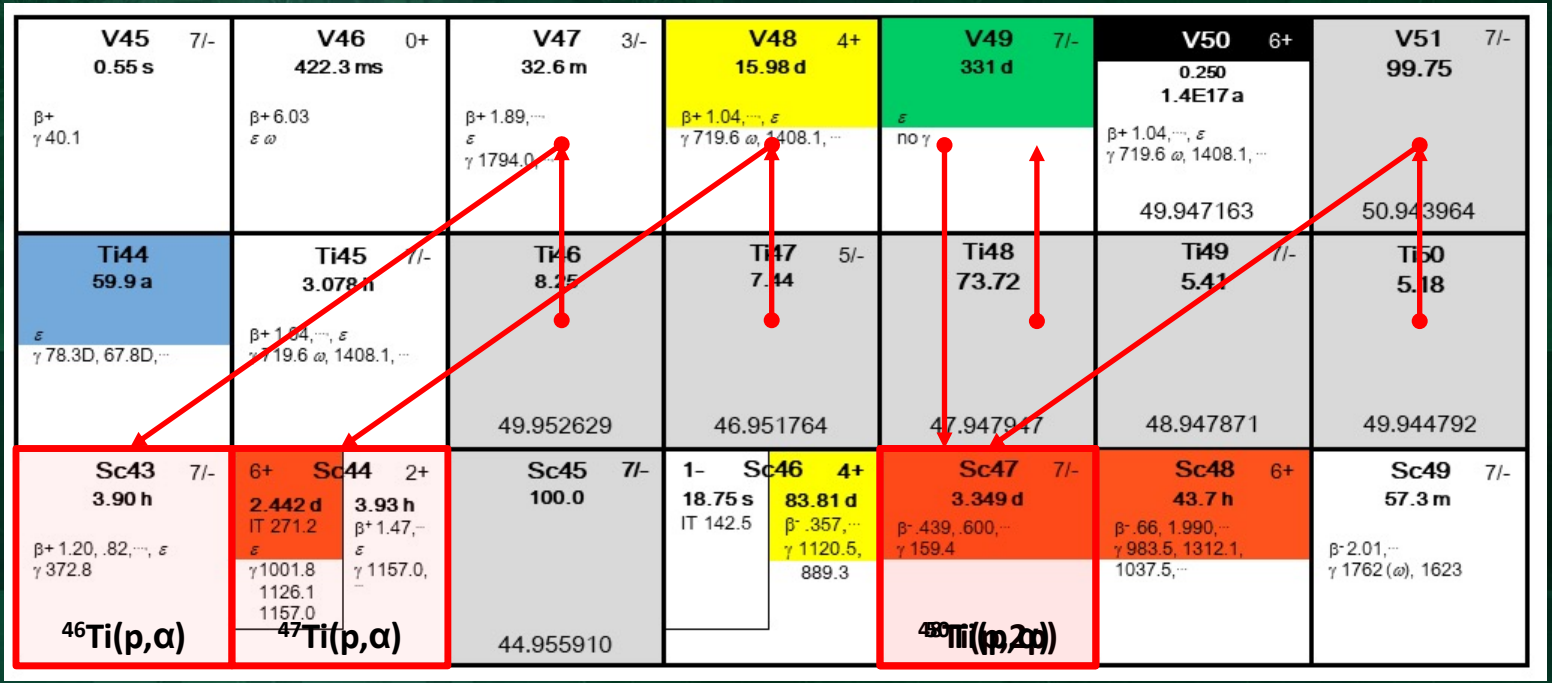
Matched Pair Radionuclides: ^{43}Sc and ^{47}Sc



- Disease diagnosis, dosimetry evaluation, therapy, and assessment of response with identical pharmacokinetic profiles
- Potential production and separation using the same cyclotron, targets and separation chemistry

L. Schrevens et. al. The Role of PET Scan in Diagnosis, Staging, and Management of Non-Small Cell Lung Cancer. *The Oncologist*, 2004, vol. 9, no. 6, pgs 633-643
Langner, Jens.. MCS Thesis, University of Applied Sciences, Dresden, DE 2003
Farwell, M.D.; Pryma, D.A.; Mankoff, D.A. *Cancer*. 2014, vol. 120, no. 22, pgs 3433-3445
Simone II, C.B.; Hahn, S.M. *Clin Cancer Res*; 19(18), 2013

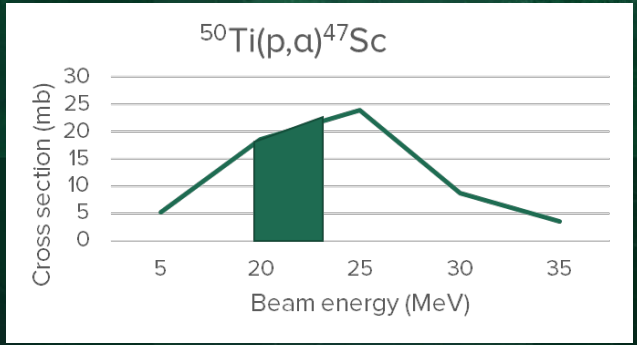
Nuclear Reactions on Titanium

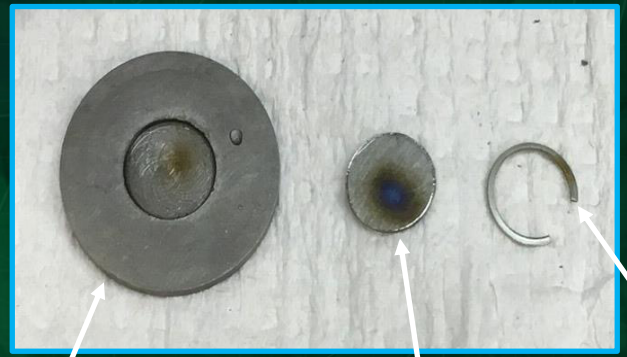


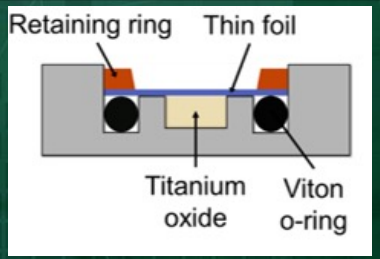
National Nuclear Data Center. Chart of the Nuclides. http://www.nndc.bnl.gov/chart/ (accessed 08/06/2018)

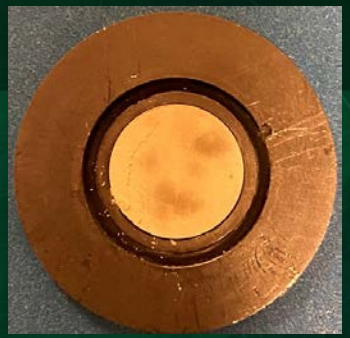
Targetry – natural and enriched Ti

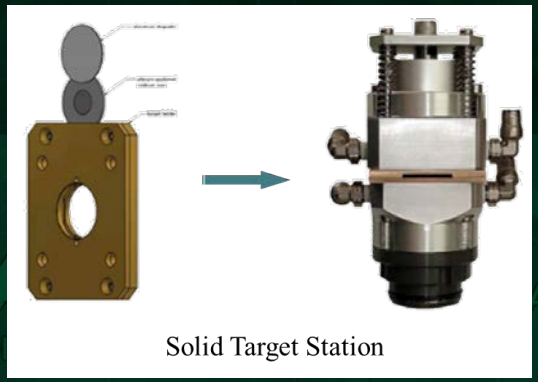
- **Irradiation: 24.0 MeV protons**
- **Ti foils or pressed TiO_2 power**



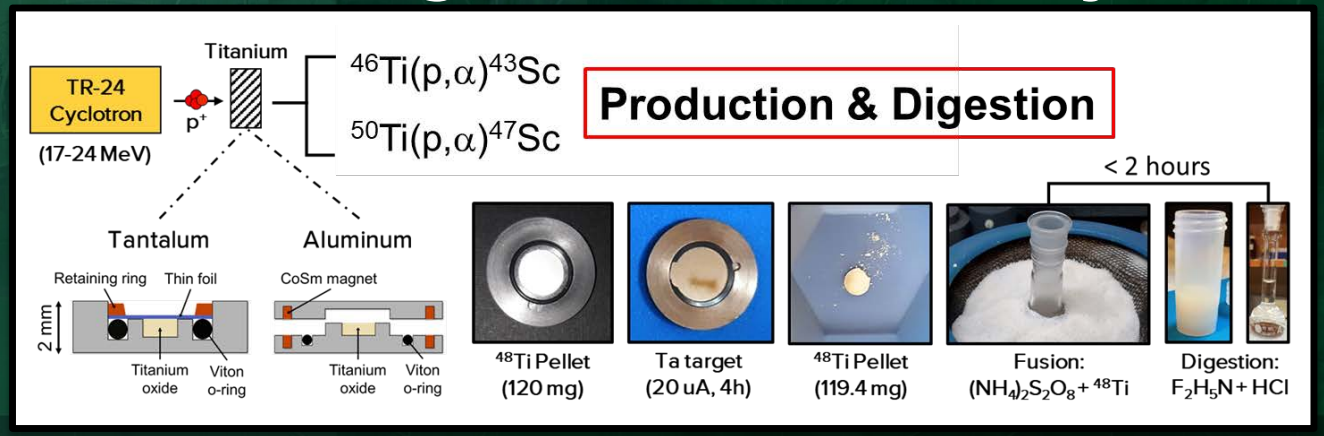


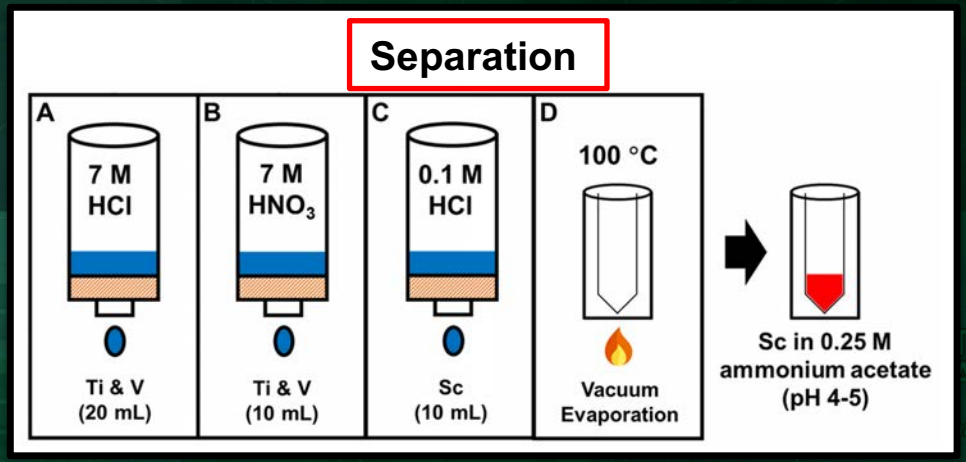






^{43}Sc and ^{47}Sc targets and chemistry

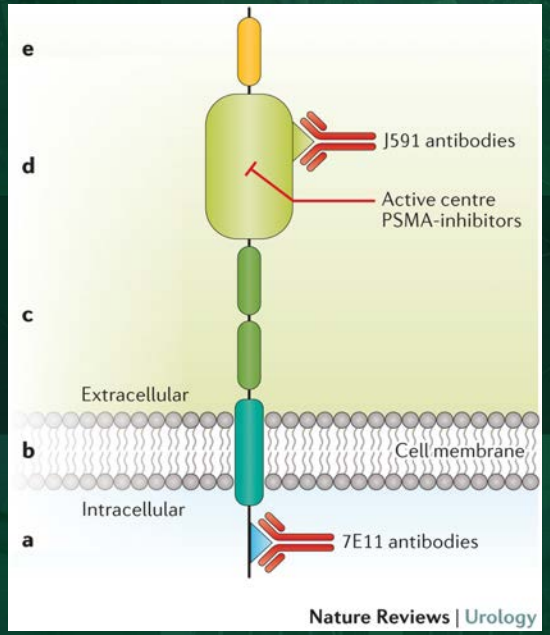


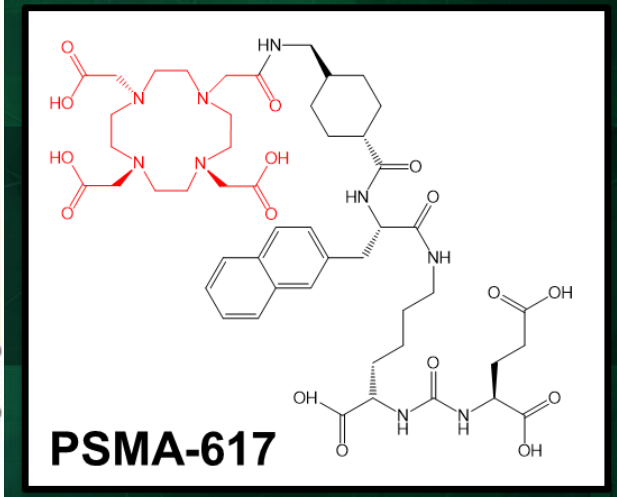


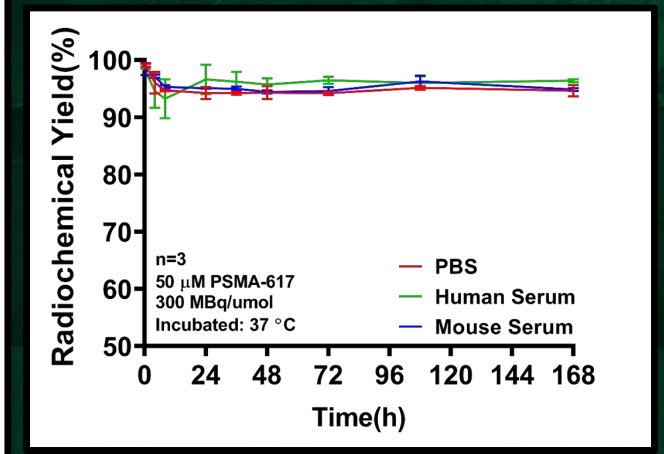
Loveless et al JNM 2020

Prostate Specific Membrane Antigen (PSMA)

Expression of prostate-specific membrane antigen (PSMA), a transmembrane protein is increased in prostate cancer.

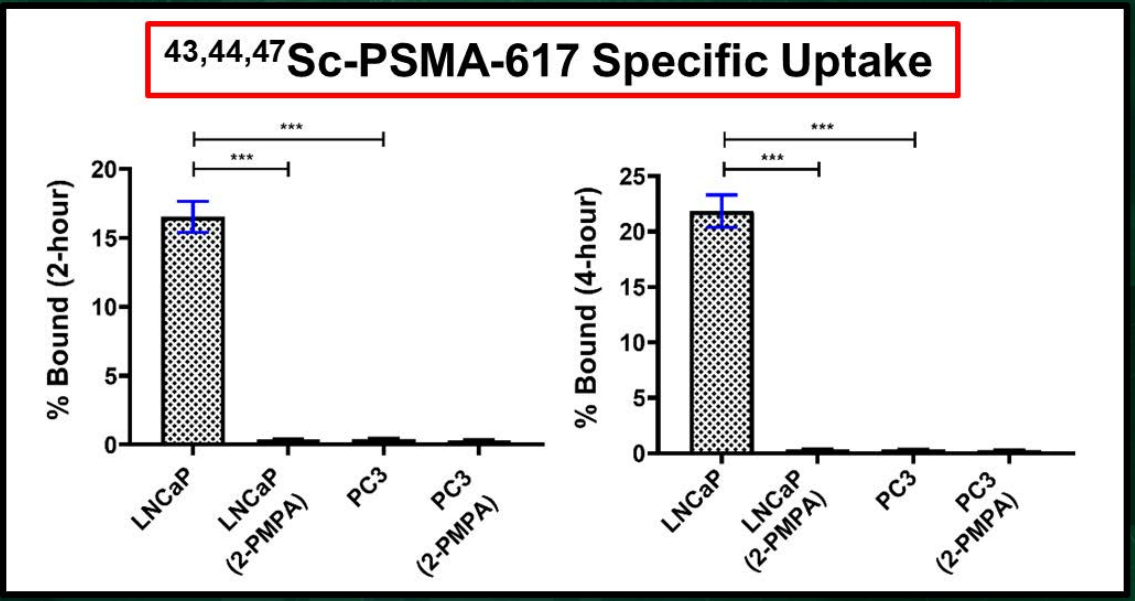


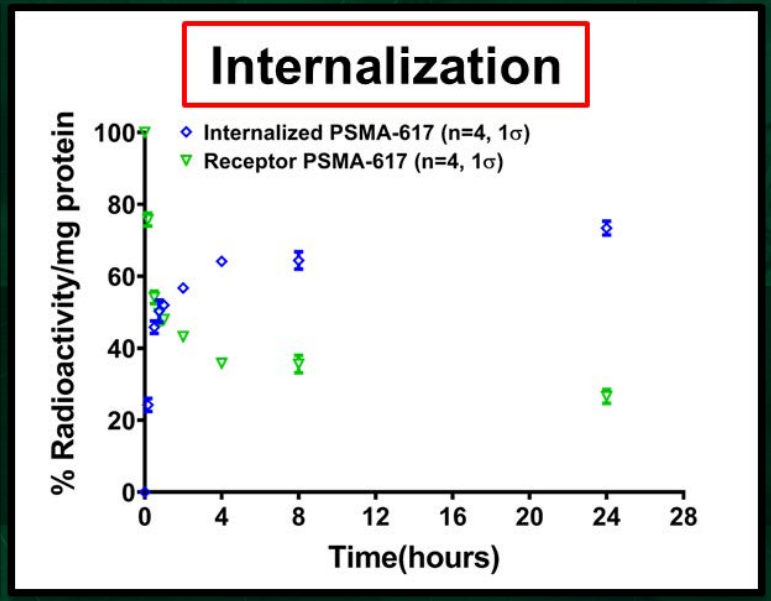




Maurer et al Nature Reviews Urology 13, 226–235 (2016)

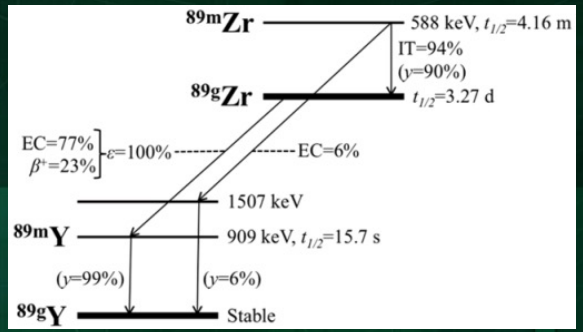
Preclinical Evaluation of [^{43,47}Sc]Sc-PSMA-617

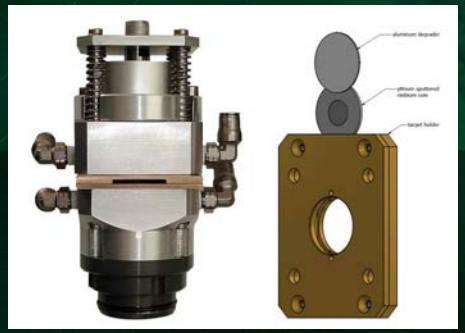




Zirconium-89

- Half-life of 3.27 d – well suited for study of pharmacokinetics of antibodies (achieve optimal biodistribution ~4-5 d)
- Scouting in preparation for antibody therapy, confirming tumor targeting, and estimating dosimetry
- Generally inert to biological systems
- Decay properties
  - EC = 76.6%
  - β^+ = 22.3%
  - $R_{ave.}(\beta^+)$= 1.18 mm

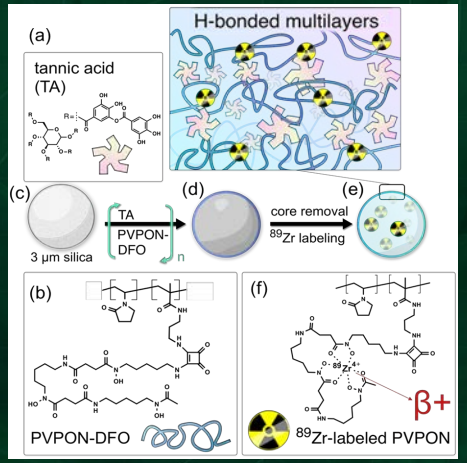


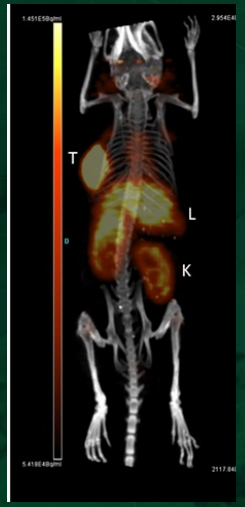


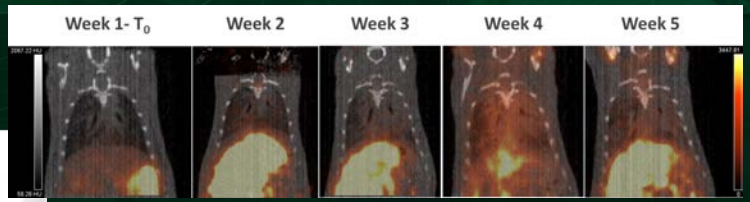
Queern et al Nuc Med Bio 201

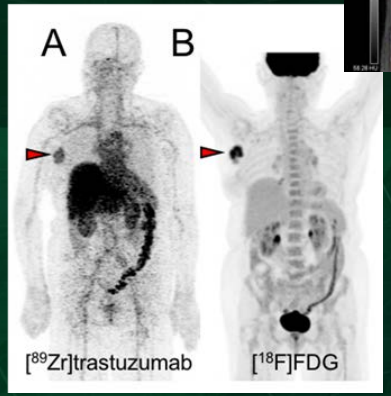
Ongoing work related to ^{89}Zr

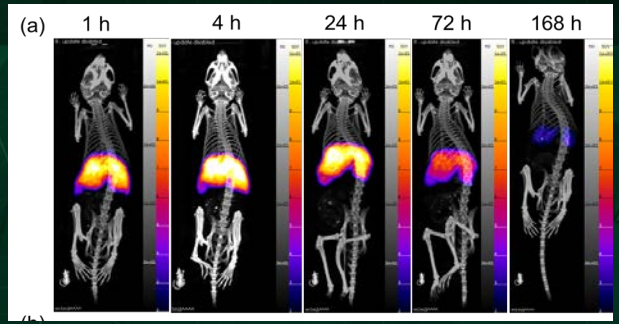
- Routine production via sputtered targets
- Internal use and shipping to external sites – nationally and internationally
- Preclinical radiochemistry – mAbs, nanoparticle and cell labeling
- Small animal imaging studies
- Preparation of GMP ^{89}Zr radiopharmaceuticals
- Early phase clinical trials:
- [^{89}Zr]Trastuzumab
- [^{89}Zr]Panitumumab











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Summary

- Radioisotopes continue to play an important role in medicine and other areas of science.
- A wide variety of half-lives, imaging characteristics and chemistries leads to a unique toolbox for the development of new nuclear medicine imaging and therapeutic agents.
- Development and increased use of these agents will require collaborations between chemists, biologists, physicists, physicians and technologists.
- We welcome new collaborations and visitors to our center (when possible).

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