From Isotopes to Images: Applications in Nuclear Medicine Part 2: Research and New Directions

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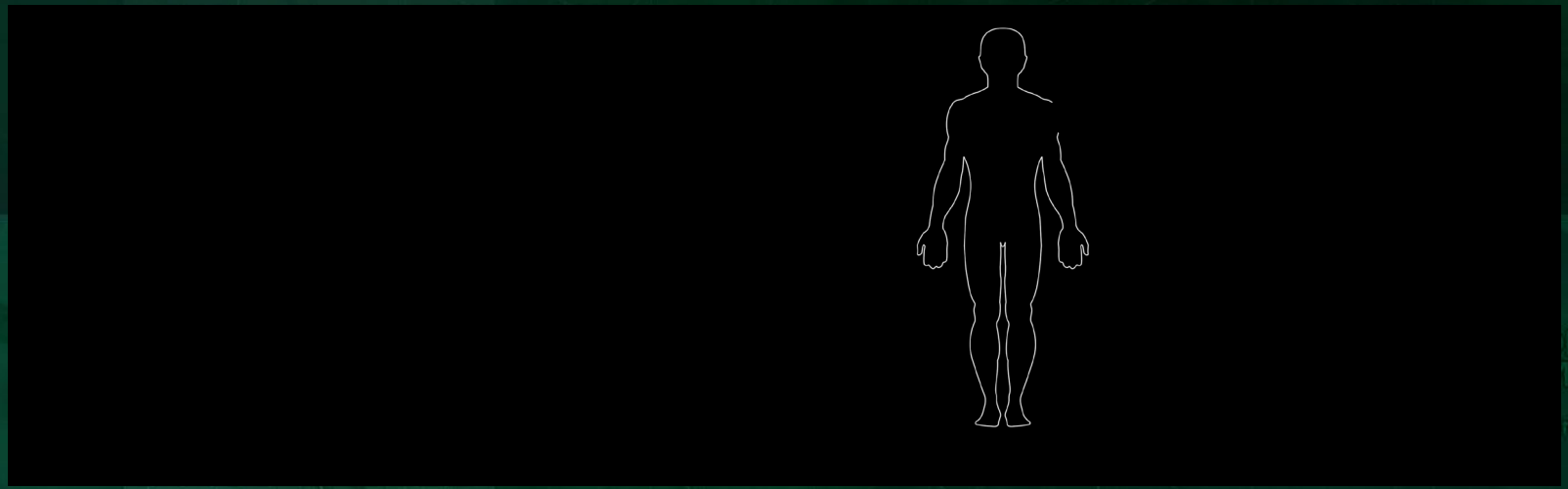
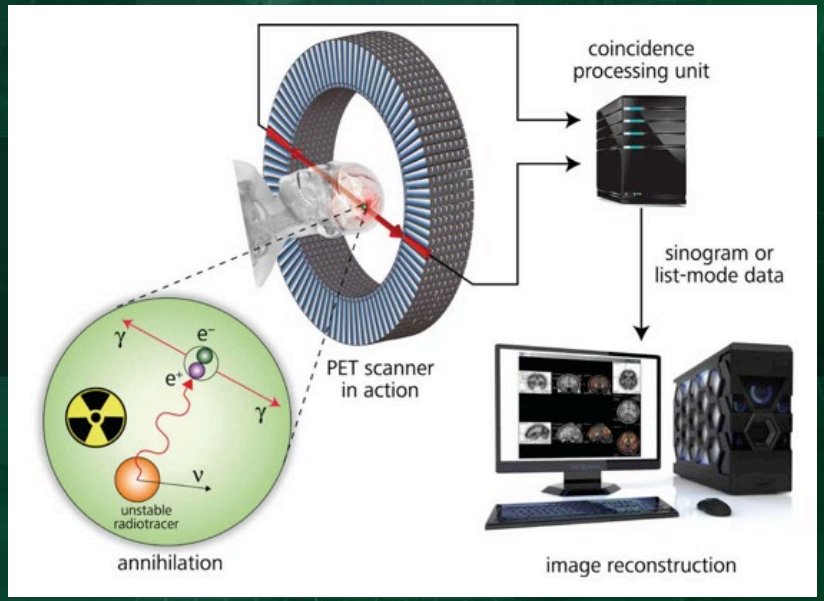
Radiopharmaceuticals

- Radiopharmaceutical: Targeting compound labeled with a radionuclide for imaging or therapy.
- Structure of the compound determines biological properties (targeting, clearance, receptor interactions).
- Radioactive label determine the imaging or therapeutic properties.

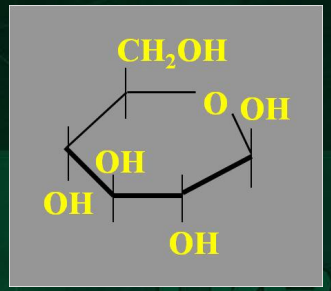


Positron Emission Tomography

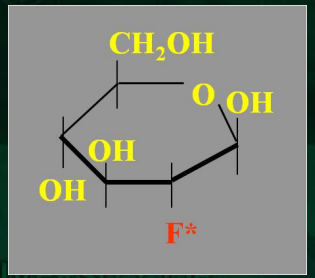
PET imaging is a very sensitive tool capable of providing quantitative information about biochemical and physiological processes in a non-invasive manner.



Glucose

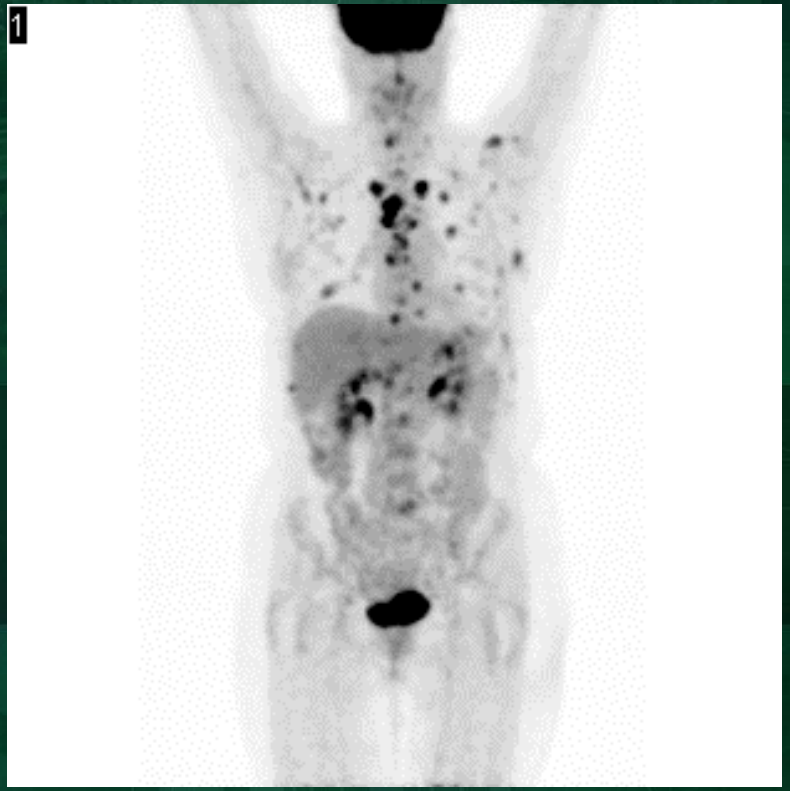


Fluorodeoxyglucose (FDG)

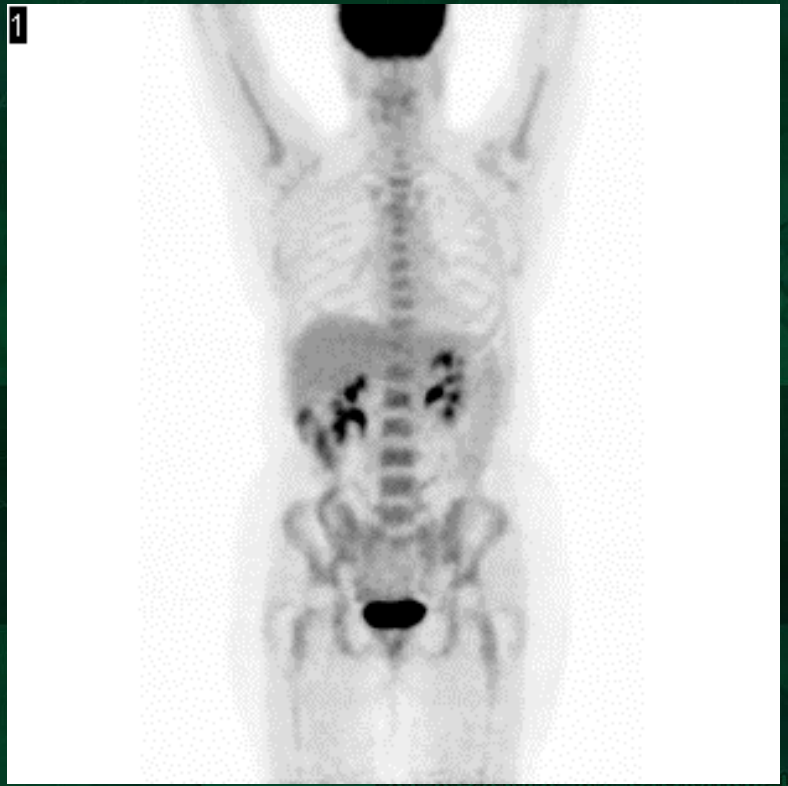


FDG:

59 year old woman with T-cell lymphoma



Initial study

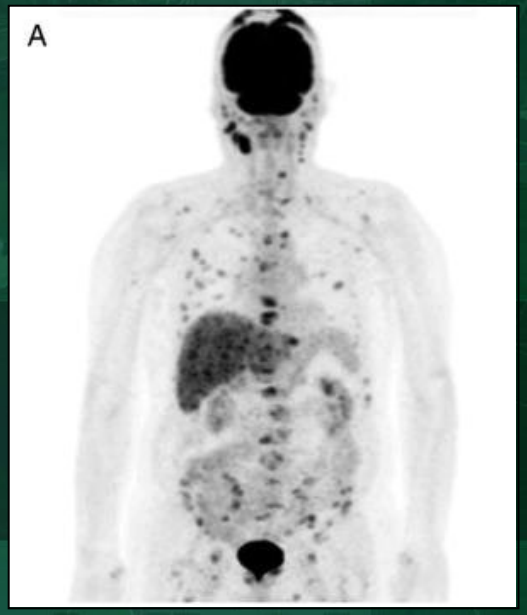


4 months later,
after chemotherapy

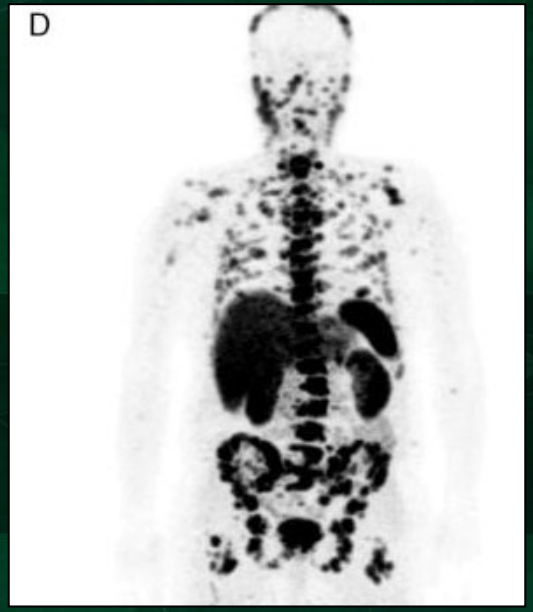
Why develop new imaging agents?

- Imaging more than detection of cancer.
- Imaging can provide more information:
  detection, **prediction of treatment response,** receptor status, oxygenation, microenvironment……

Different information can be obtained using different tracers



[^{18}F]FDG



[^{68}Ga]DOTATOC

Clinical Nuclear Medicine. 38(4):283-284, April 2013.

How to pick a radioisotope?

- Chemistry
- Half-life
- Decay Properties
- Availability
- Purity

“Standard” PET Isotopes

$^{14}N(p,\alpha)^{11}C$ $t_{½}$ = 20.3 min

$^{18}O(p,n)^{18}F$ $t_{½}$ = 109.7 min

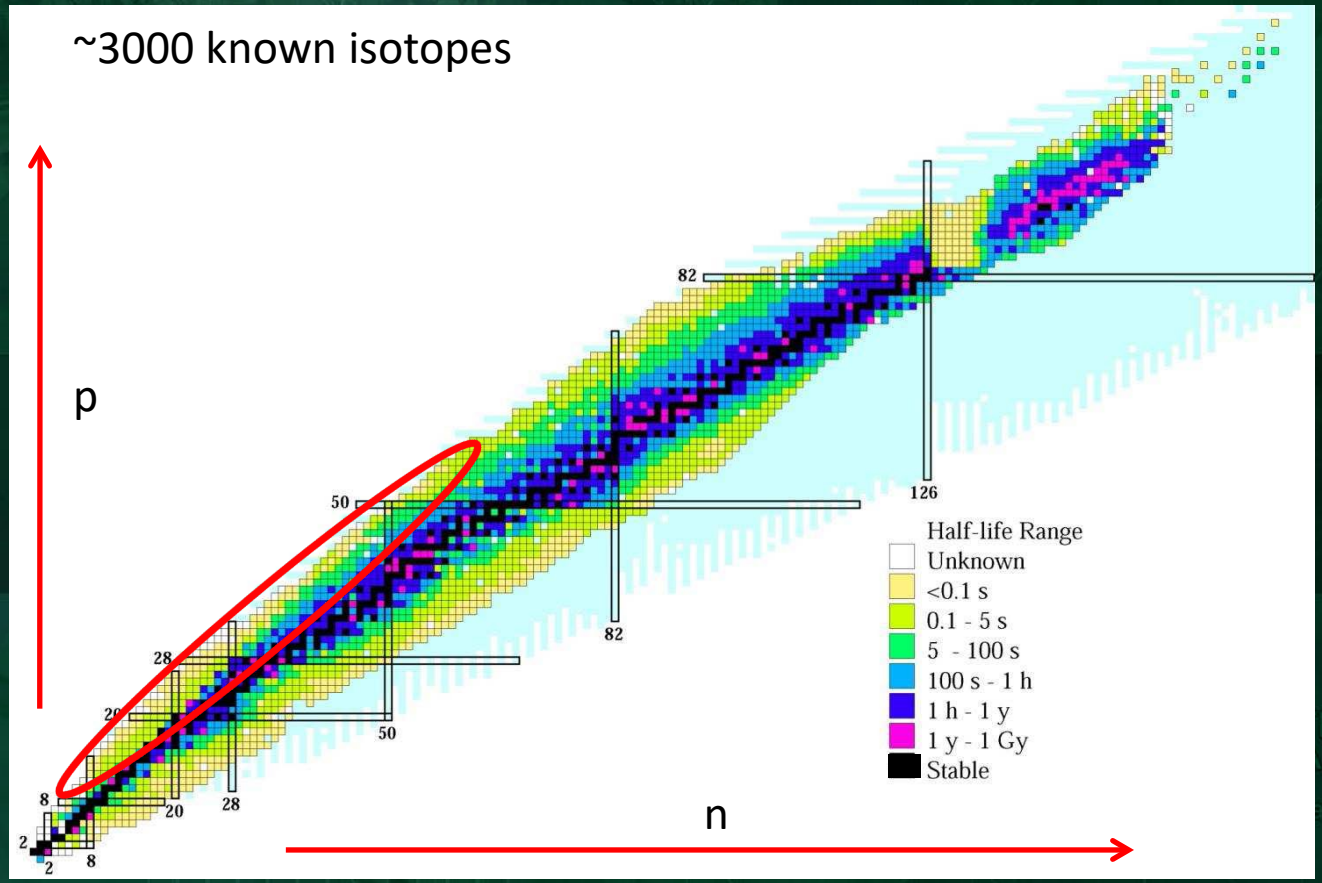
$^{16}O(p,\alpha)^{13}N$ $t_{½}$ = 9.97 min

$^{14}N(d,n)^{15}O$ $t_{½}$ = 2.0 min

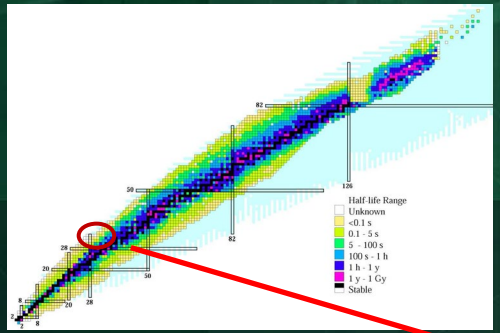
Radiometals

- Often have longer half-lives to probe longer biological processes.
- Variety of half-lives and decay characteristics available (can be used for imaging or therapy).
- Co-ordination chemistry varies, thus stable chelates are the key.

Toolbox: Chart of the Nuclides



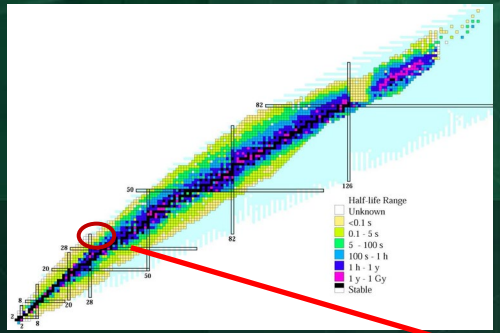
Radiometals?



First row:

Z							
	62Ga 116.12 MS ε: 100.00%	63Ga 32.4 S ε: 100.00%	64Ga 2.627 M ε: 100.00%	65Ga 15.2 M ε: 100.00%	66Ga 9.49 H ε: 100.00%	67Ga 3.2617 D ε: 100.00%	68Ga 67.71 M ε: 100.00%	69Ga STABLE 60.108%
30	61Zn 89.1 S ε: 100.00%	62Zn 9.186 H ε: 100.00%	63Zn 38.47 M ε: 100.00%	64Zn STABLE 48.63%	65Zn 243.66 D ε: 100.00%	66Zn STABLE 27.90%	67Zn STABLE 4.10%	68Zn STABLE 18.75%
29	60Cu 23.7 M ε: 100.00%	61Cu 3.333 H ε: 100.00%	62Cu 9.673 M ε: 100.00%	63Cu STABLE 69.17%	64Cu 12.701 H ε: 61.50% β-: 38.50%	65Cu STABLE 30.83%	66Cu 5.120 M β-: 100.00%	67Cu 61.83 H β-: 100.00%
28	59Ni 7.6E+4 Y ε: 100.00%	60Ni STABLE 26.223%	61Ni STABLE 1.140%	62Ni STABLE 3.634%	63Ni 100.1 Y β-: 100.00%	64Ni STABLE 0.926%	65Ni 2.5172 H β-: 100.00%	66Ni 54.6 H β-: 100.00%
27	58Co 70.86 D ε: 100.00%	59Co STABLE 100%	60Co 1925.28 D β-: 100.00%	61Co 1.650 H β-: 100.00%	62Co 1.50 M β-: 100.00%	63Co 27.4 S β-: 100.00%	64Co 0.30 S β-: 100.00%	65Co 1.20 S β-: 100.00%

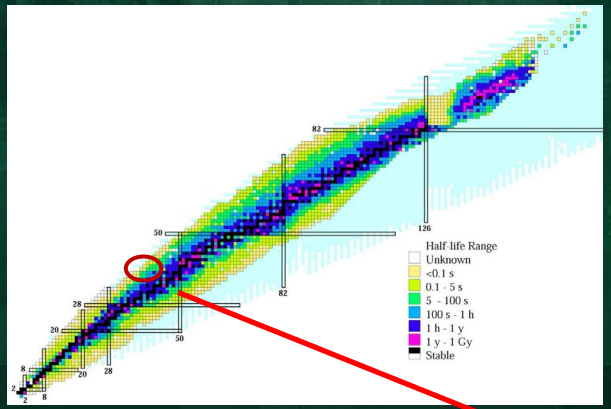
Radiometals?



First row:

Z	28	27	28	29	30	31	32
	54Ni 114.2 MS ε: 100.00%	55Ni 204.7 MS ε: 100.00%	56Ni 6.075 D ε: 100.00%	57Ni 35.60 H ε: 100.00%	58Ni STABLE 68.077%	59Ni 7.6E+4 Y ε: 100.00%	60Ni STABLE 26.223%
27	53Co 240 MS ε: 100.00%	54Co 193 MS ε: 100.00%	55Co 17.53 H ε: 100.00%	56Co 77.236 D ε: 100.00%	57Co 271.74 D ε: 100.00%	58Co 70.86 D ε: 100.00%	59Co STABLE 100%
26	52Fe 8.725 H ε: 100.00%	53Fe 8.51 M ε: 100.00%	54Fe STABLE 5.845%	55Fe 2.744 Y ε: 100.00%	56Fe STABLE 91.754%	57Fe STABLE 2.119%	58Fe STABLE 0.282%
25	51Mn 46.2 M ε: 100.00%	52Mn 5.591 D ε: 100.00%	53Mn 3.74E+6 Y ε: 100.00%	54Mn 312.20 D ε: 100.00% β-: 9.3E-5%	55Mn STABLE 100%	56Mn 2.5789 H β-: 100.00%	57Mn 85.4 S β-: 100.00%
24	50Cr >1.3E+18 Y 4.345% 2ε	51Cr 27.7025 D ε: 100.00%	52Cr STABLE 83.789%	53Cr STABLE 9.501%	54Cr STABLE 2.365%	55Cr 3.497 M β-: 100.00%	56Cr 5.94 M β-: 100.00%

Radiometals?



Second row:

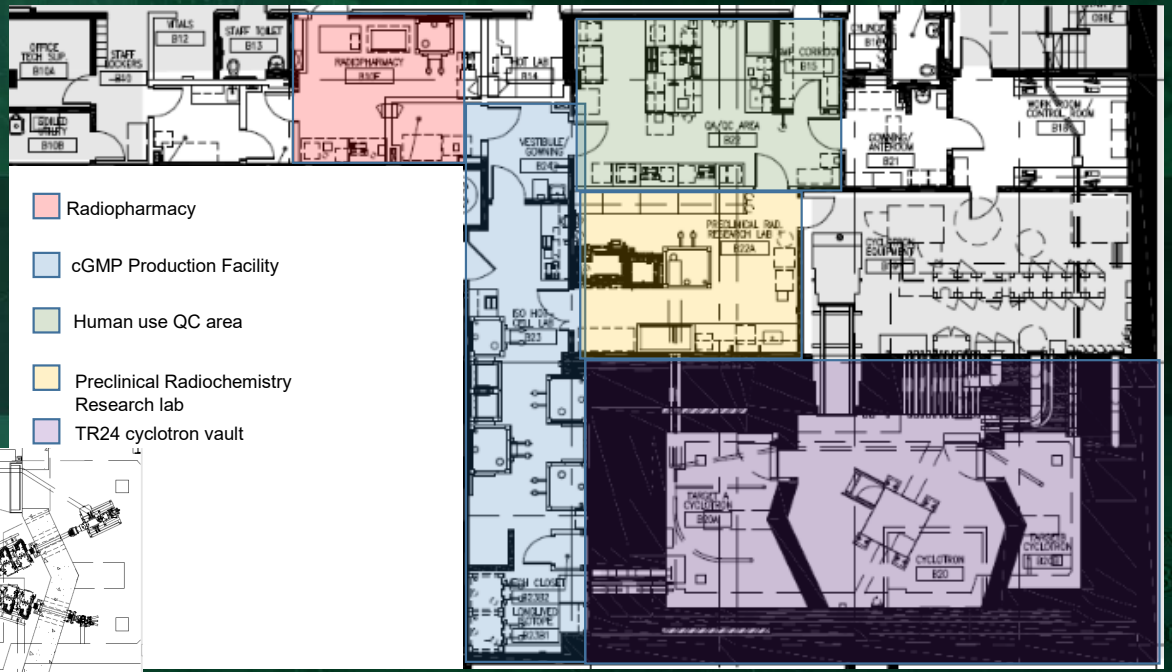
	45	46	47	48	49	50	51
41	86Nb 88 S ε: 100.00%	87Nb 3.75 M ε: 100.00%	88Nb 14.55 M ε: 100.00%	89Nb 2.03 H ε: 100.00%	90Nb 14.60 H ε: 100.00%	91Nb 6.8E+2 Y ε: 100.00%	92Nb 3.47E+7 Y ε: 100.00% β- < 0.05%
40	85Zr 7.86 M ε: 100.00%	86Zr 16.5 H ε: 100.00%	87Zr 1.68 H ε: 100.00%	88Zr 83.4 D ε: 100.00%	89Zr 78.41 H ε: 100.00%	90Zr STABLE 51.45%	91Zr STABLE 11.22%
39	84Y 4.6 S ε: 100.00%	85Y 2.68 H ε: 100.00%	86Y 14.74 H ε: 100.00%	87Y 79.8 H ε: 100.00%	88Y 106.626 D ε: 100.00%	89Y STABLE 100%	90Y 64.053 H β-: 100.00%
38	83Sr 32.41 H ε: 100.00%	84Sr STABLE 0.56%	85Sr 64.84 D ε: 100.00%	86Sr STABLE 9.86%	87Sr STABLE 7.00%	88Sr STABLE 82.58%	89Sr 50.53 D β-: 100.00%

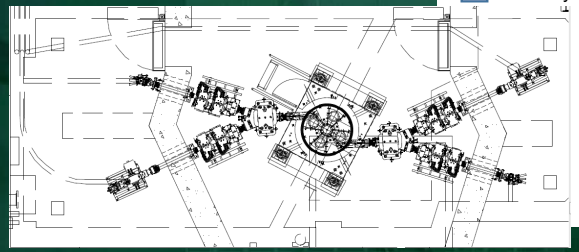
The UAB Cyclotron Facility
Current Production and Research Activities

- Isotope production and separation chemistry
- Radiochemistry for new imaging agents
- Characterization of new radiopharmaceuticals
- Translation into clinical trials
- Support of ongoing existing clinical trials

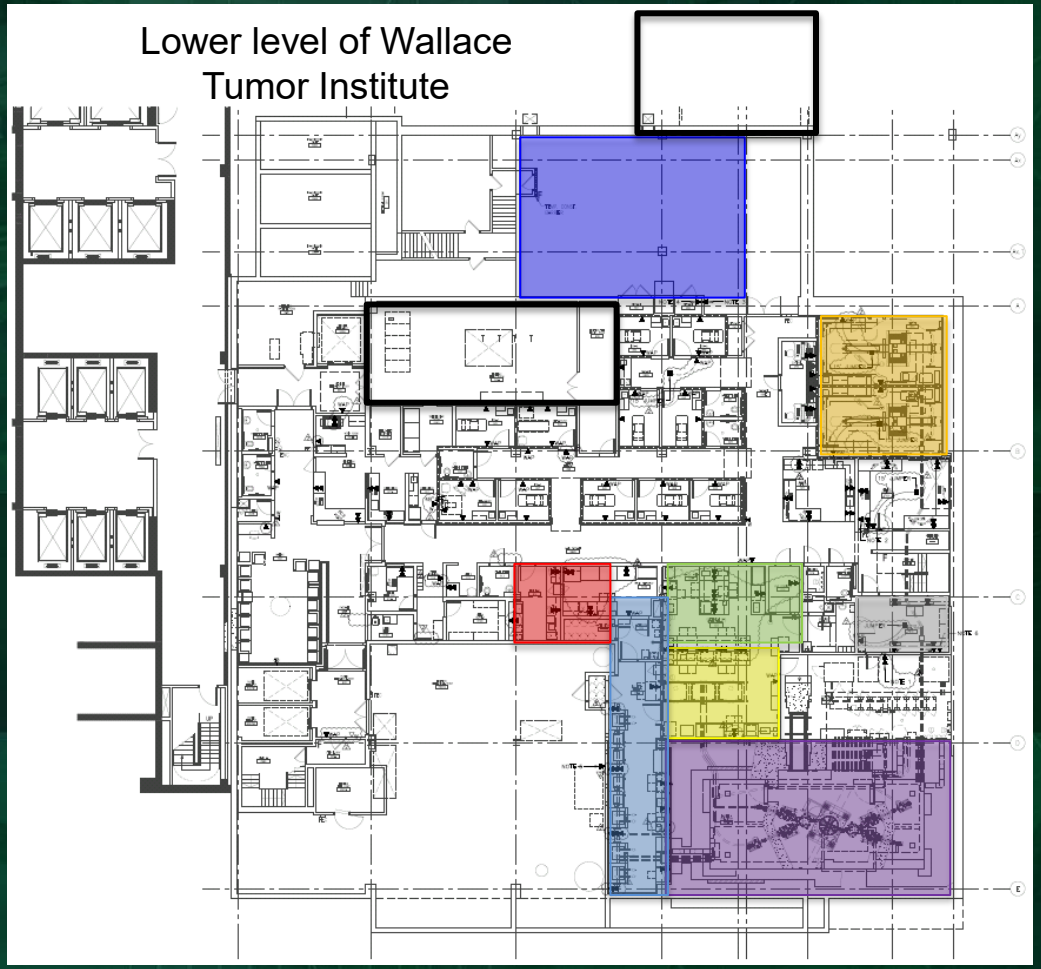
UAB Cyclotron Facility

The UAB Cyclotron Facility enables a broad scope of research and cutting-edge patient care through initiatives ranging from novel isotope production to developing and supplying state-of-the-art molecular imaging agents for clinical trials and routine patient care.





UAB Cyclotron and Advanced Imaging Facilities



- GE Signa 3-T PET/MRI
- Two GE 710 TOF PET/CTs
- Shell space

- Cyclotron control room
- TR-24 cyclotron
- Preclinical radiochemistry
- Human use QC
- cGMP production
- Radiopharmacy

GMP Space

- 6 minicells
- 4 large hotcells
- 6 chemistry modue
- Shielded laminar flow hood
- Dose drawing area

Clinical QC Area

- 2 RadioHPLC
- 2 GCs (residual solvents)
- 2 TLCs
- Additional equipment for sterility testing etc

Research Space (adjacent to facility, non-GMP)

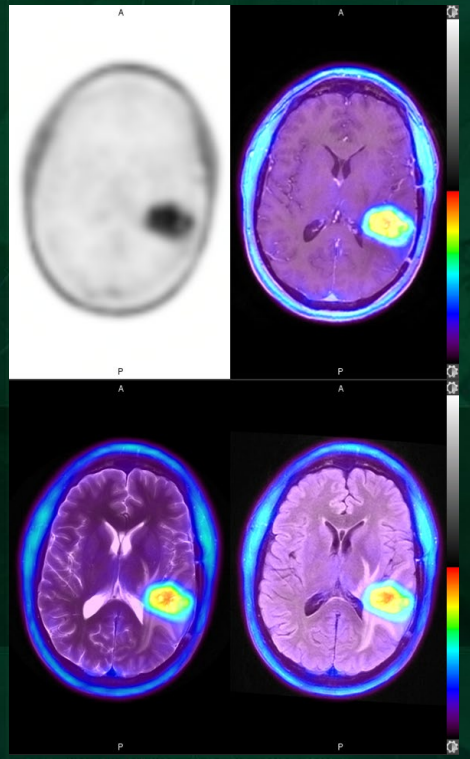
- 4 minicells with acid resistant coating
- 1 large hotcell
- Shielded fume hood
- Analytical equipment

Additional Research Space (3rd and 6th floor WTI and 1st floor LHL)

- 2 minicells , 1 large hotcell
- 4 shielded fumehoods
- Fumehoods for organic chemistry
- Analytical equipment (HPLC, TLC, QTOP, ICP-MS)
- Cell culture and animal imaging facilities

UAB Cyclotron Facility Research Achievements

- **First patient scanned with an imaging agent produced at the UAB cyclotron facility**
  - **January 5th, 2016**
- Renovation to enhance research space and ensure compliance with FDA regulations is complete
- Isotopes produced to date:
  - ^{18}F, ^{11}C, ^{15}O, ^{13}N, ^{89}Zr, ^{52}Mn, ^{55}Co, ^{64}Cu, ^{44}Sc, ^{48}V, ^{45}Ti
- Auxiliary chemistry equipment
  - ICP-MS and QTOF



[^{18}F]FLT PET/MRI of a Glioblastoma patient
UAB Cyclotron and Advanced Imaging Facilities

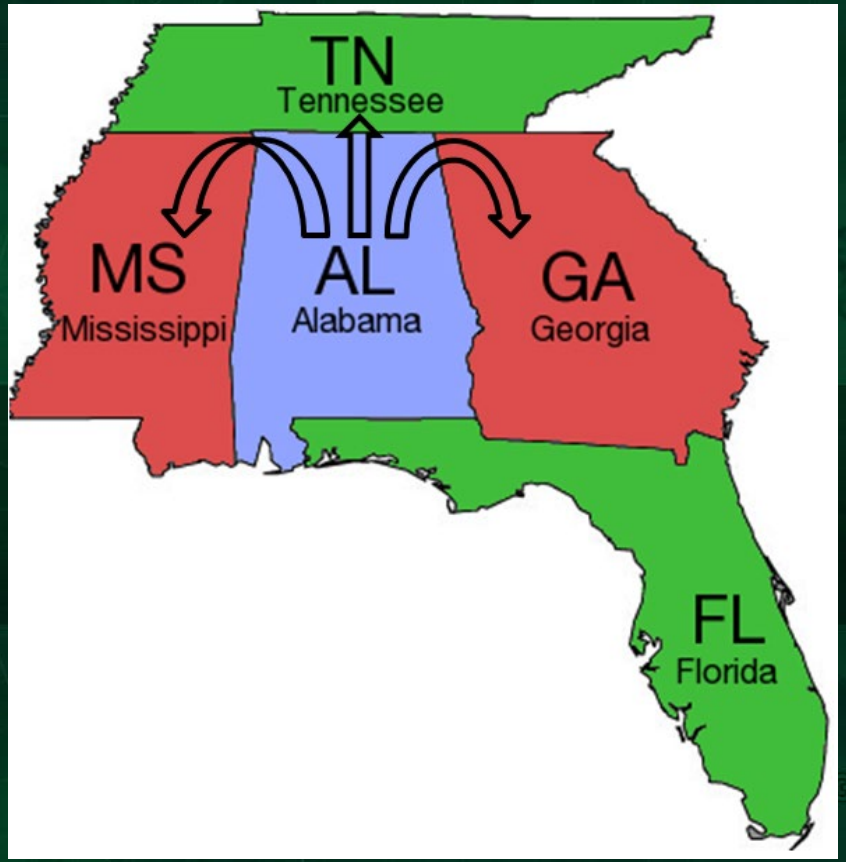
UAB Cyclotron Facility: Status of Radiotracers for Human Use

Radiopharmaceutical	Use	Status
[^{18}F]FPEB	mGluR5	IND approved
[^{18}F]FLT	Proliferation	IND approved
[^{13}N]NH_3	Cardiac blood flow	IND approved
[^{68}Ga]DOTATATE	SSTR status	FDA approved
[^{18}F]THK5351	Tau	IND approved
[^{18}F]FMISO	Hypoxia	IND submitted
[^{89}Zr]Trastuzumab	HER2 status (breast cancer)	IRB submitted
[^{68}Ga]PSMA-11	PSMA status (prostate cancer)	IRB in progress
[^{18}F]FET	Amino acid transport	Chemistry initiated
[^{11}C]PiB	Amyloid	Chemistry initiated
[^{18}F]DPA-714	TSPO	Chemistry initiated

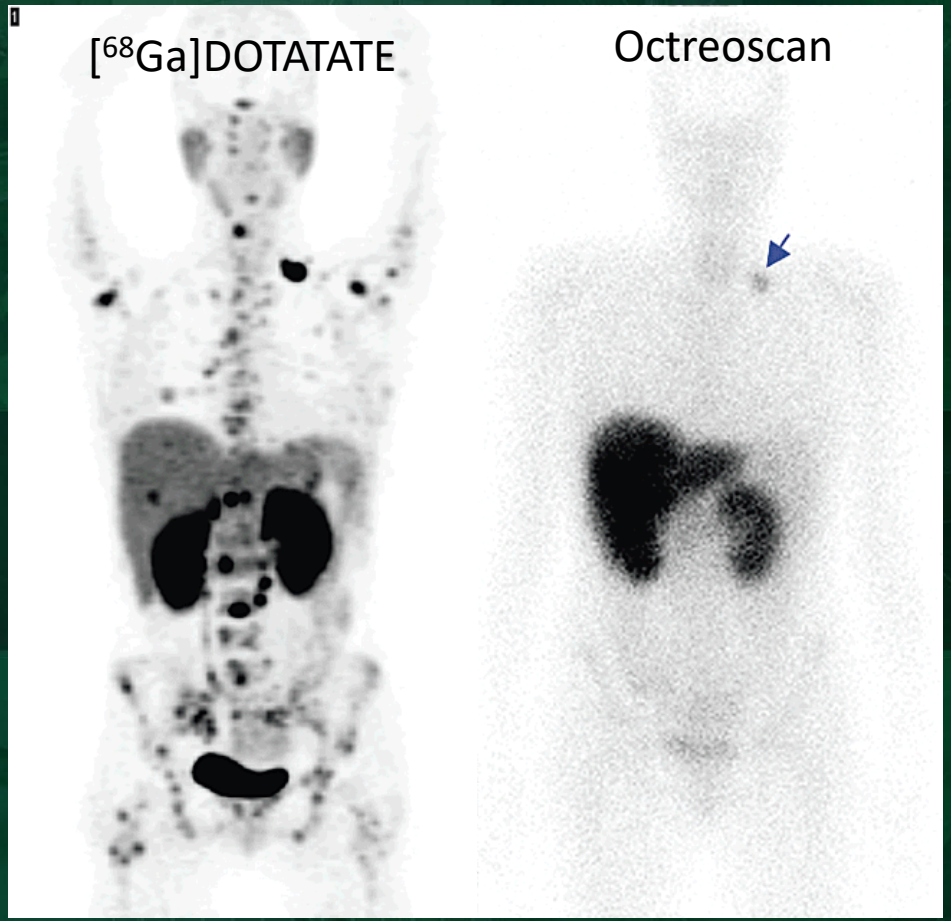
UAB Cyclotron Facility: Southeast Center and Nationwide supply

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, ^{52}Mn, ^{64}Cu and other isotopes to other research facilities throughout the country and potentially internationally.



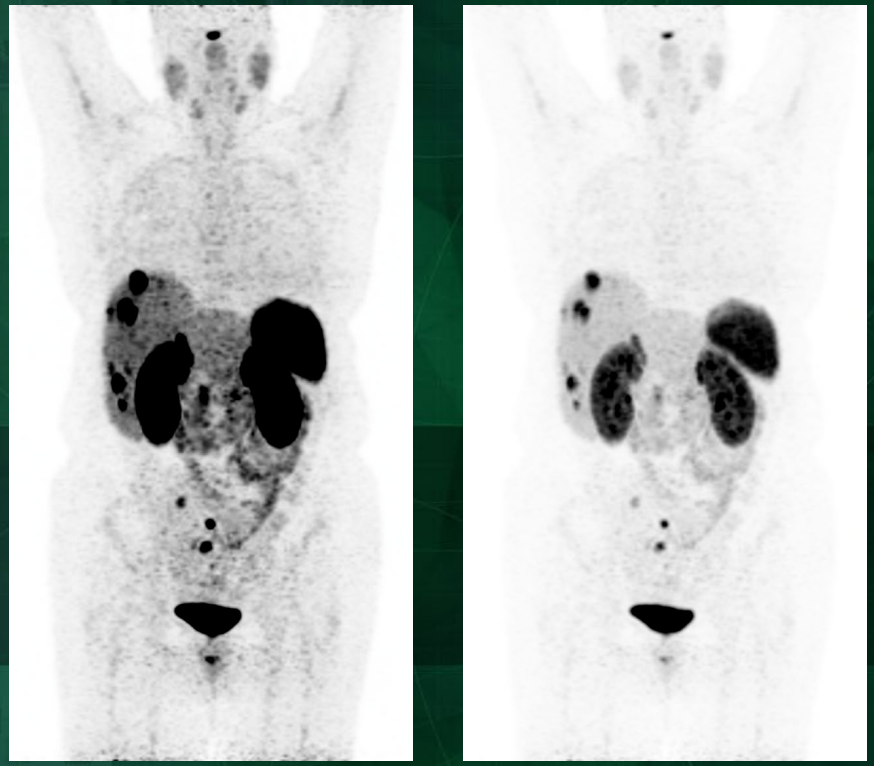
UAB Cyclotron Facility : NetSpot ([^{68}Ga]DOTATATE)



Scans at UAB started June 2017

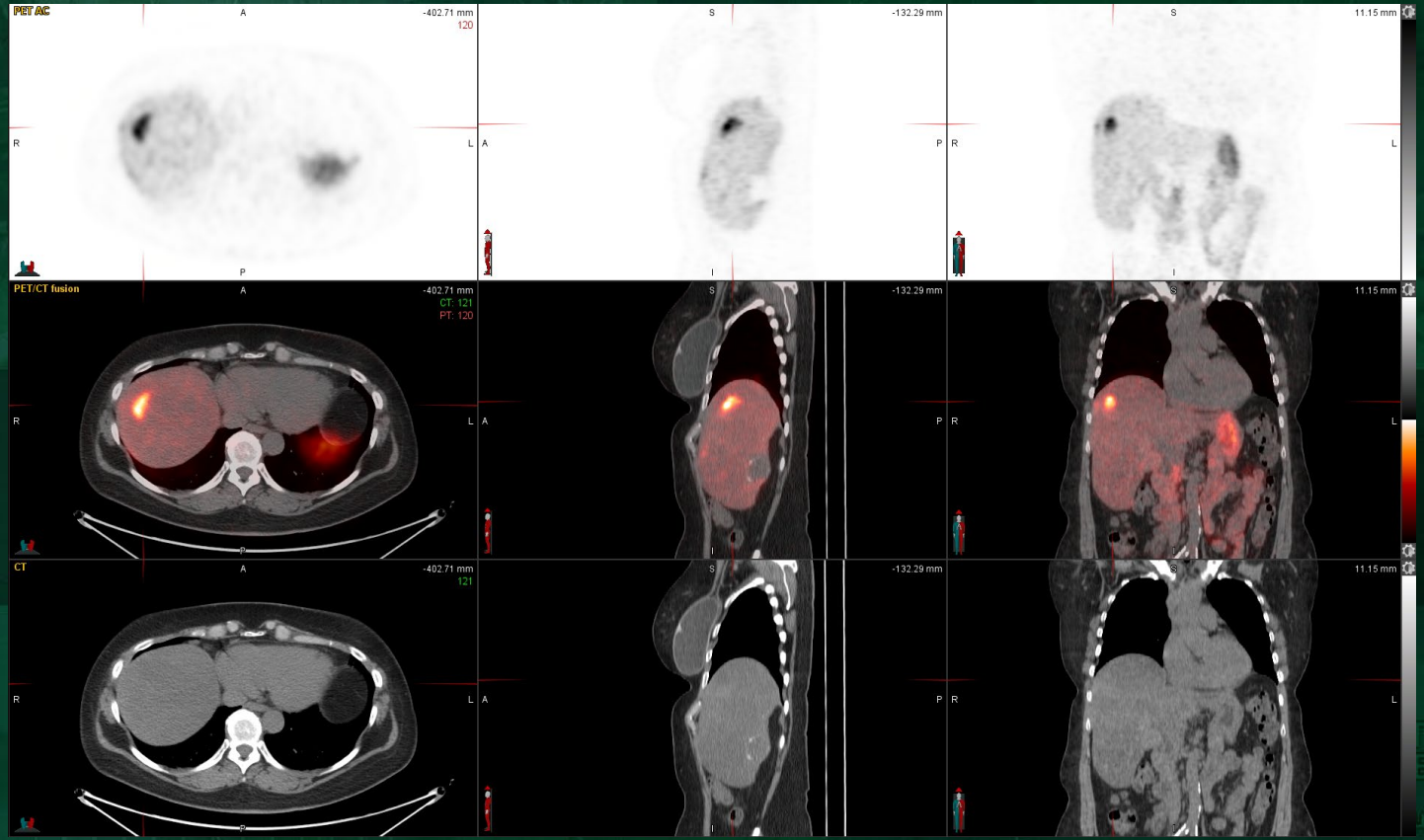
Journal of Medical Imaging and Radiation Oncology
Volume 56, Issue 1, pages 40-47, 17 2012

UAB Cyclotron Facility : NetSpot ([^{68}Ga]DOTATATE)



59 year old woman with metastatic neuroendocrine tumors arising from the small bowel
She is being treated with Sandostatin for carcinoid syndrome
She has undergone multiple transarterial hepatic chemoembolization (TACE) procedures

UAB Cyclotron Facility : NetSpot ([^{68}Ga]DOTATATE)



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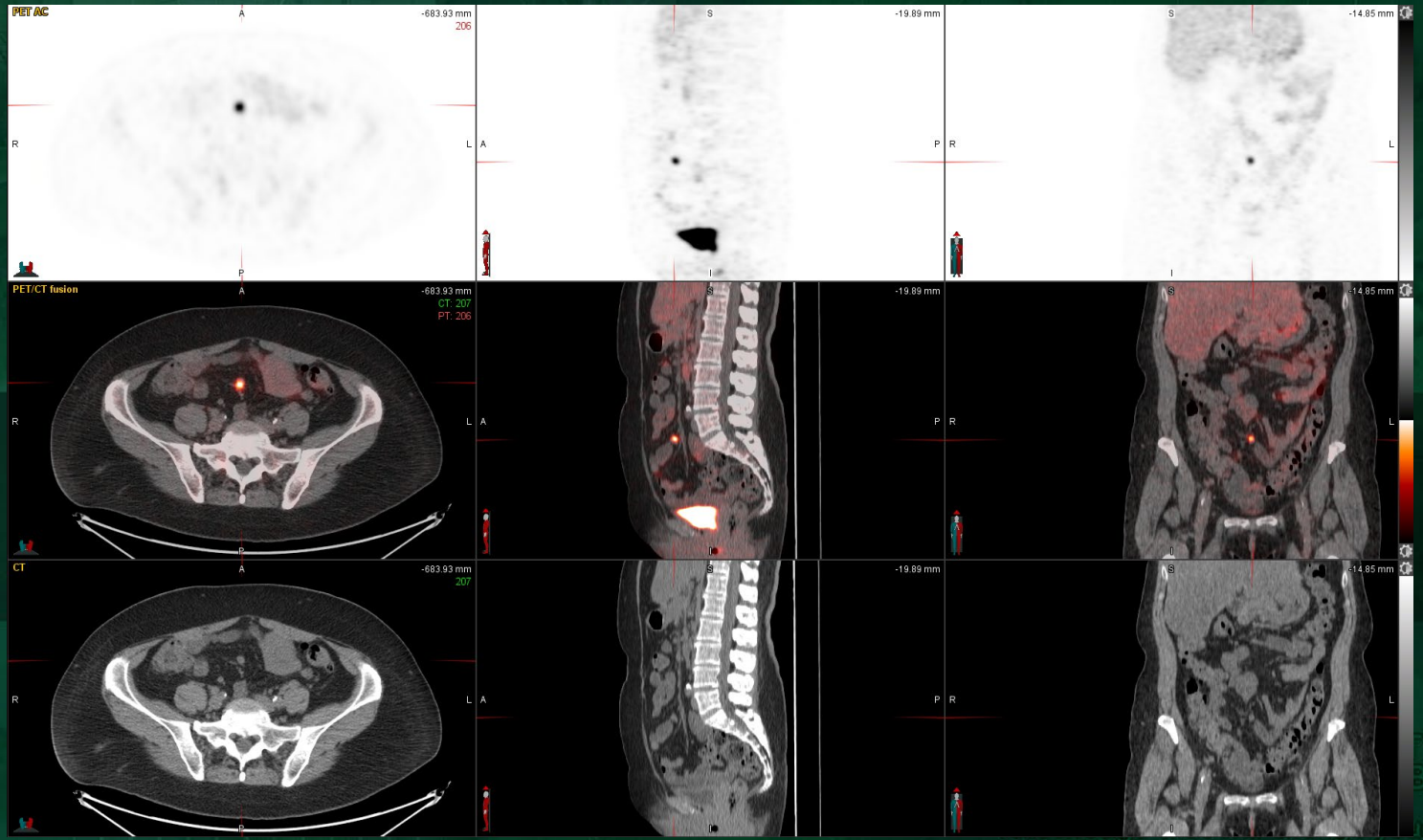
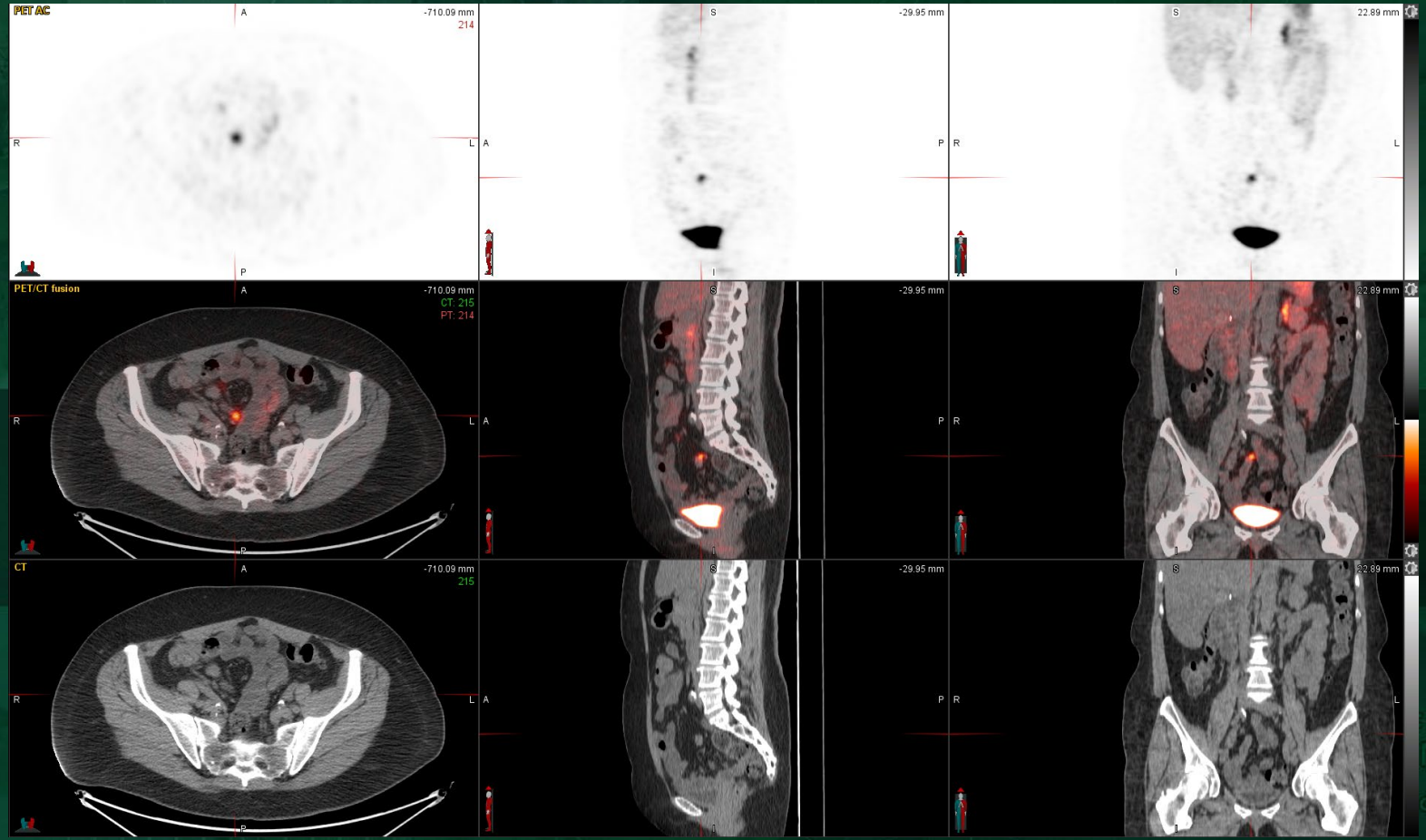
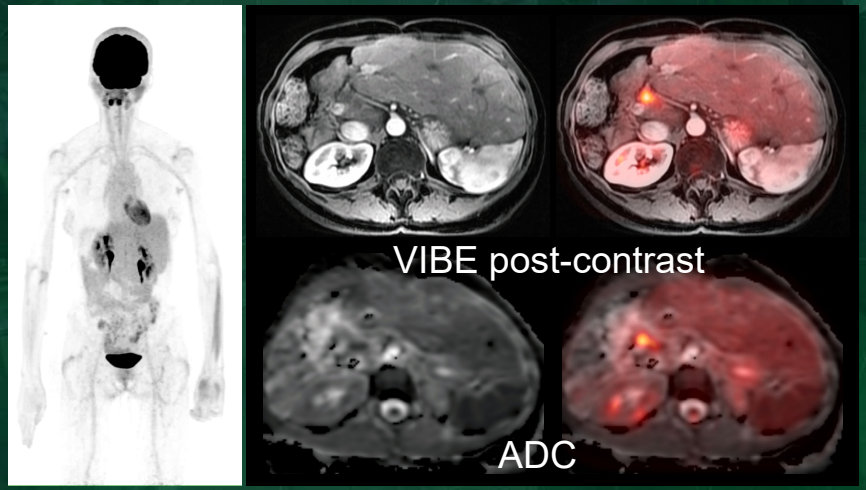


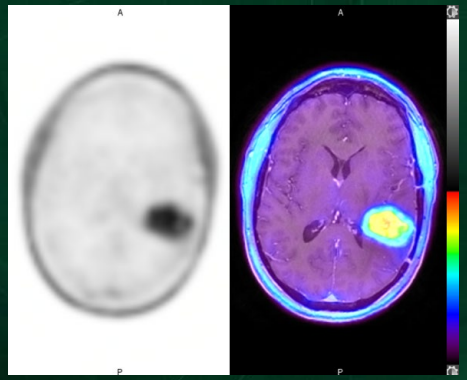
UAB Cyclotron Facility : NetSpot ([^{68}Ga]DOTATATE)



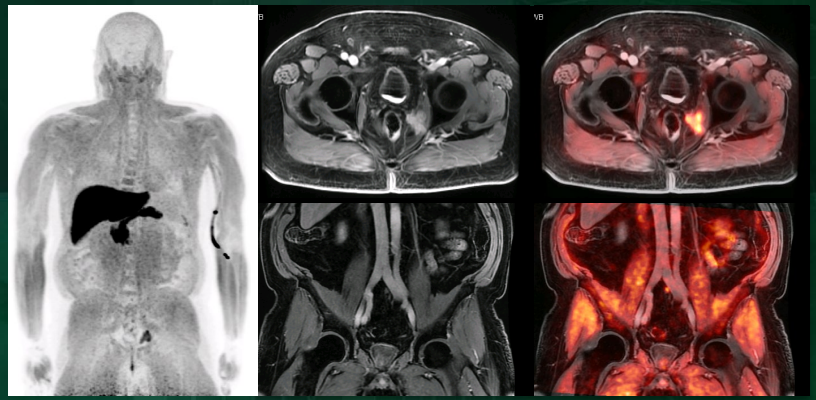
UAB Cyclotron Facility : $[^{13}N]NH_3$



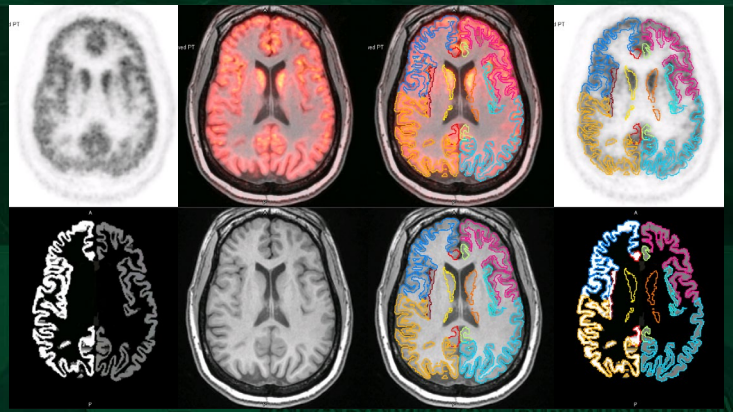
Clinical FDG-PET/MRI for recurrent cholangiocarcinoma



[^{18}F]FLT-PET in a patient
with recurrent glioblastoma



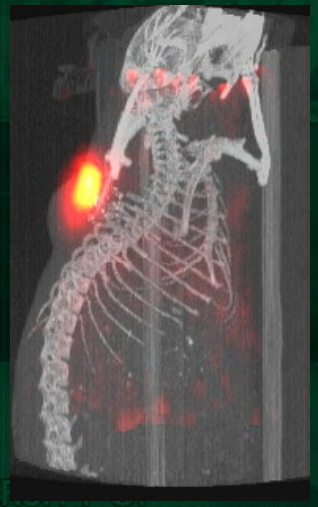
Clinical fluciclovine-PET/MRI for recurrent prostate cancer



FPEB-PET for mGluR5
with auto-segmentation

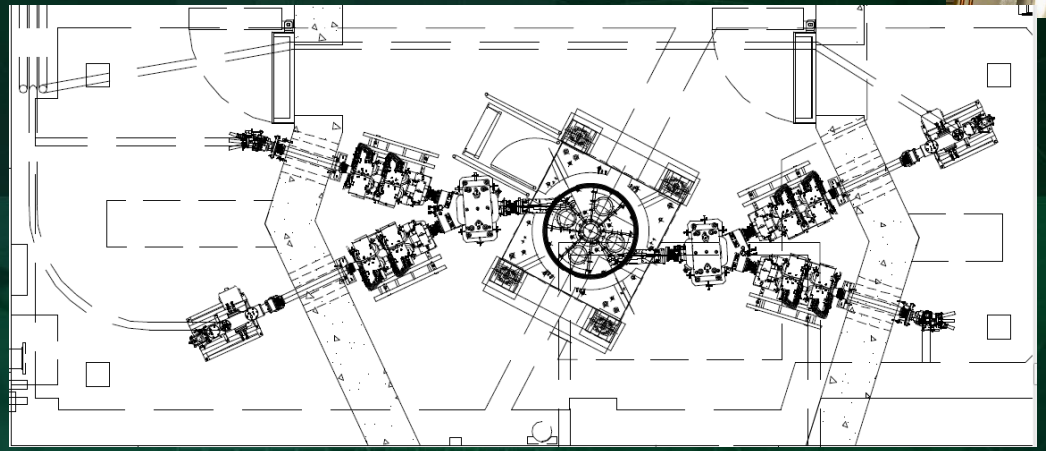
UAB Cyclotron Facility Highlights: Preclinical Imaging

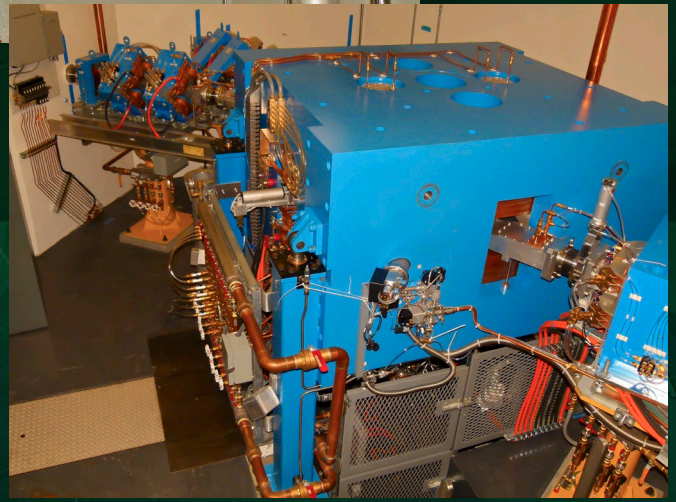
- ^{18}F agents for oncology imaging
  - Preclinical PET Imaging of a Breast Cancer Selective Phosphodiesterase (PDE10A) as a Means to Monitor Anticancer Drug Response
- ^{18}F amino acids for neuro-oncology imaging
  - PET Tumor and Proliferation Imaging via Cationic Amino Acid Transport
  - [^{18}F]MeFAMP for oncologic imaging via system A amino acid transport
- ^{89}Zr, ^{55}Co and ^{52}Mn agents for lung and oncology imaging
  - Lung fibrosis imaging
  - PSMA imaging in prostate cancer
  - Imaging of LAT1 in prostate cancer
  - Development of targeted radiolabeled antibodies for ablation therapy



The UAB TR24 Cyclotron

TR 24
Advanced Cyclotron Systems, Inc. (ACSI)
15-24 MeV protons; variable energy
300 µA (total)
2 extraction ports
Solid, liquid, and gas targets
4 beamlines



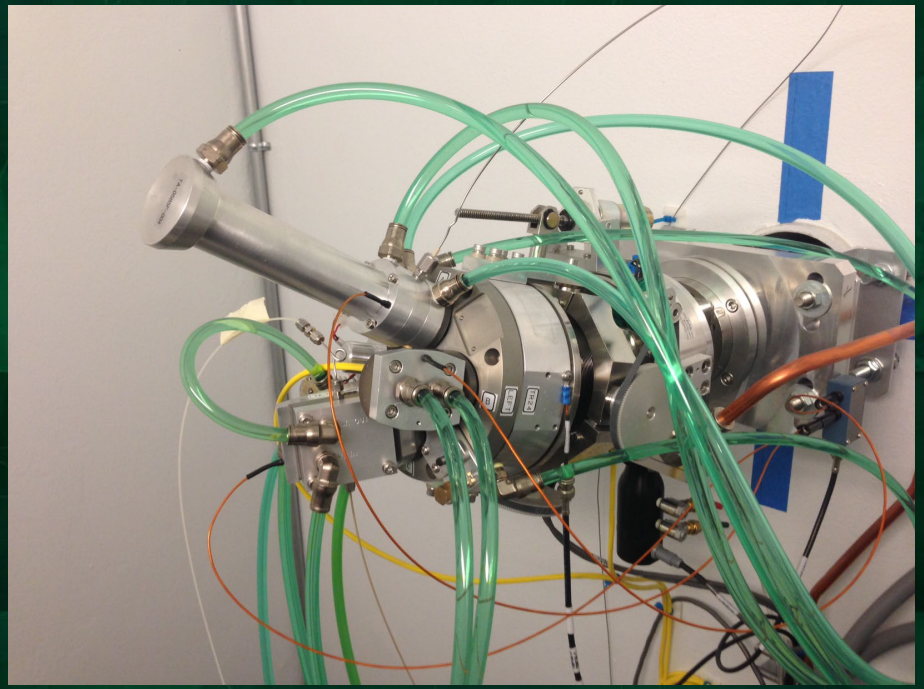


UAB Cyclotron Facility: Radioisotopes (beyond ^{18}F, ^{11}C, ^{13}N, ^{15}O)

Isotope	Half-Life	Target Material	Status
^{44}Sc	3.9 h	^{Nat}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	Production ramping up
$^{76,77}Br$	14.7 h	$^{76.77}Se$ (Kr)	Targets in design phase
^{89}Zr	3.27 d	^{89}Y	Routine production for preclinical and soon to be human use

The UAB TR24 Cyclotron

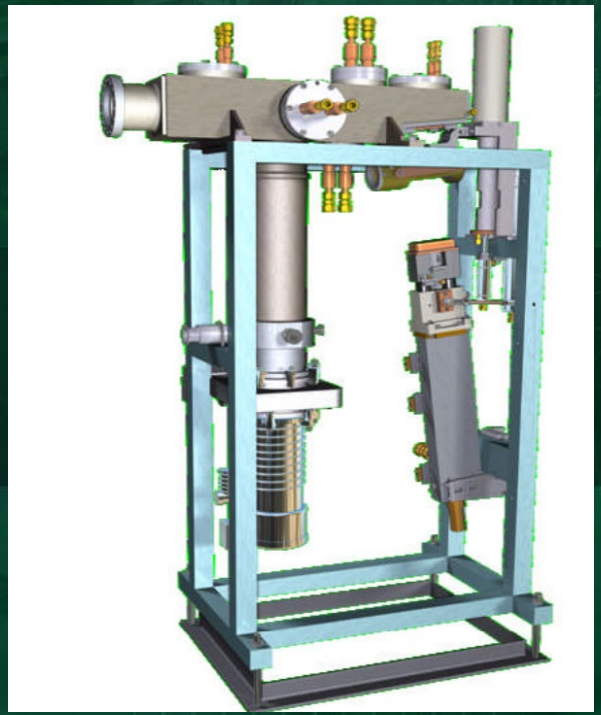
TR 24
Advanced Cyclotron Systems, Inc. (ACSI)
15-24 MeV protons; variable energy
300 µA (total)
2 extraction ports
Solid, liquid, and gas targets
4 beamlines



THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Knowledge that will change your world

Targetry systems (ACSI)
High power station (~300 µA)



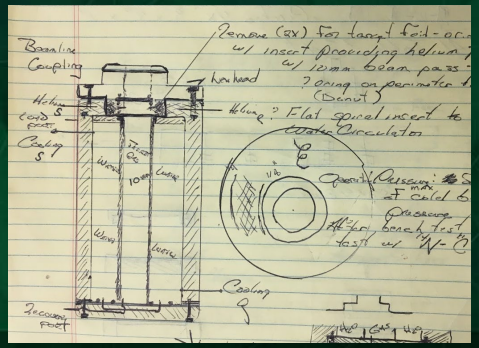
Targetry Systems
In House Design and Construction

- Collaborative engineering and machining in house
- Brainstorming and student involvement
- Collaborations with other institutions – PSI, Bern, Wisc, Penn

H. Doane

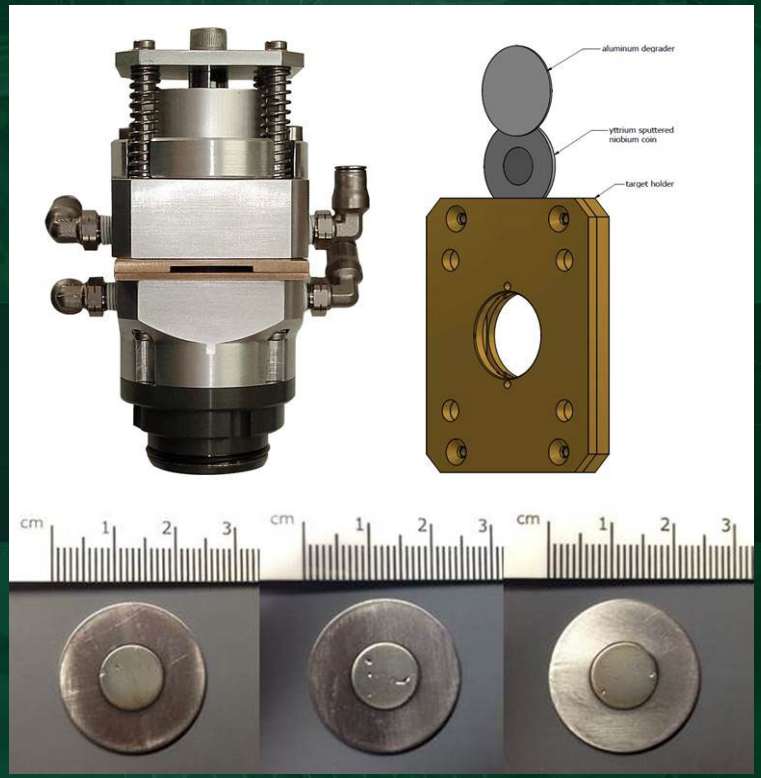
S. Ferran

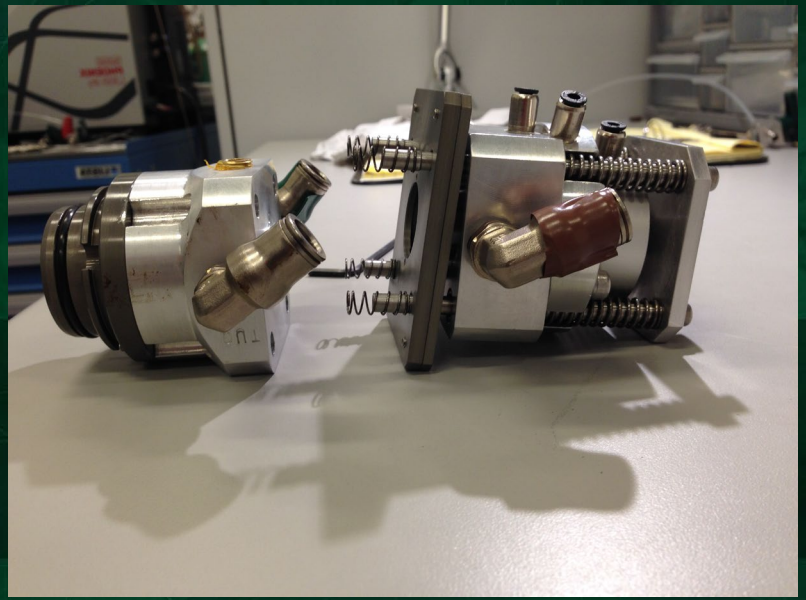
C.S. Loveless



D. Long
(UAB Machine Shop)

Targetry systems (ACSI)





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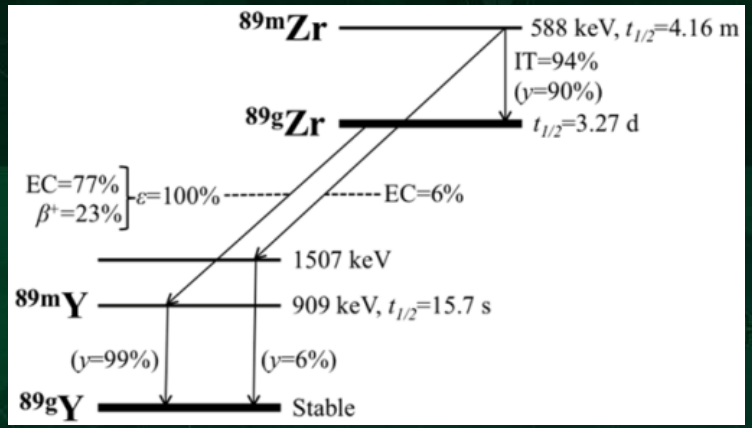
Knowledge that will change your world

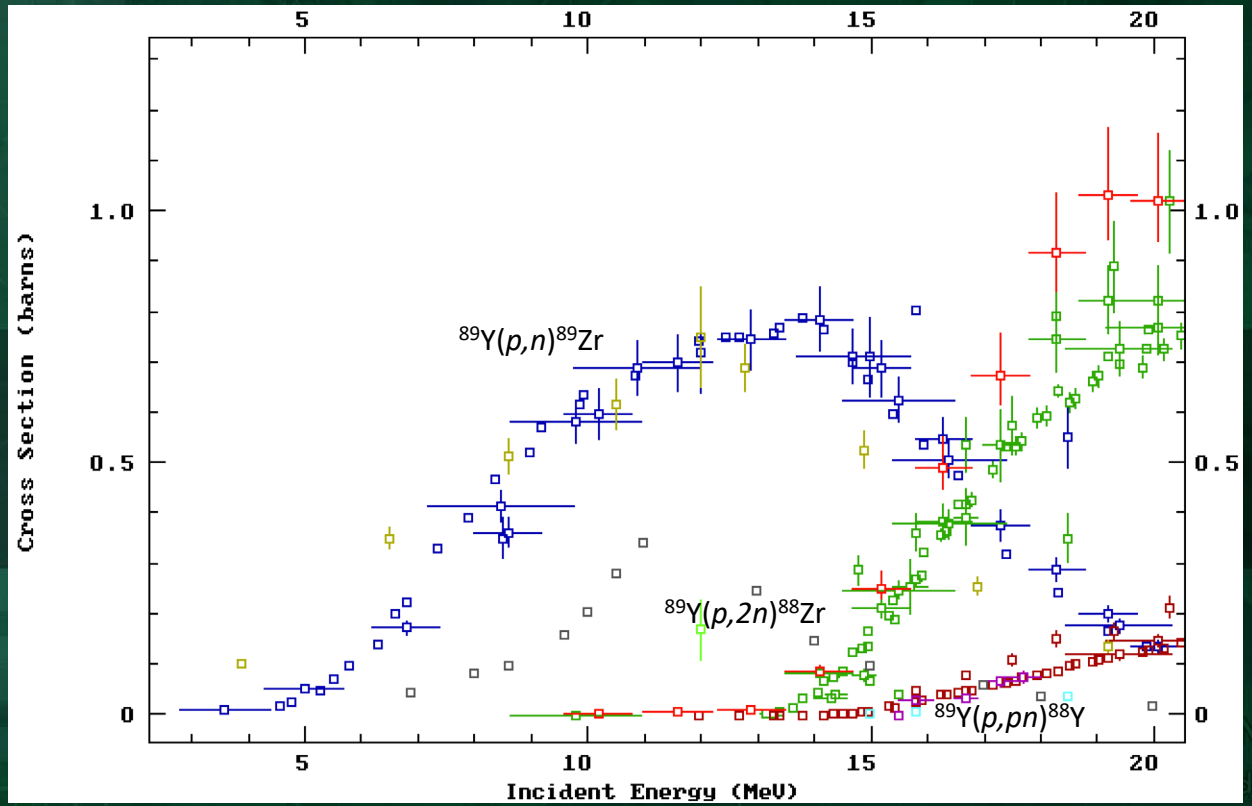
Zirconium-89

- Half-life of 3.27 d – well suited for study of pharmacokinetics of antibodies (achieve optimal biodistribution ~4-5 d)
- Scouting in preparation for immunotherapy, 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



Zr-89 production and purification

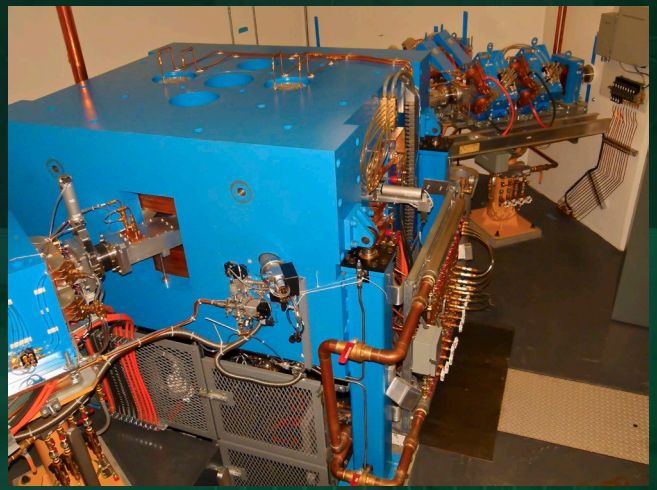
- $^{89}Y(p,n)^{89}Zr$

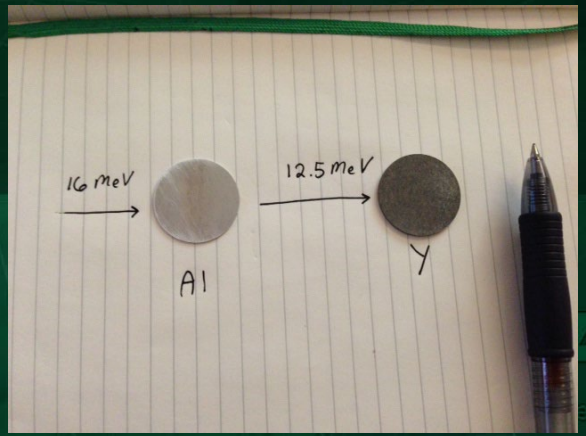


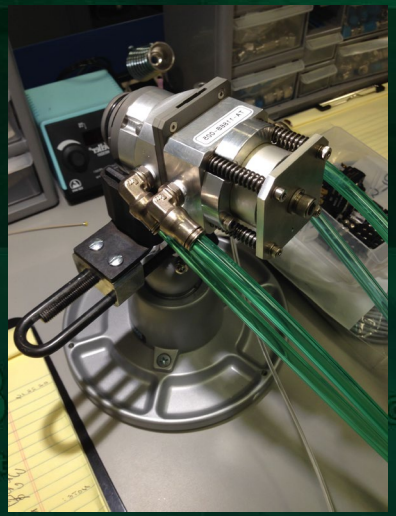
Zr-89 production

- $^{89}Y(p,n)^{89}Zr$

87Zr 1.68 H ε: 100.00%	88Zr 83.4 D ε: 100.00%	89Zr 78.41 H ε: 100.00%	90Zr STABLE 51.45%	91Zr STABLE 11.22%	92Zr STABLE 17.15%	93Zr 1.53E+6 Y β-: 100.00%
86Y 14.74 H ε: 100.00%	87Y 79.8 H ε: 100.00%	88Y 106.626 D ε: 100.00%	89Y STABLE 100%	90Y 64.053 H β-: 100.00%	91Y 58.51 D β-: 100.00%	92Y 3.54 H β-: 100.00%

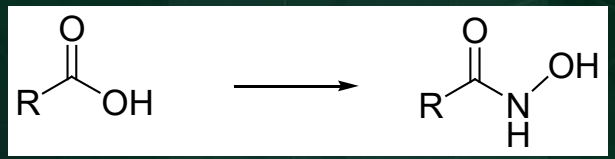




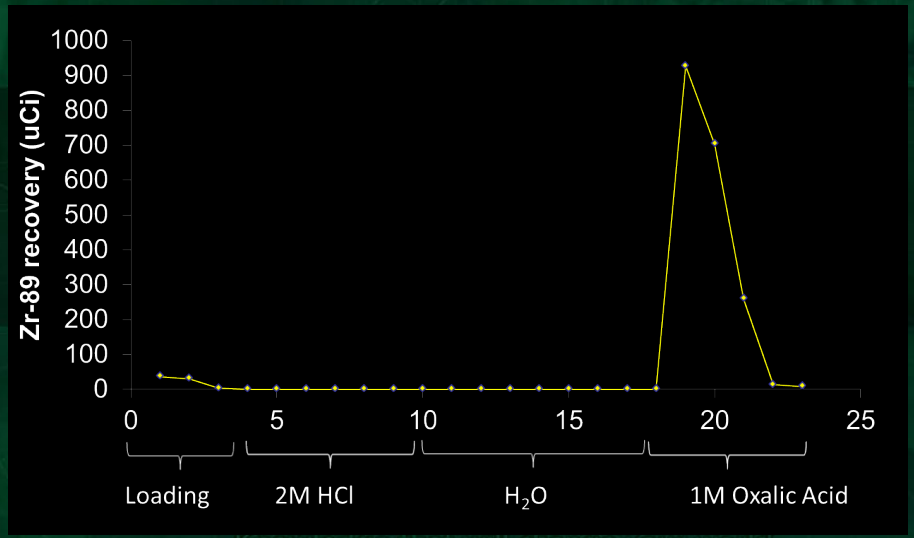


^{89}Zr purification

- Purified by hydroxamate resin
  - Modified Accell Plus resin (Waters)
    - Weak cation exchange resin

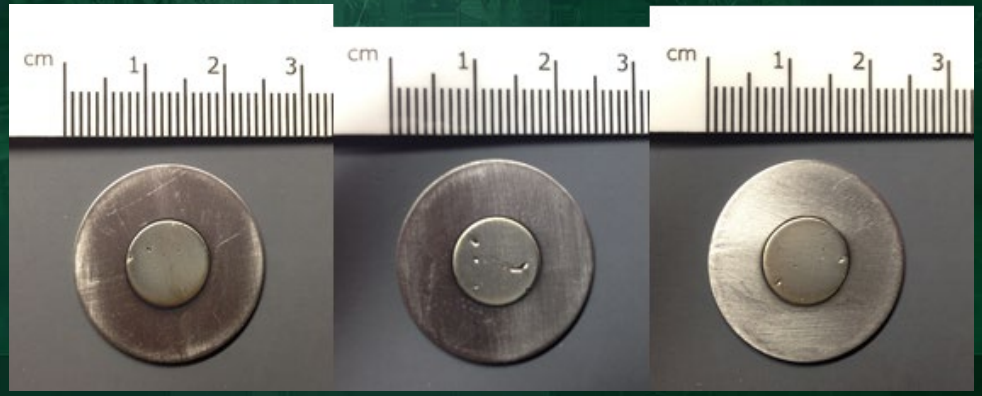


Accell resin Hydroxamate resin



Verel et al J Nuc Med 2003

^{89}Zr New Targets, Scale Up and Automated Separation



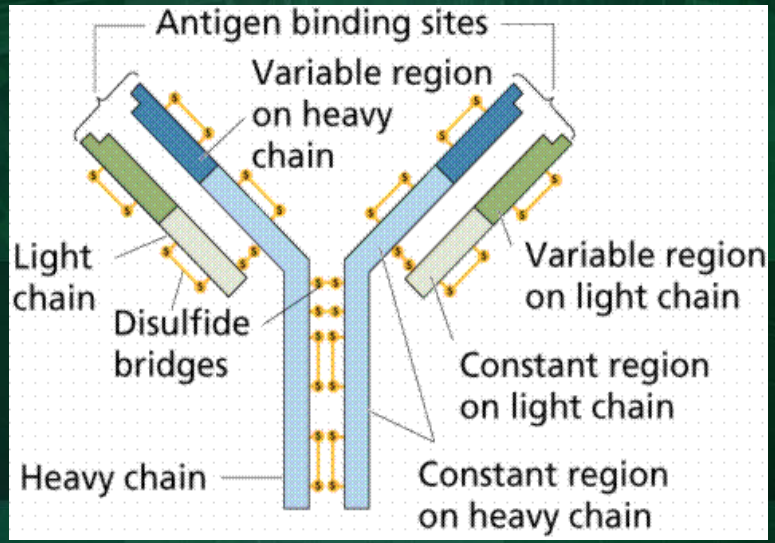
Dissolved in 4mL of heated 2M HCl
Dissolution time: 15-30 minutes
Yttrium eluted in 20mL of 2M HCl
Zr-89 eluted in <500µL 1M Oxalic acid

Typical run:

2 hour bombardment, 40 uA, 13 MeV
30 mCi in hand

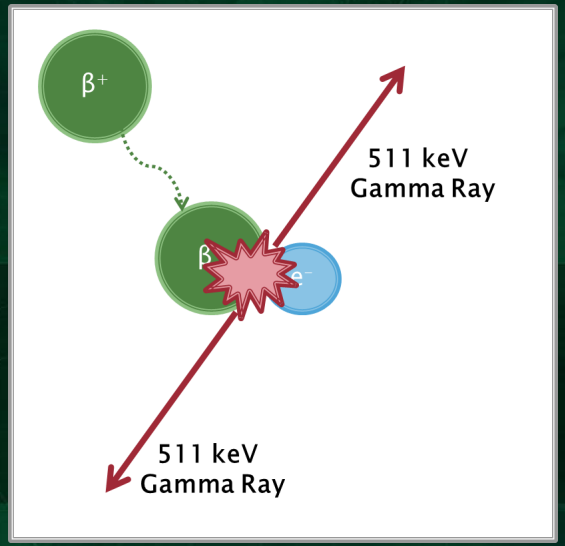
Queern et al Nuc Med Bio 2017

Imaging with Antibodies:



Specificity

+



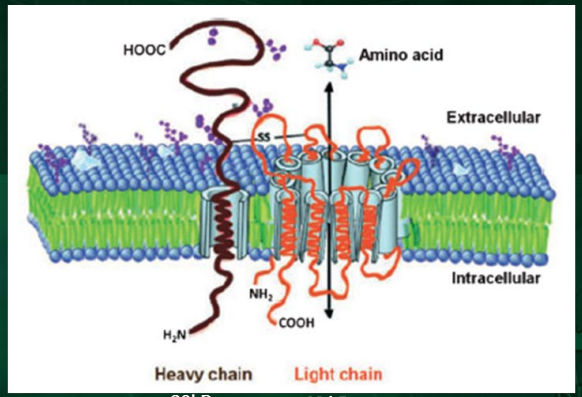
Sensitivity

Why Antibodies?

- Antibodies (and/or fragments) are very selective targeting agents.
- A wide variety of antibody based therapeutics have been developed in the last 2 decades.
- Antibody imaging offers the potential of:
  - Stratifying patients that may benefit from antibody therapy
  - Monitoring the course of therapy
  - Paving the way for next generation targeted radiotherapeutics

Imaging of L-type amino acid transporter-1 (LAT1)

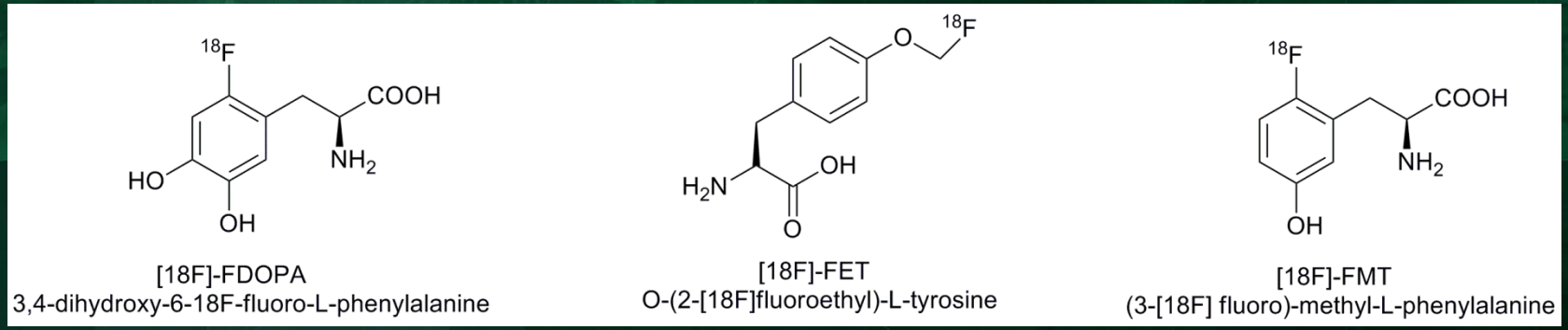
- A system L transporter
- Transmembrane glycoprotein that selectively transports large and neutral amino acids such as leucine, isoleucine, valine, phenylalanine, tyrosine, tryptophan, methionine and histidine
- Only amino acid transporter that plays a role in cell proliferation
- Increased expression and transport activity observed in many cancer cells



Masuko, T., Ohno, Y., Masuko, K., Yagi, H., Uejima, S., Takechi, M., and Hashimoto, Y. (2011) *Cancer science 102*, 25-35

LAT-1 Amino Acid Substrates

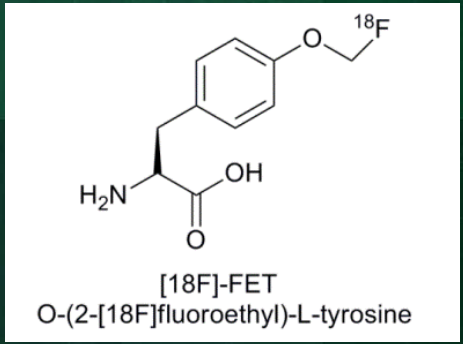
- Responsible for the transport of ^{18}F labeled aromatic amino acids



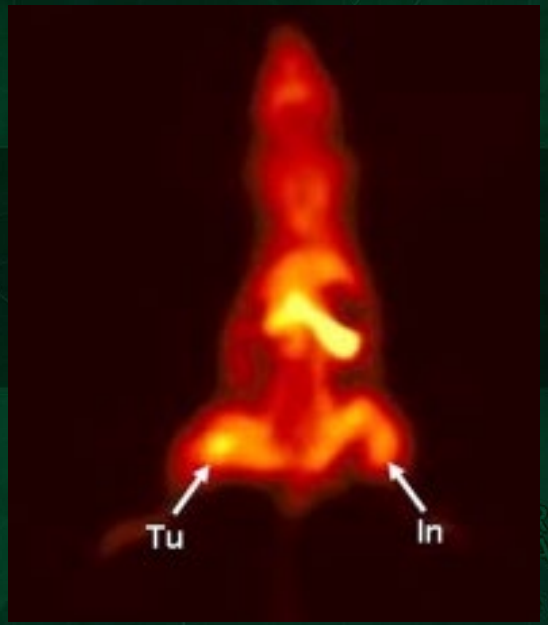
- Substrates for system L transport
- Have shown promise as tumor imaging agents

LAT-1 Amino Acid Substrates

- One of the major limitation of ^{18}F labeled system L substrates is the relatively low tumor to normal tissue ratios due to bidirectional transport



[18F]-FET
O-(2-[18F]fluoroethyl)-L-tyrosine

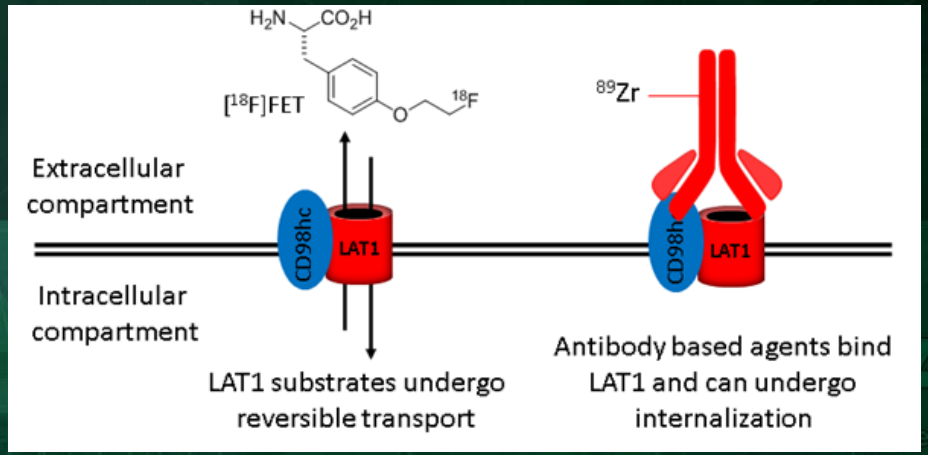


Lee, T.S., Ahn, S.H., Moon, B.S. *et al* Nucl. Med. Bio., **2009**, 36(6), 681-686

Can the LAT-1 transporter be directly imaged?

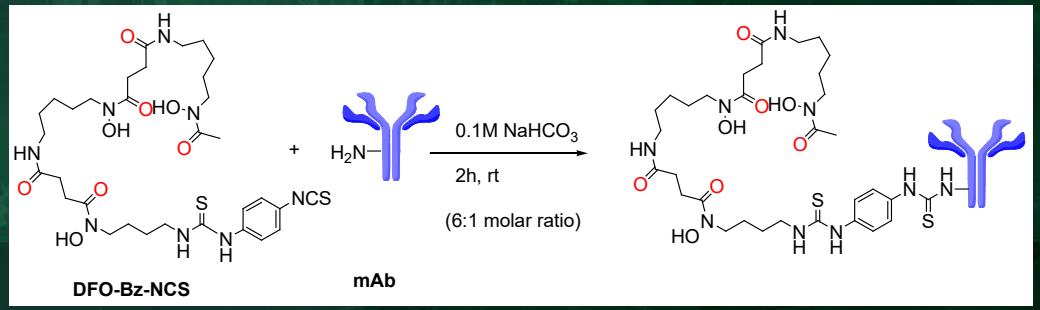
- Use of anti-LAT-1 antibodies may allow for measuring of LAT1 protein expression profile in normal and cancerous cells
- Masuko et al. have developed three rat monoclonal antibodies against LAT-1, Ab2-LAT-1, Sol 22 and Sol 131

Masuko *et al*. Cancer Sci. **2008** 99, 1000-1007

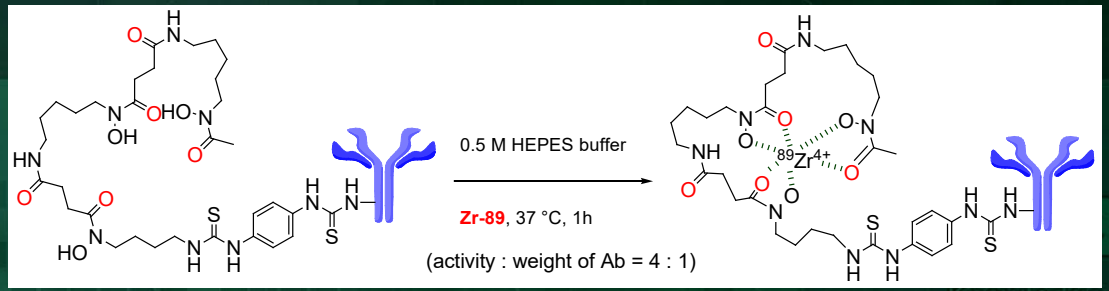


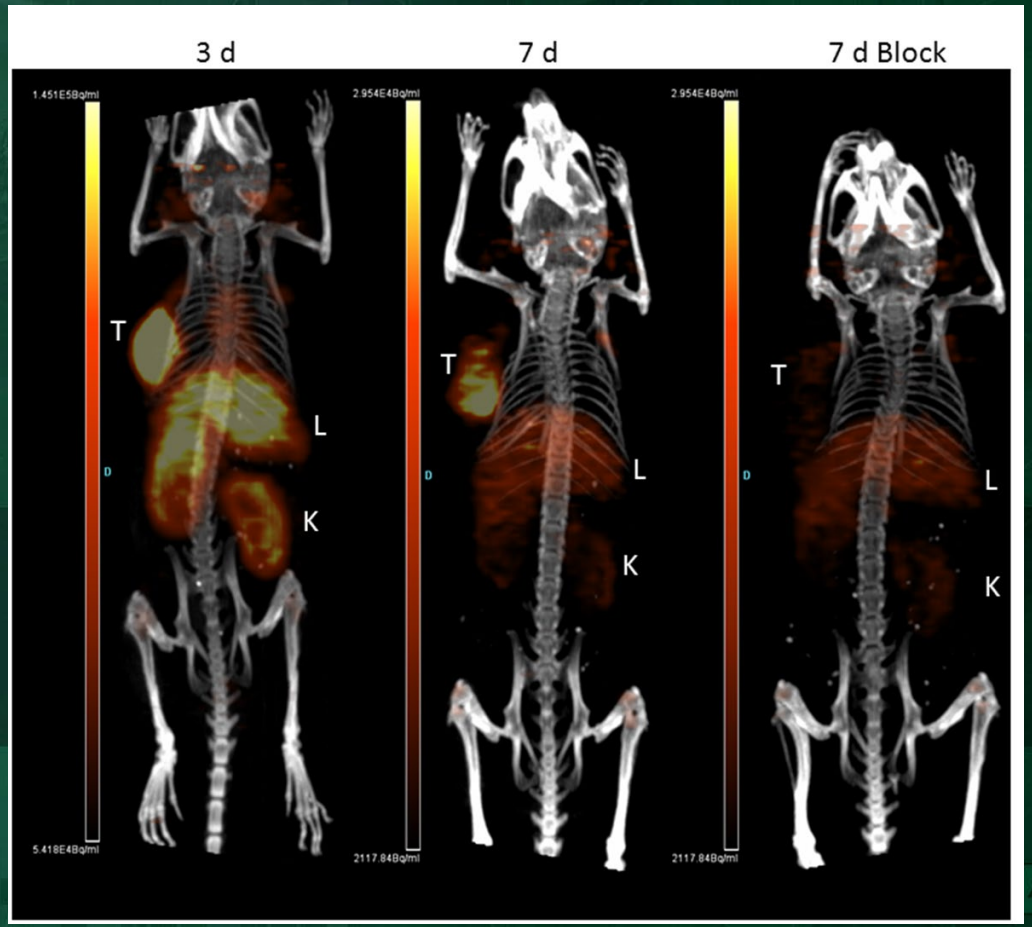
^{89}Zr: Conjugation and Labeling

(a) mAb conjugation to DFO-Bz-NCS

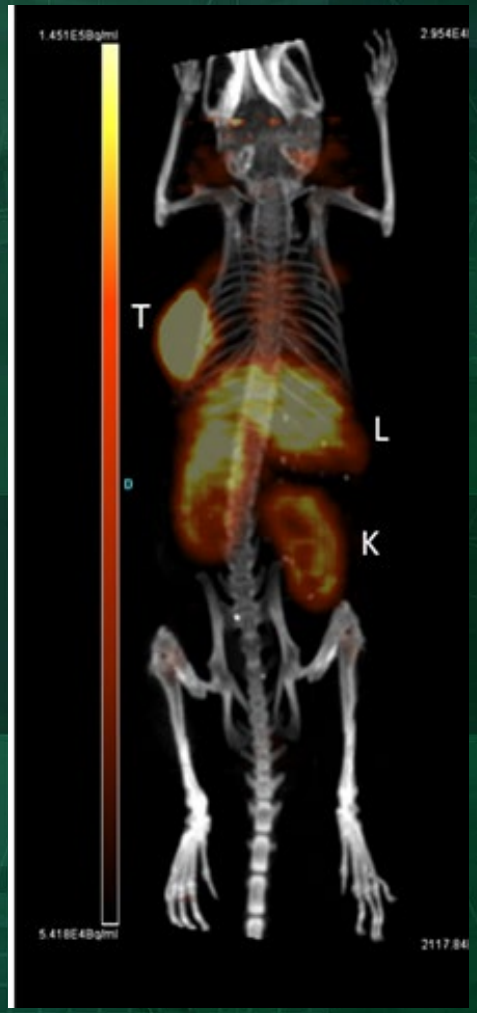


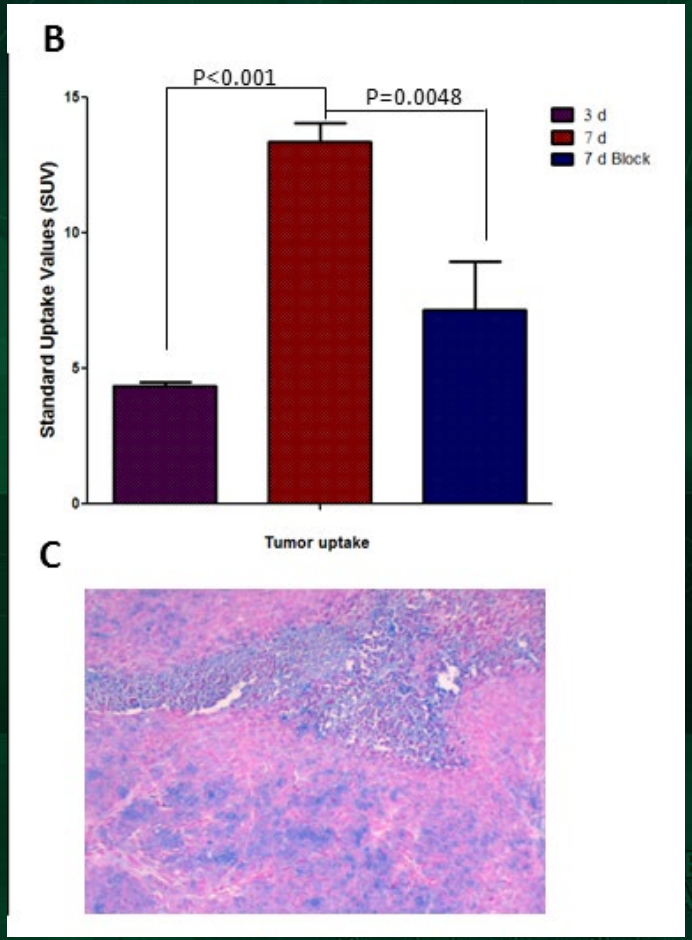
(b) Radiolabeling of DFO-Bz-NCS-Trastuzumab





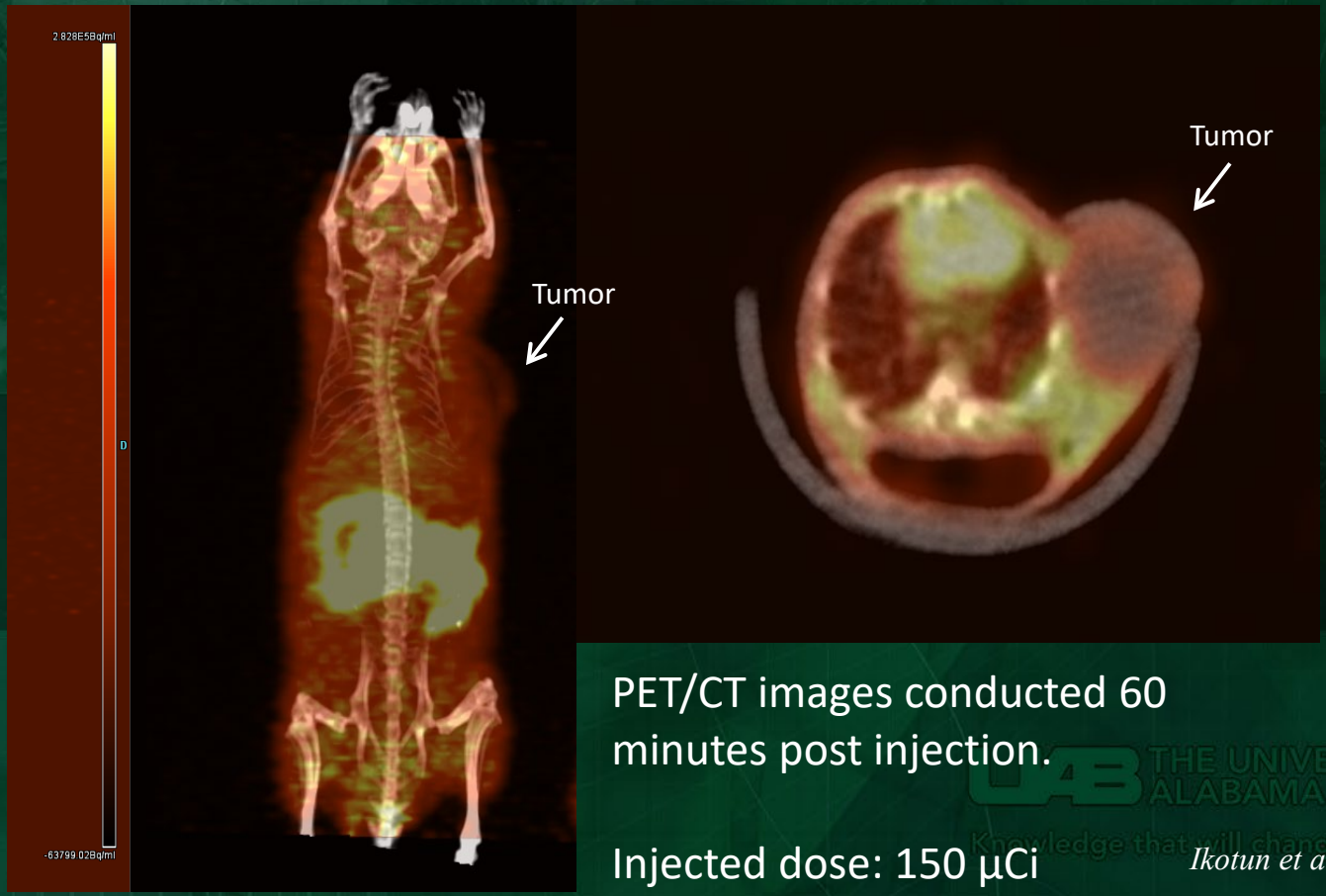
Ikotun et al. PLOS ONE 2013





Ikotun et al. PLOS ONE 2013

[^{18}F]-FET Imaging



PET/CT images conducted 60 minutes post injection.

Injected dose: 150 µCi

Ikotun et al. PLOS ONE 2013

Imaging of LAT1

- Anti-LAT-1 antibodies can be radiolabeled with ^{89}Zr
- ^{89}Zr radiolabeled anti-LAT-1 antibody shows specific binding to LAT-1 transporter
- Improved tumor to non-target organ uptake is observed with antibody based PET agent compared to currently available radiolabeled amino acids
- Imaging with novel ^{18}F amino acids may show provide complementary information

Human Epidermal Growth Factor Receptor 2 (HER2)

- Transmembrane receptor
- No known natural ligands
- Amplified in approximately 20 % of invasive breast cancers
- Associated with increased tumor aggressiveness, resistance to therapies, and increased mortality

Anti-HER2 Antibodies

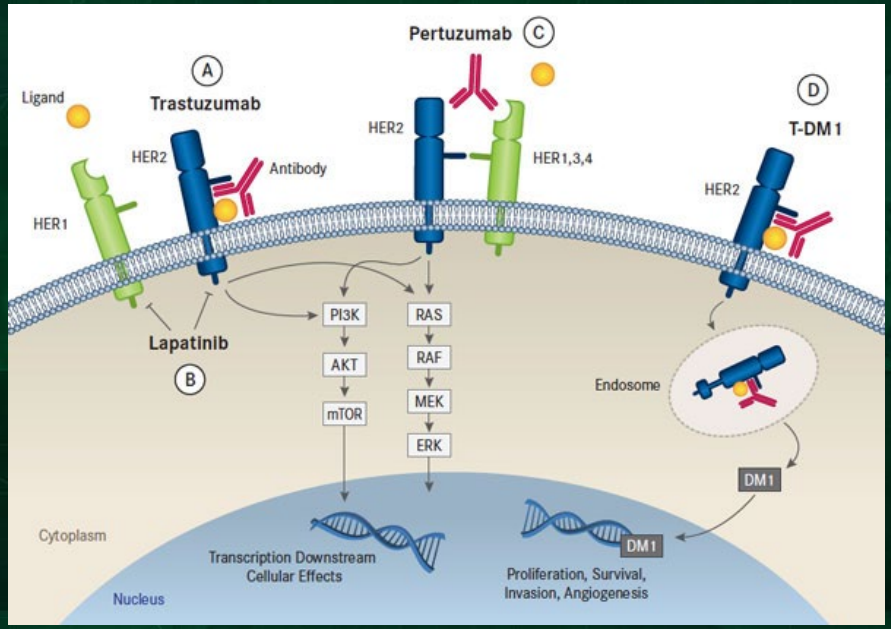
Trastuzumab

- Binds to domain IV
- Suppresses HER2 signaling activity

Pertuzumab

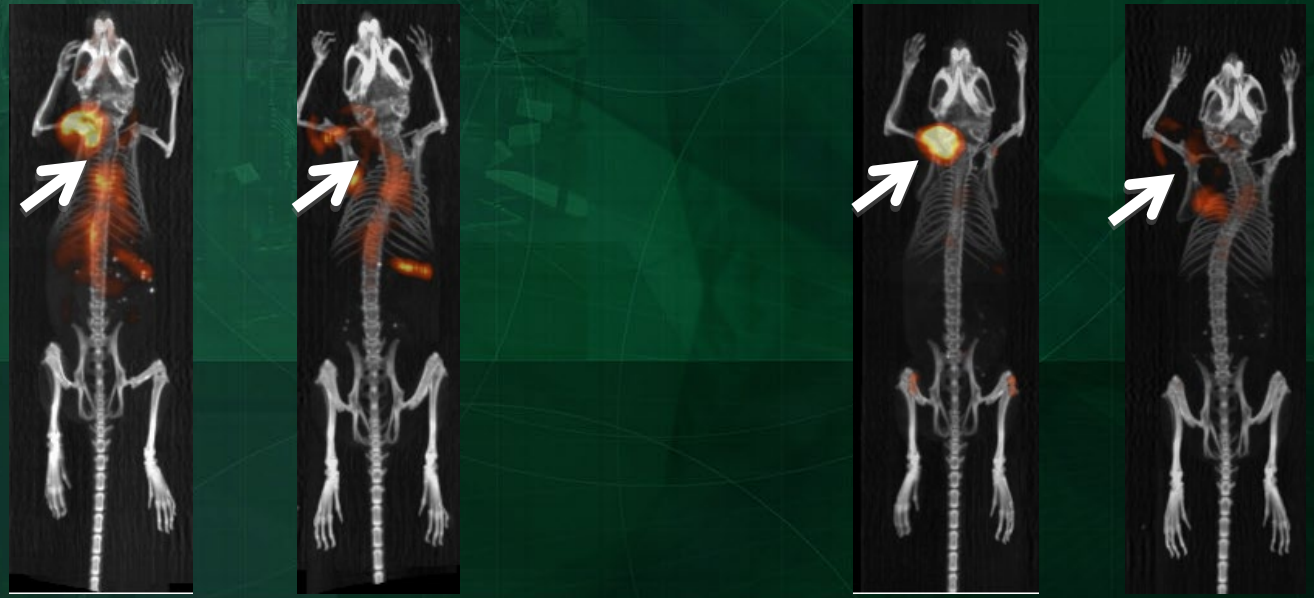
- Binds to domain II
- Inhibit HER2 dimerization by sterically preventing HER2 pairing with other growth factor receptors

Marks tumor cells for immunological attack through antibody-dependent cell-mediated cytotoxicity



http://www.onclive.com/publications/contemporary-oncology/2014/February-2014/Antibody-Drug-Conjugates-and-T-DM1

^{89}Zr-DFO-Trastuzumab



Her2+ Her2- Her2+ Her2-

24 h 96 h

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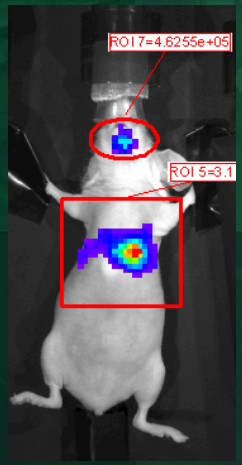
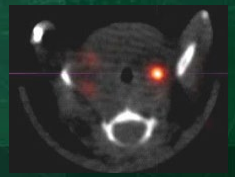
Knowledge that will change your world

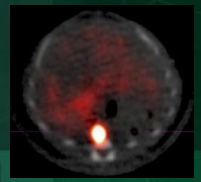
Chang et al, Pharmaceuticals, 2012

^{89}Zr-DFO-Trastuzumab Imaging Metastasis

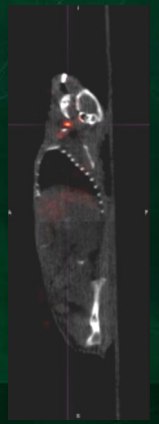


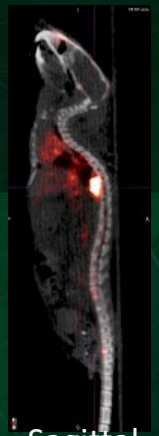
Bioluminescent Imaging



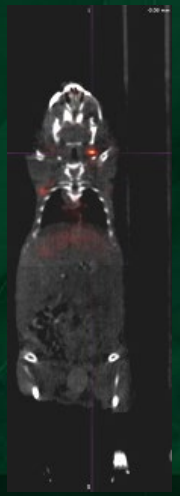


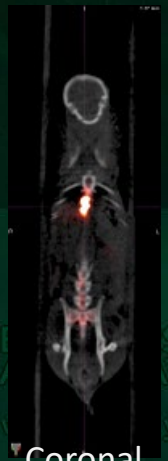
Axial





Sagittal





Coronal

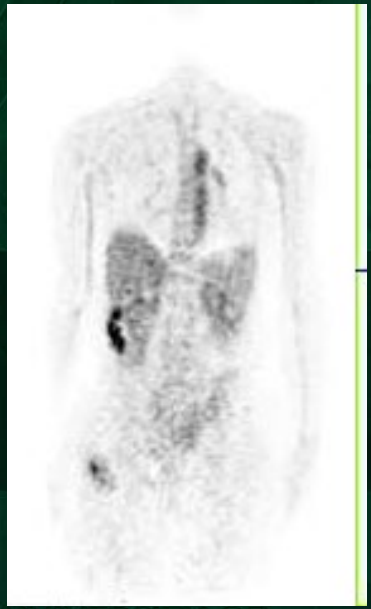
Chang et al, Pharmaceuticals, 2012

^{89}Zr-DFO-Trastuzumab
Washington University Clinical Trial

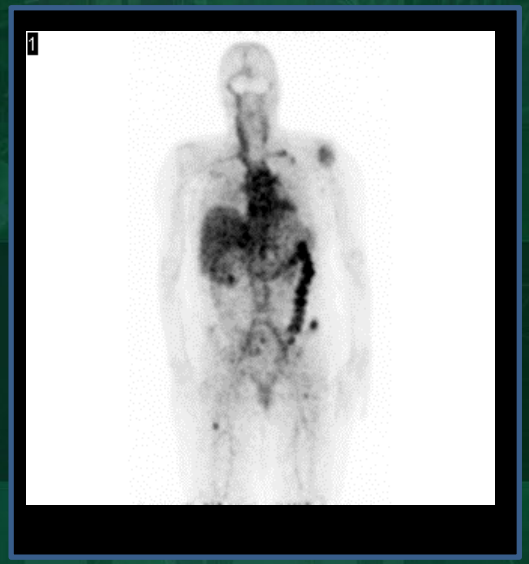
Assessment of HER2 Receptors in Breast Carcinoma by Positron Emission Tomography (PET) Using ^{89} Zr-Trastuzumab

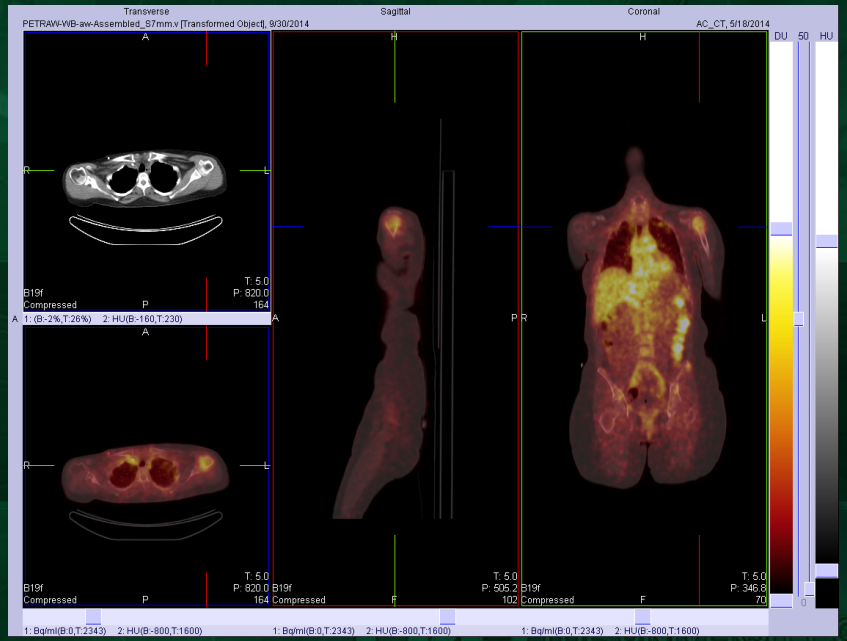
PI: Farrokh Dehdashti

Arms	Assigned Interventions
Experimental: Cohort 1 ^{89}Zr-Trastuzumab Human Dosimetry and Safety	Drug: ^{89}Zr-Trastuzumab Human Dosimetry and Safety PET Imaging following administration of ^{89}Zr labeled Trastuzumab for calculation of human dosimetry and overall safety Drug: HER2 Positive Lesion Detection and Safety Detection of HER2 Positive Breast Cancer with ^{89}Zr Labeled Trastuzumab and PET imaging
Experimental: Cohort 2: Lesion Detection and Safety HER2 Positive Lesion Detection and Safety	Drug: ^{89}Zr-Trastuzumab Human Dosimetry and Safety PET Imaging following administration of ^{89}Zr labeled Trastuzumab for calculation of human dosimetry and overall safety Drug: HER2 Positive Lesion Detection and Safety Detection of HER2 Positive Breast Cancer with ^{89}Zr Labeled Trastuzumab and PET imaging



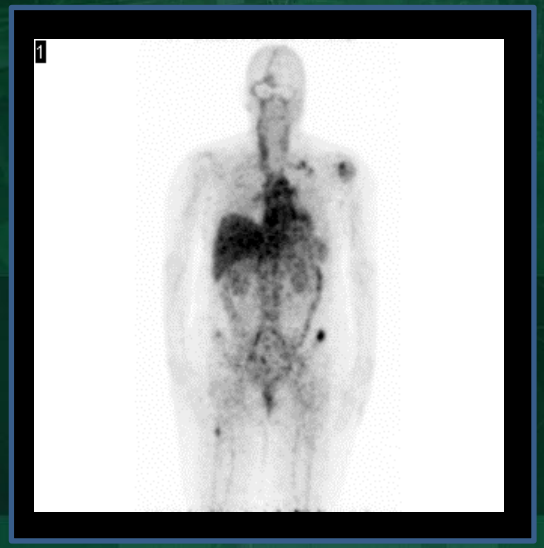
^{89}Zr-Trastuzumab Clinical Trial: Day 2

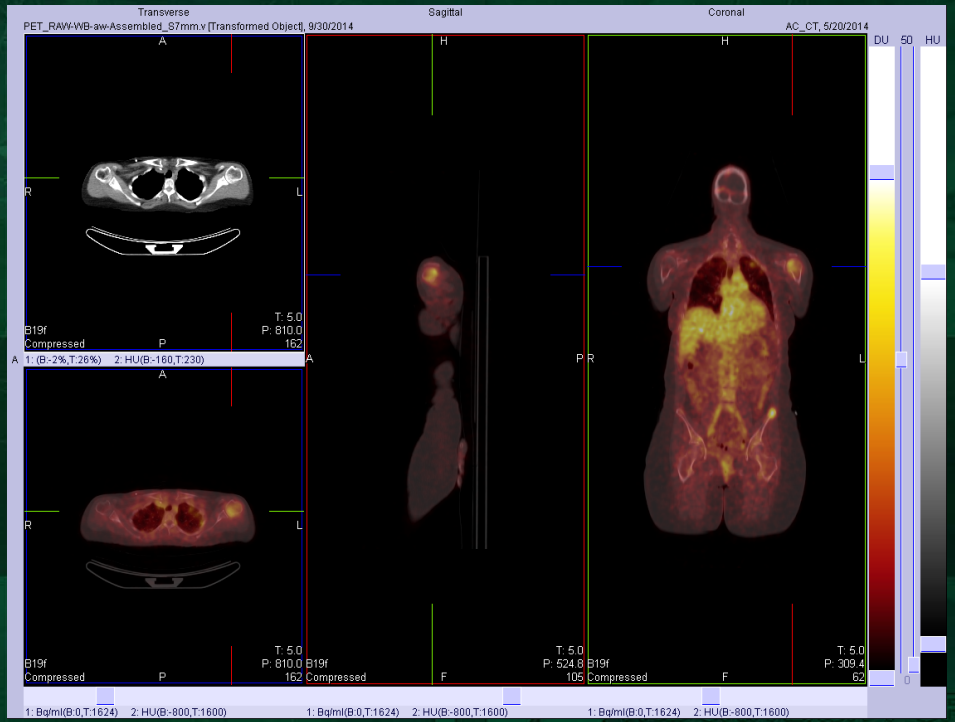




Laforest et al, Mol Imaging and Biol, 2016

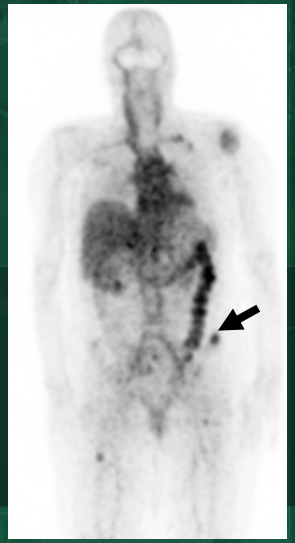
^{89}Zr-Trastuzumab Clinical Trial: Day 5



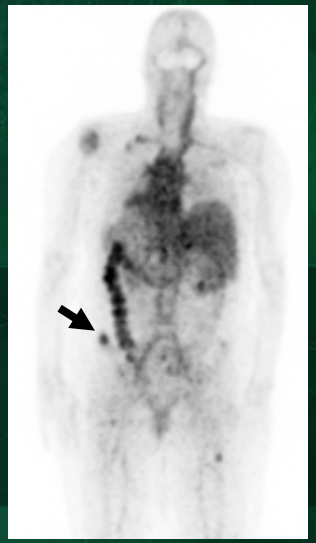


Laforest et al, Mol Imaging and Biol, 2016

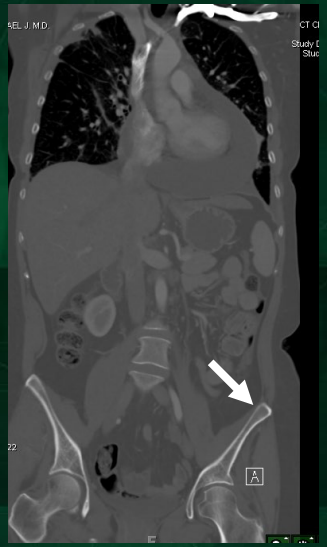
Metastatic **Setting: ER+/PR-/HER2+ Metastatic Breast Cancer**



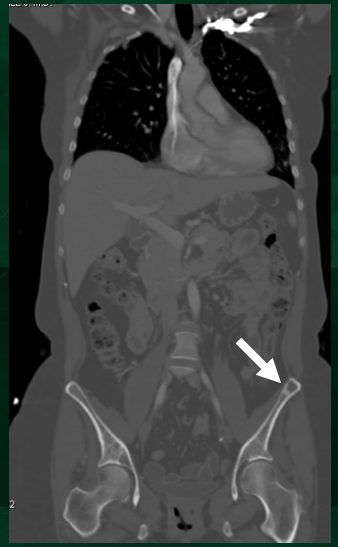
ANT 5/2014



POST 5/2014



CT 4/2014

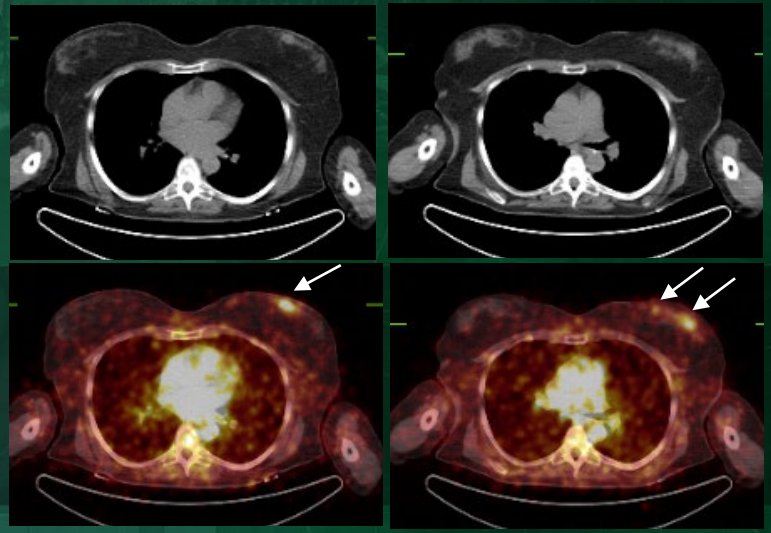


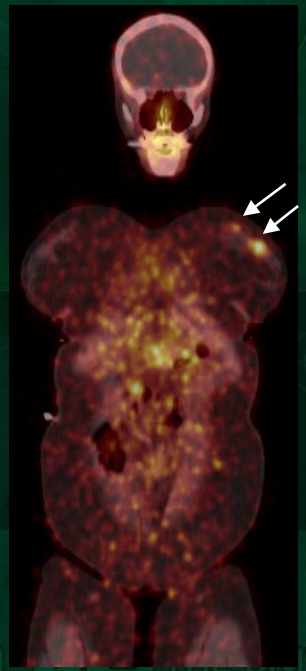
CT 8/2014

1 Metastatic Regimen, 1 cycle

Laforest et al, Mol Imaging and Biol, 2016

Neoadjuvant setting: ER+/PR-/HER2+





Multicentric Primary Breast Cancers

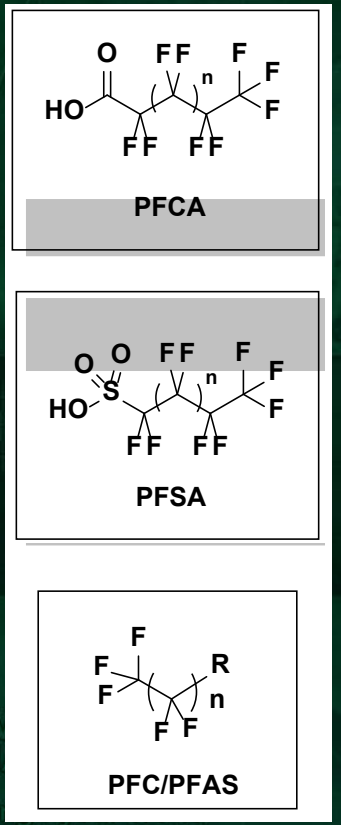
Laforest et al, Mol Imaging and Biol, 2016

^{89}Zr-Trastuzumab Future Directions (UAB)

- Soon to be starting a new trial investigating the ^{89}Zr-Trastuzumab uptake and correlations with response to targeted HER2 therapy.

Radiotracers outside of medicine : [^{18}F]PFAS

- Perfluoroalkyl compounds are persistent environmental pollutants (POPs) with bioaccumulation potential, toxicity possibility in biological organics and have long range transport potential.
  - Very slow break down in the environment
  - High thermal stability
- Widely used to make everyday products more resistant to stains, grease and water, such as non stick cookware, stain resistance in carpets and furniture, waterproofing clothes and mattresses, some food packaging and firefighting materials.
- Fortunately, PFOS is no longer manufactured in the US and PFOA should be phased out soon, however there are many other derivatives that could still do harm.

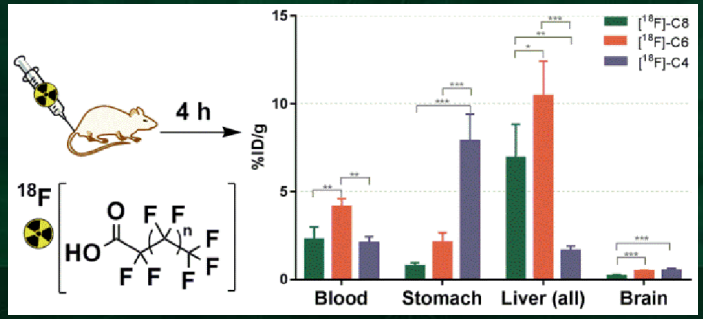


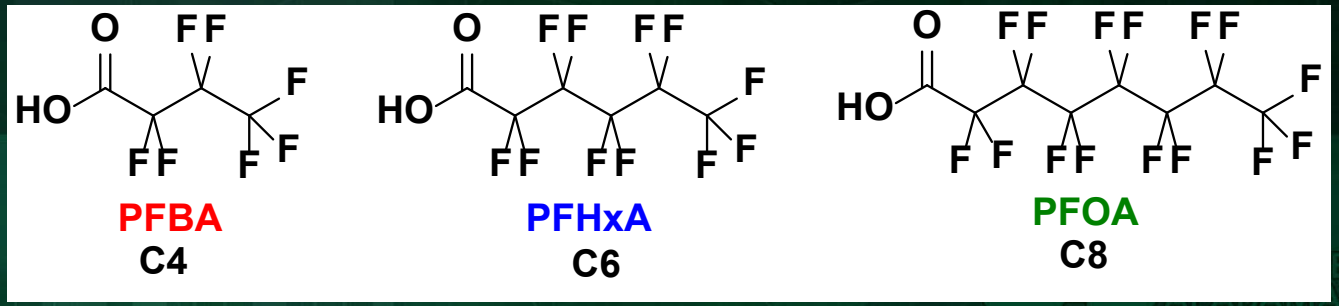
Radiotracers outside of medicine : [^{18}F]PFAS

- PFAS found in water supplies, from long term contamination from firefighting foam, fast food wrappers and other materials.
- Known to bioaccumulate but many long term health effects unknown.
- Environmental contamination from spills:

Radiotracers outside of medicine : [^{18}F]PFAS

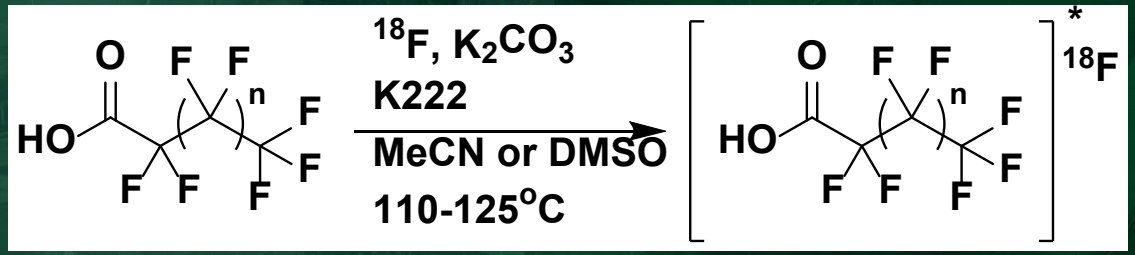
- Routes of bioaccumulation and biological kinetics?
- Radiotracers could be useful tools
- Goal: Radiolabel PFAS with ^{18}F





Burkemper et al. Environ Sci Tech Lett 2017

Radiotracers outside of medicine : [^{18}F]PFAS



^{18}F separation

- Trap ^{18}F on QMA cartridge
- Release with 2-3 mg K_2CO_3 in H_2O into 1 mL of MeCN + 4-5 mg K222

Drying Process

- Dry down in 110°C oil bath and gentle Ar flow
- Azeotropic distillation with 3 x 1 mL additions of MeCN

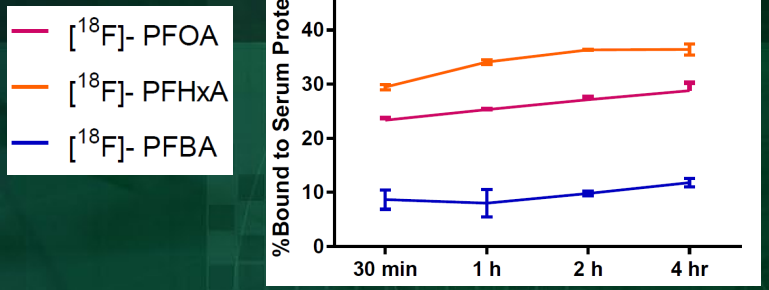
Radiolabeling

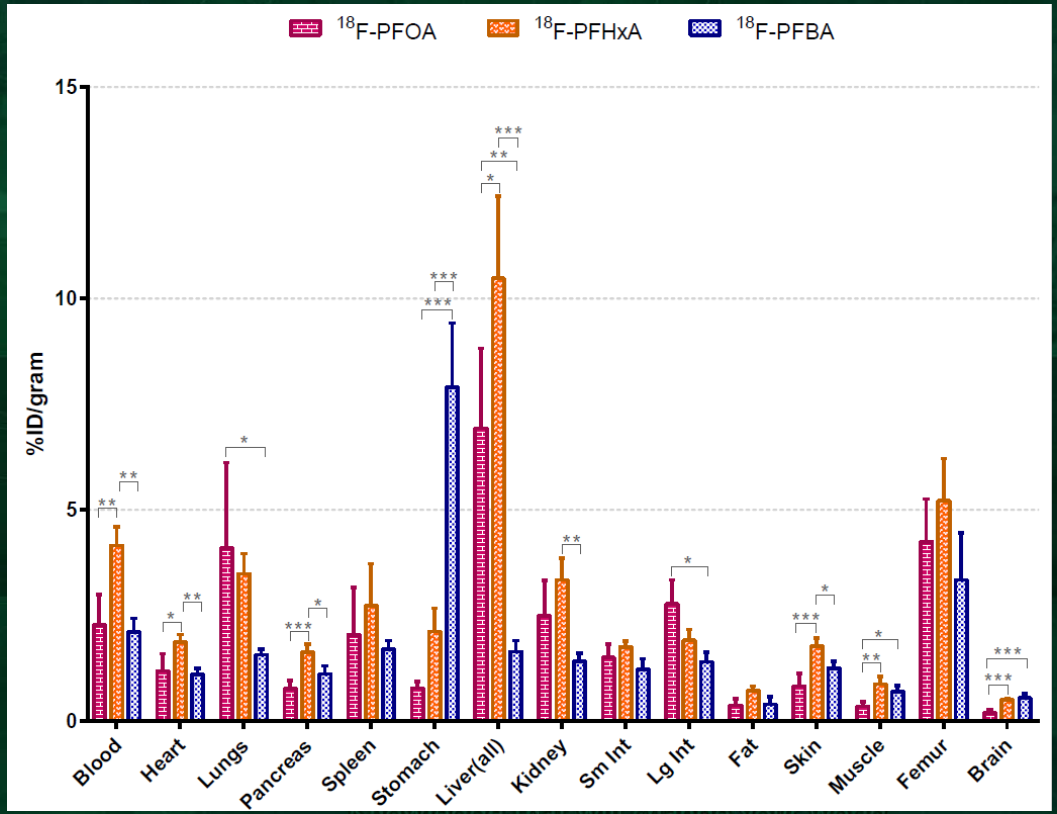
- Add compound in ~0.5 mL of desired solvent
- Heat reaction in oil bath at specified temperature for 10-20 min

Burkemper et al. Environ Sci Tech Lett 2017

Radiotracers outside of medicine : [^{18}F]PFAS

- Healthy mice were injected with 100 µCi of tracer in 100 µL of solution
- Mice were humanely sacrificed at 4 h post injection (n = 4 per tracer)





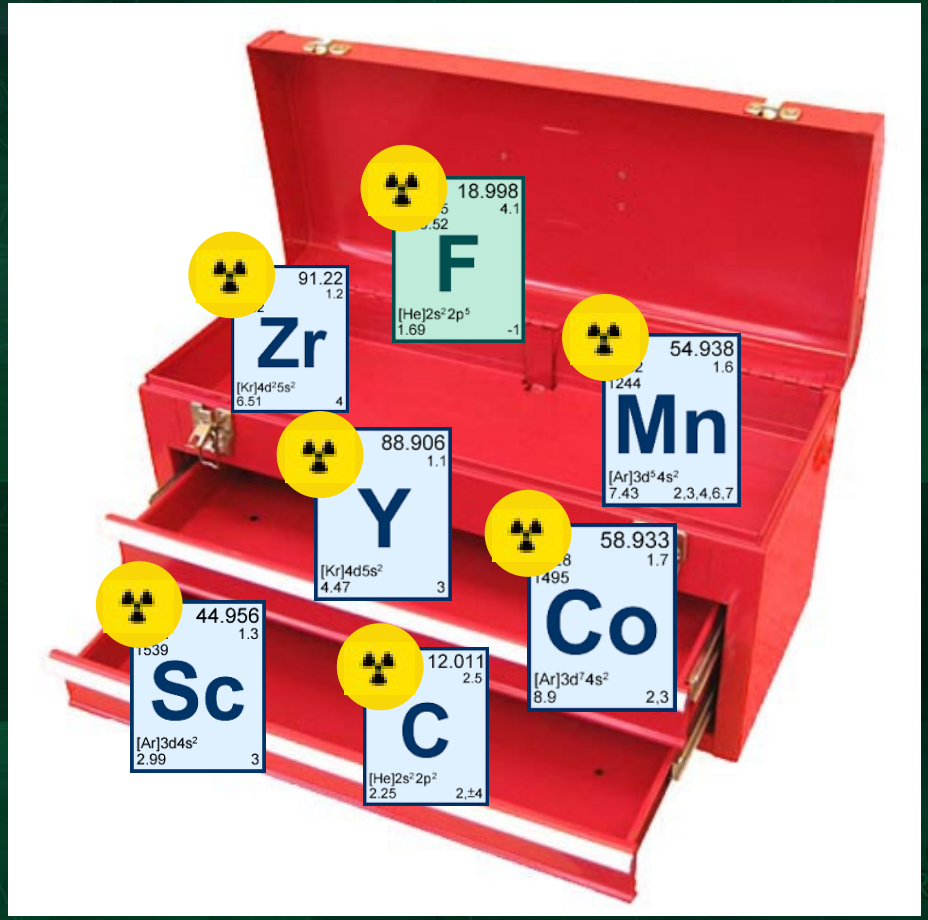
Burkemper et al. Environ Sci Tech Lett 2017

Radiotracers outside of medicine : [^{18}F]PFAS

- New tool to study biological distribution of PFAS.
- Could be used to study families of PFAS structures.
- Use in environmental remediation studies?

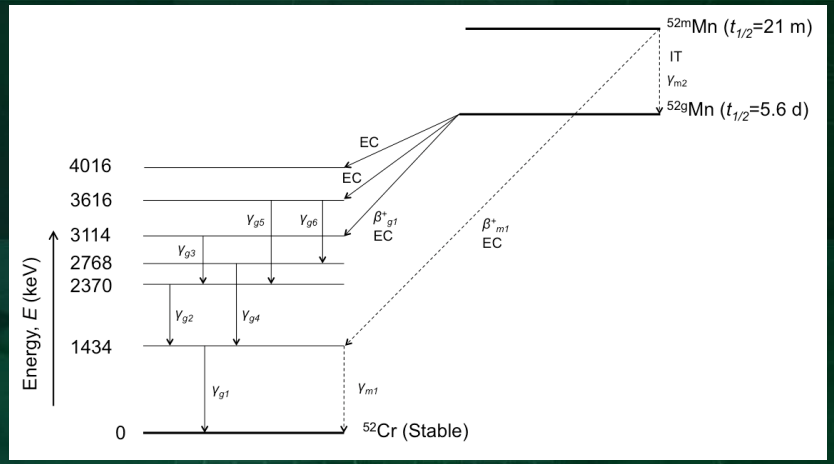
What's Next?

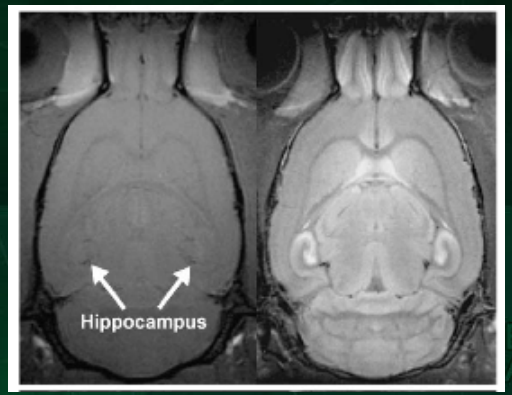
Expanding the Toolbox.

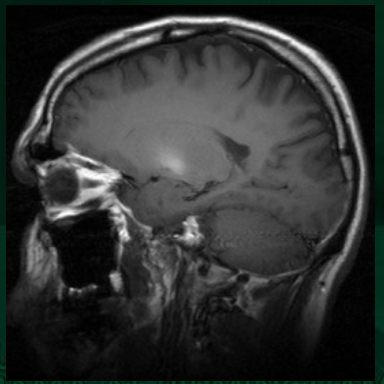


Development of Novel Radionuclides
Examples: ^{52}Mn

- PET analogue for Mn MRI agents.
- Biological roles in plants and animals
- Mechanism of Manganese toxicity (manganism)





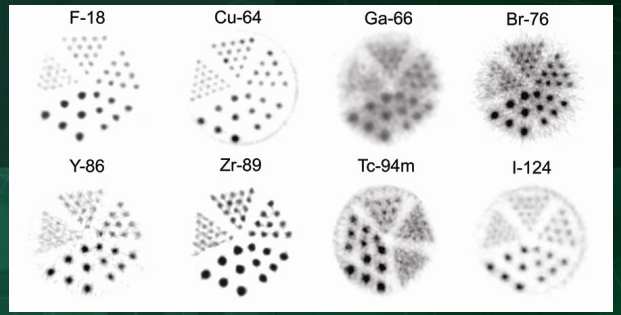


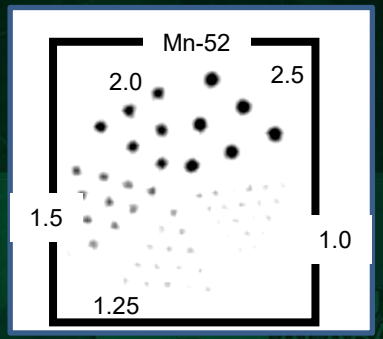
^{52}Mn Characteristics

		Production		Positron Emission		Gamma Radiation
	Half-Life	Most Common Target	Target Natural Abundance	Weighted Average Energy	Total Intensity	Gamma Factor
				(keV)		($R \cdot cm^2 \cdot mCi^{-1} \cdot h^{-1}$)
^{52g}Mn	5.6 d	^{52}Cr(p,n) (S)	83.8%	242	29.6%	18.4
^{124}I	4.2 d	^{124}Te(p,n) (S)	4.7%	820	22.7%	6.6
^{89}Zr	3.3 d	^{nat}Y(p,n) (S)	100.0%	396	22.7%	6.6
^{86}Y	14.7 h	^{86}Sr(p,n) (S)	9.9%	660	31.9%	18.9
^{64}Cu	12.7 h	^{64}Ni(p,n) (S)	0.9%	278	17.6%	1.1
^{18}F	110 m	^{18}O(p,n) (L)	0.2%	250	96.7%	5.7
^{66}Ga	9.5 h	^{66}Zn(p,n) (S)	69.2%	1750	57%	11.6
^{68}Ga	68 m	^{68}Ge (Gen)	-	830	88.9%	5.4
^{11}C	20 m	^{14}N(p,α) (G)	99.6%	386	99.8%	5.9

Targets: (S)=solid; (L)=liquid; (G)=gas; (Gen)=generator.

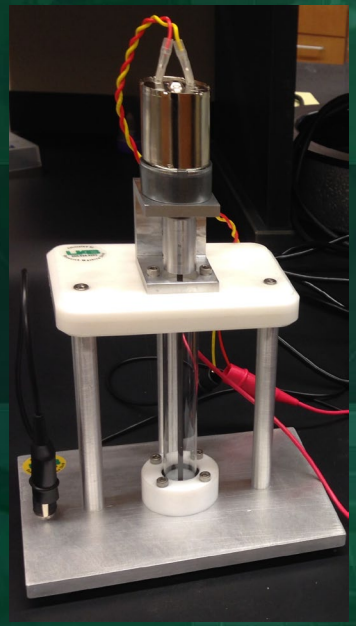
Data in table take from or accessed via: BNL/NNDC; IAEA; Smith, D.S.; Stabin, M.G. *Health Phys.* 2012.

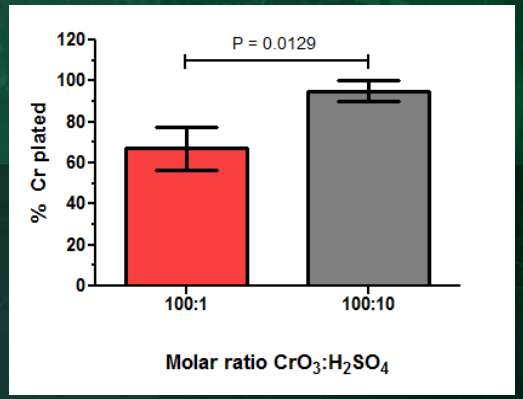


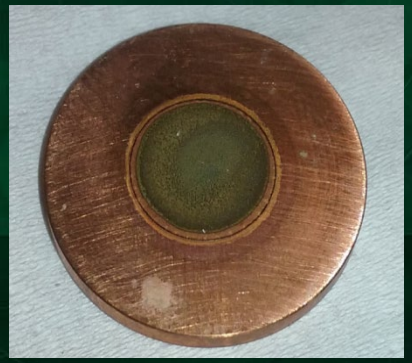


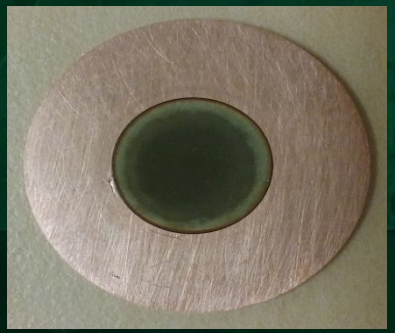
^{52}Mn Production (UAB)

- Produced via ^{52}Cr(p,n)^{52}Mn reaction
- Targetry using natural composition and enriched Cr electroplated targets





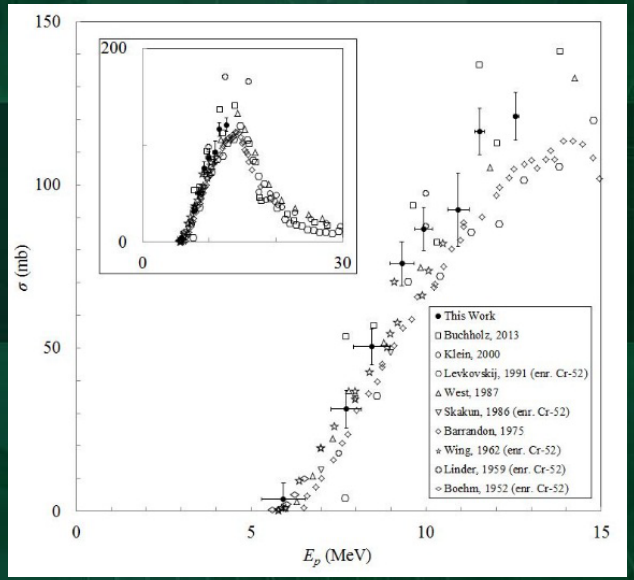


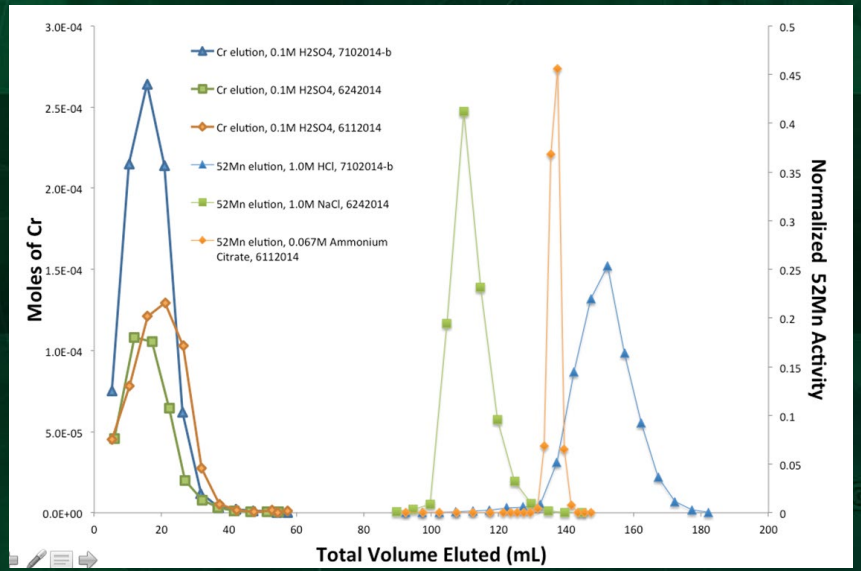


Conditions
Coin: copper
Rod: platinum
Time: 24 h

^{52}Mn Targets, Bombardment and Purification

- Cross section and yield measurements using thin foils
- Separation via ion chromatography

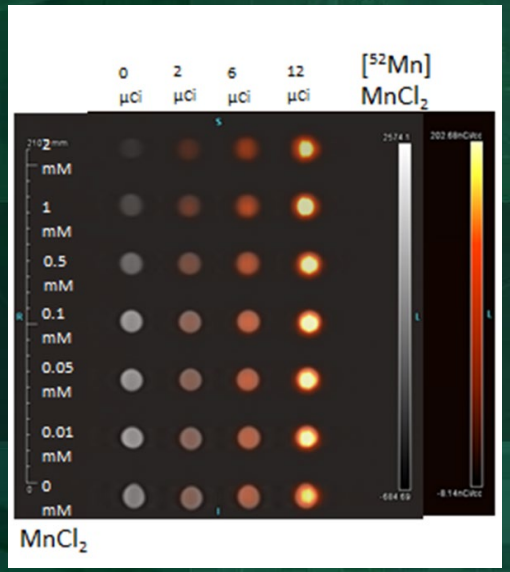


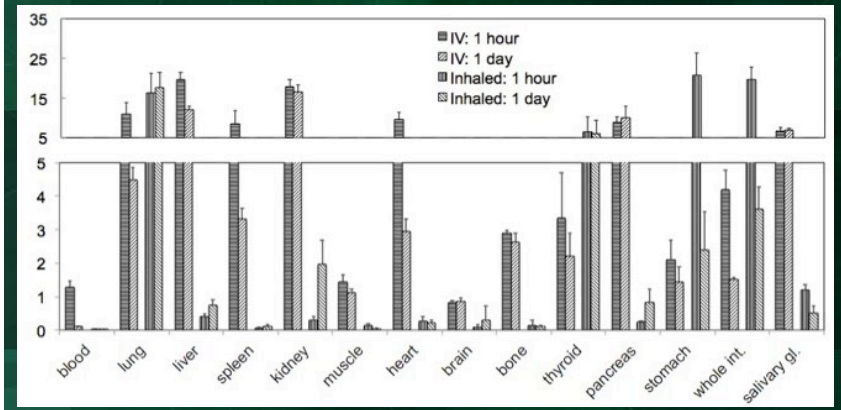


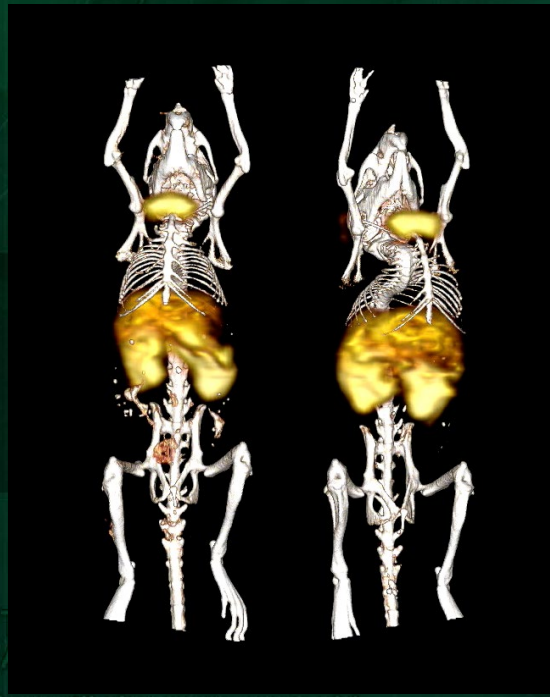
Wooten et al. Appl Rad Isot 2015

^{52}Mn Characterization

- Imaging characteristics and preliminary animal studies

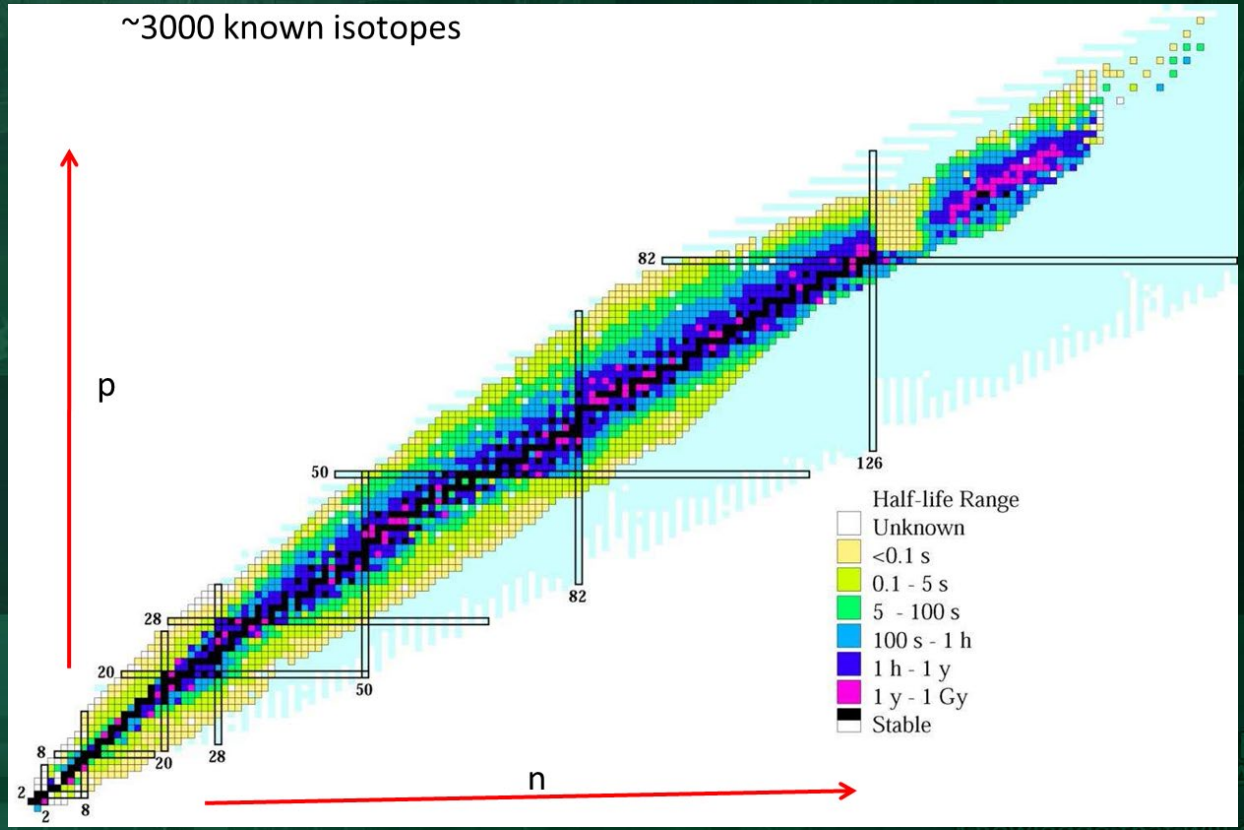




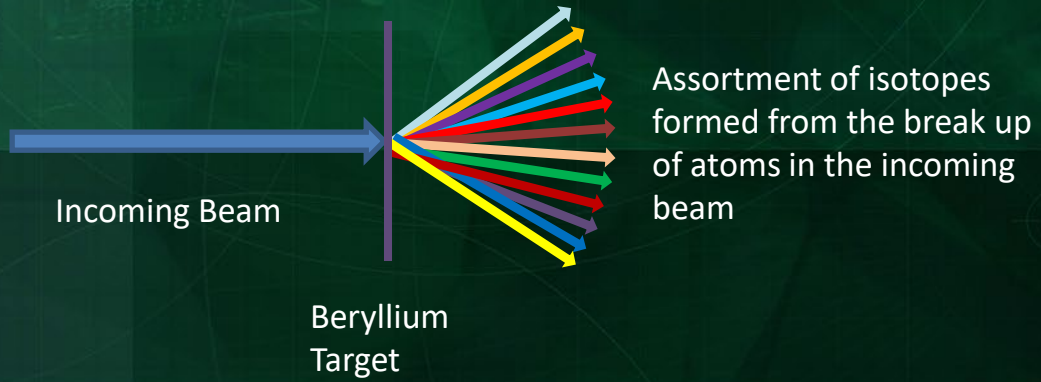


Wooten et al. PLoS ONE 2017

Other Isotopes?



Production of Radionuclides by Heavy Ion Fragmentation



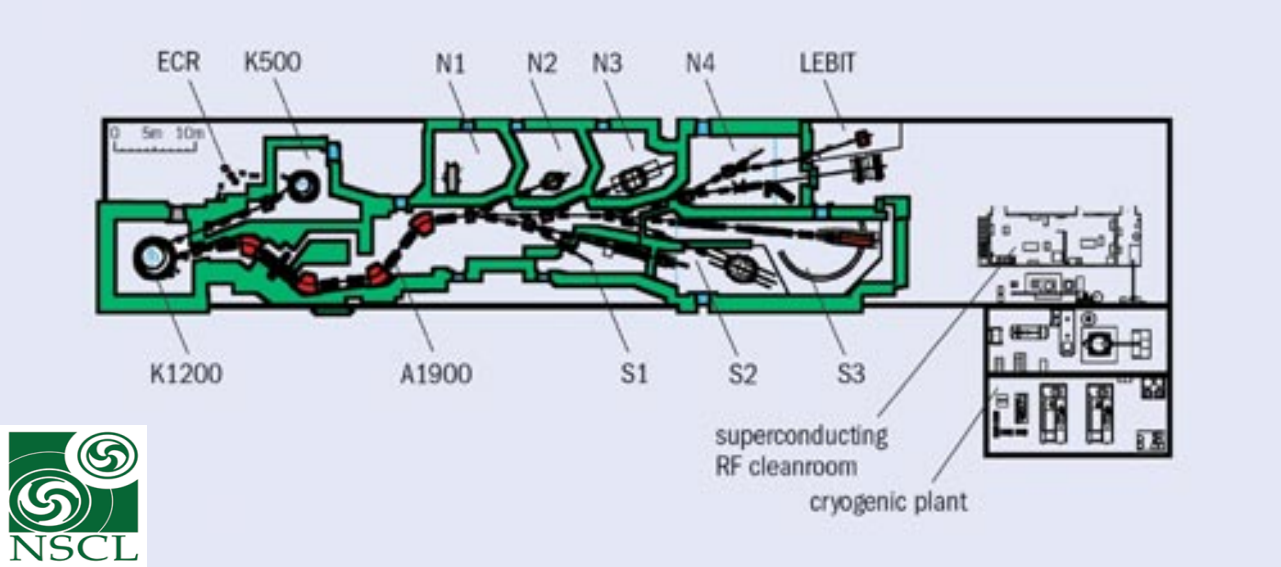
Potential Isotopes of Interest

Isotope	Decay Mode	Half-life	Application
^{32}Si	β-, 221keV no γ	162y	Tracer; geology, botany
^{44}Ti	ε, γ-78.3, 67.8keV	59.2y	Medicine, astrophysics, Nuclear Structure
^{48}V	β+, 694keV γ-983.5, 1312.1keV	15.98d	Stockpile Stewardship, Medicine
^{67}Cu	**β-, 390, 480, 580keV** **γ-184.6keV**	**2.6d**	**Medicine**
^{85}Kr	β-, 687keV γ-514.0keV	10.76y	Astrophysics, Stockpile Stewardship
Eu*		24d-37y	Stockpile Stewardship
^{211}Rn	γ-674.1, 1363.0, 678.4keV α-5.784,5.851MeV	14.6h	Medicine
^{225}Ra	β-, 320keV γ-40.3keV	14.9d	Medicine, Electric Dipole Moment
^{225}Ac	α-5.829, 5.793, 5.731MeV	10.0d	Medicine

*A range of Eu isotopes are of interest, A~147 – 154.

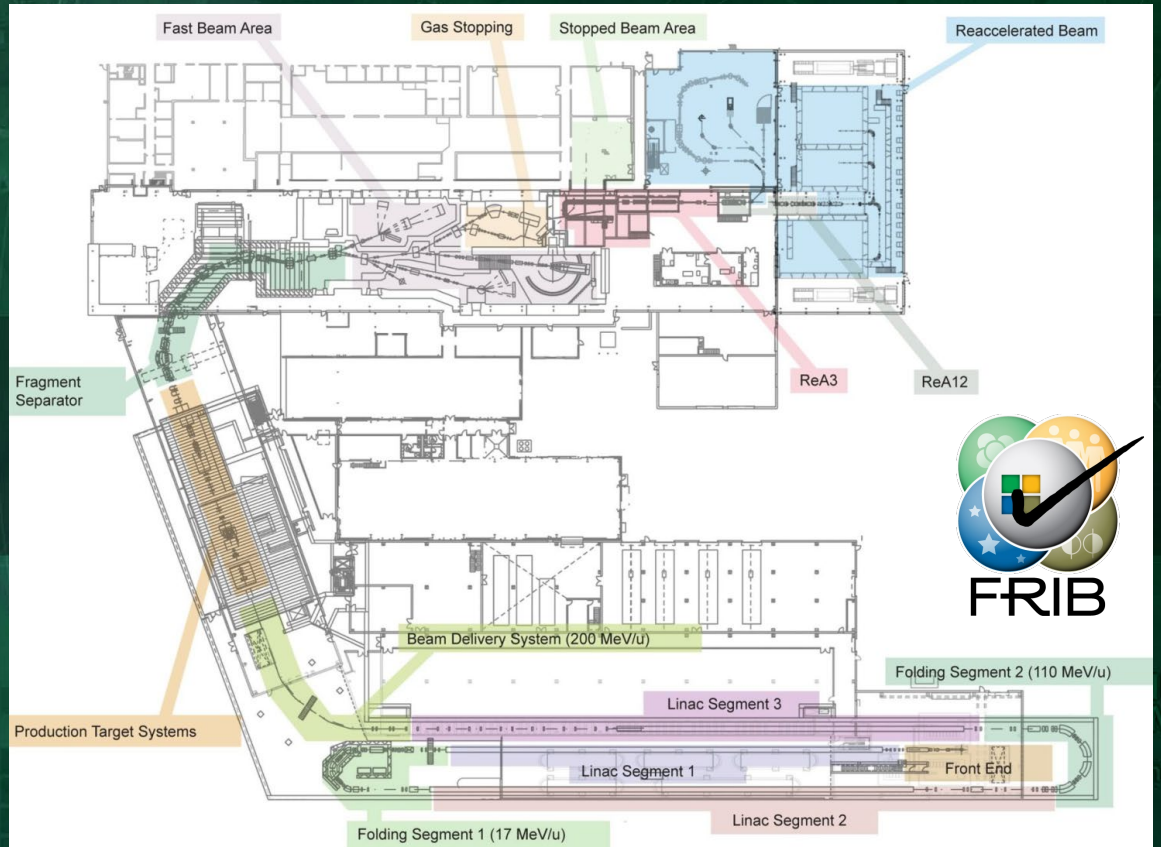
National Superconducting Cyclotron Laboratory (NSCL)

Located at Michigan State University

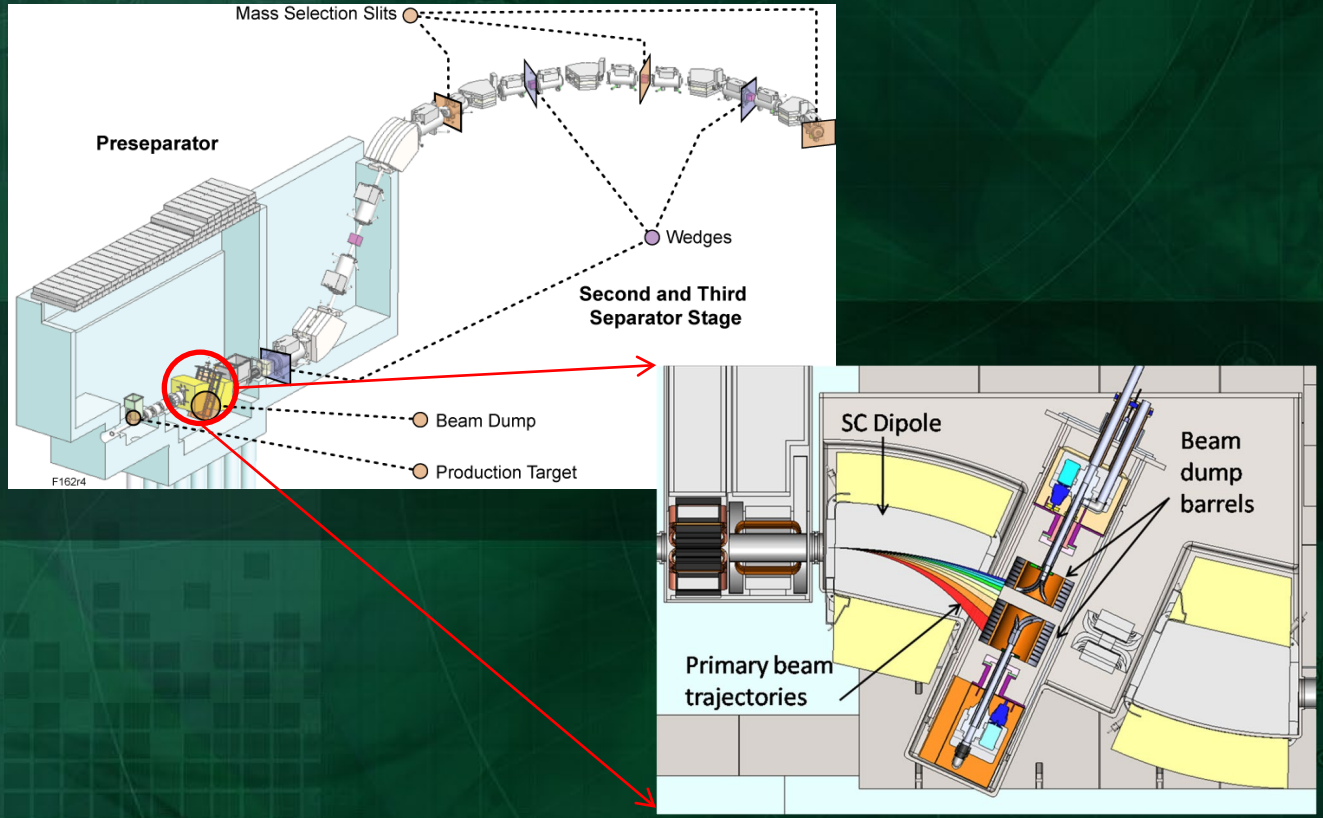


Upgrade of NSCL to FRIB

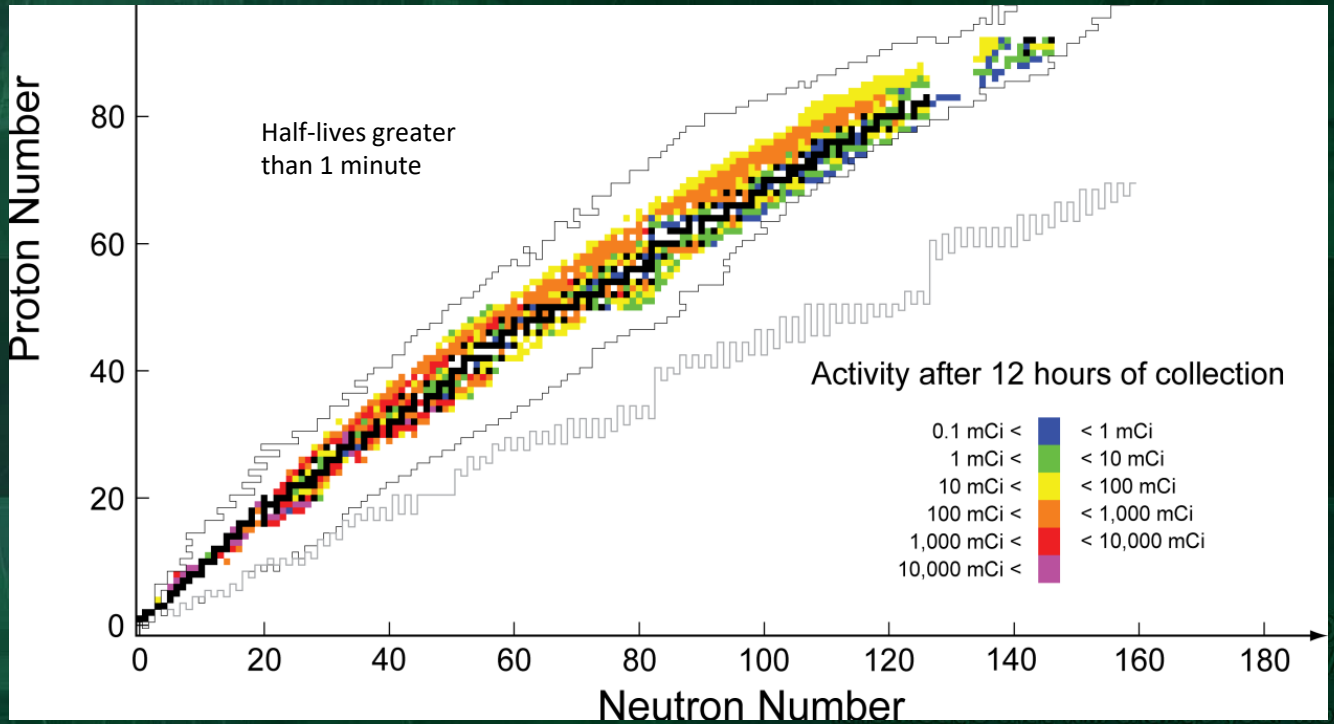
(Facility for Rare Isotope Beams)



Schematic of Proposed Secondary Beam Separator and Beam Dump at FRIB

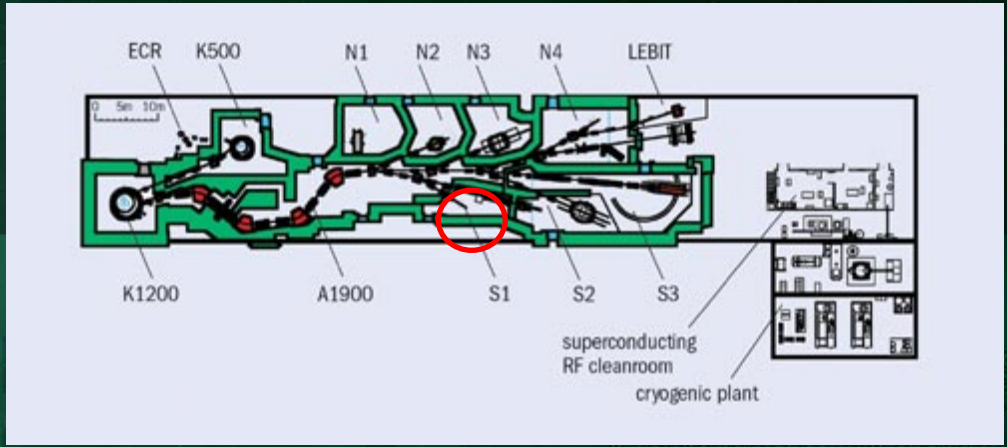


Why is Isotope Harvesting Important?



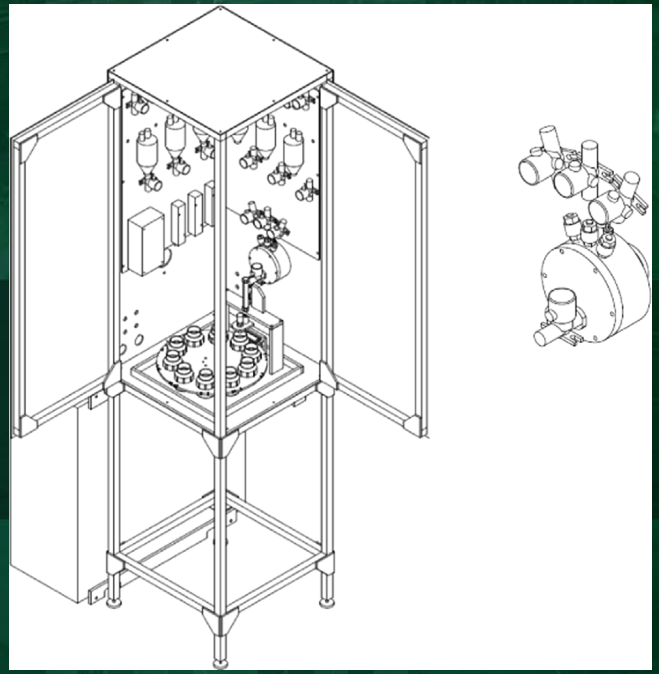
Preliminary experiments performed at the national superconducting cyclotron laboratory (NSCL)

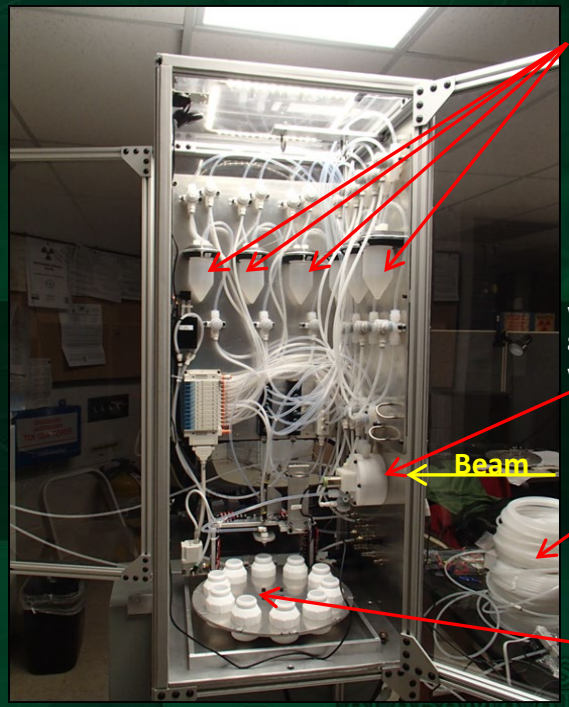
- End station that serves as a mock beam dump
- Effectively collect isotopes to show that we can collect beam in our end station
- Chemistry!



Pen, A., Mastren, T., et al, NIM A, 2014

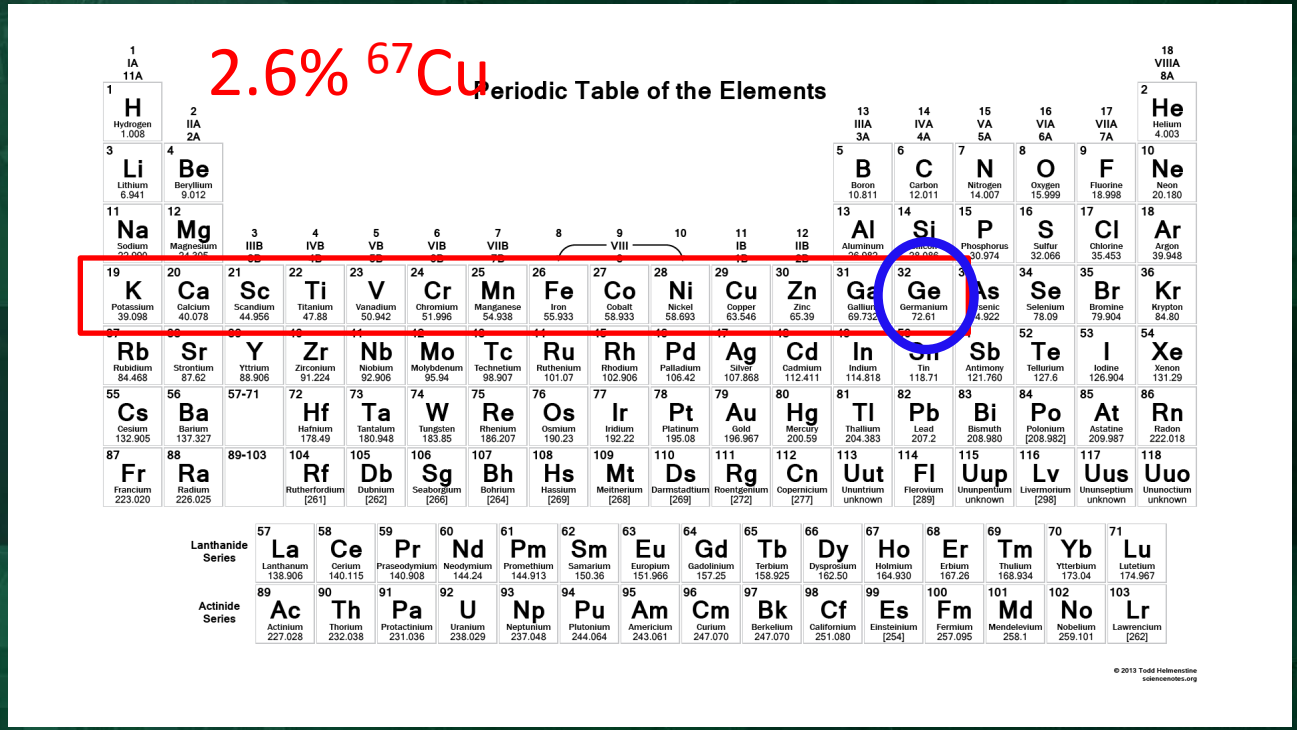
End Station Design (Hope College)



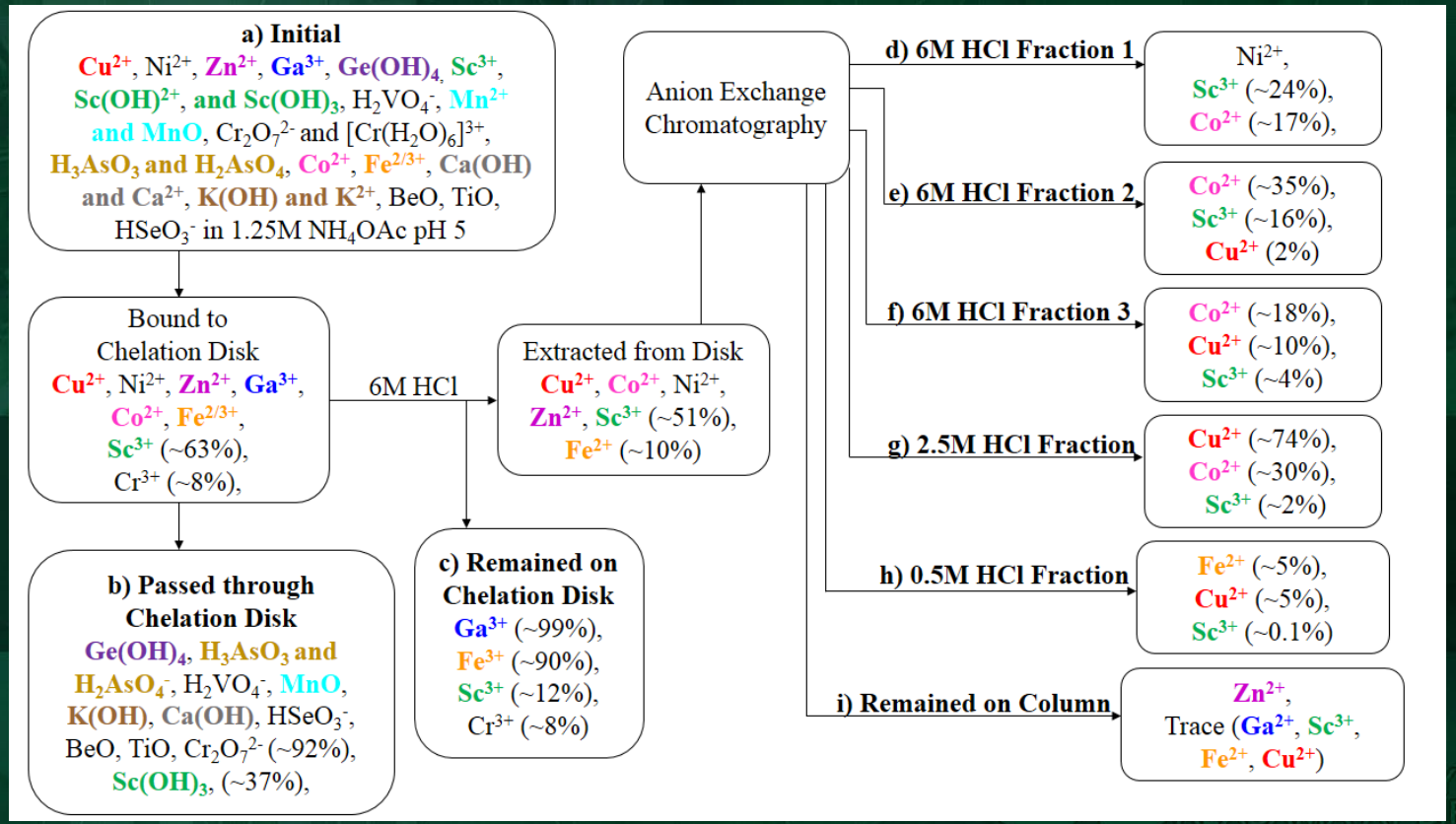


Pen, A., et al, NIM A, 2014

^{76}Ge Beam Fragmentation Products without Wedge

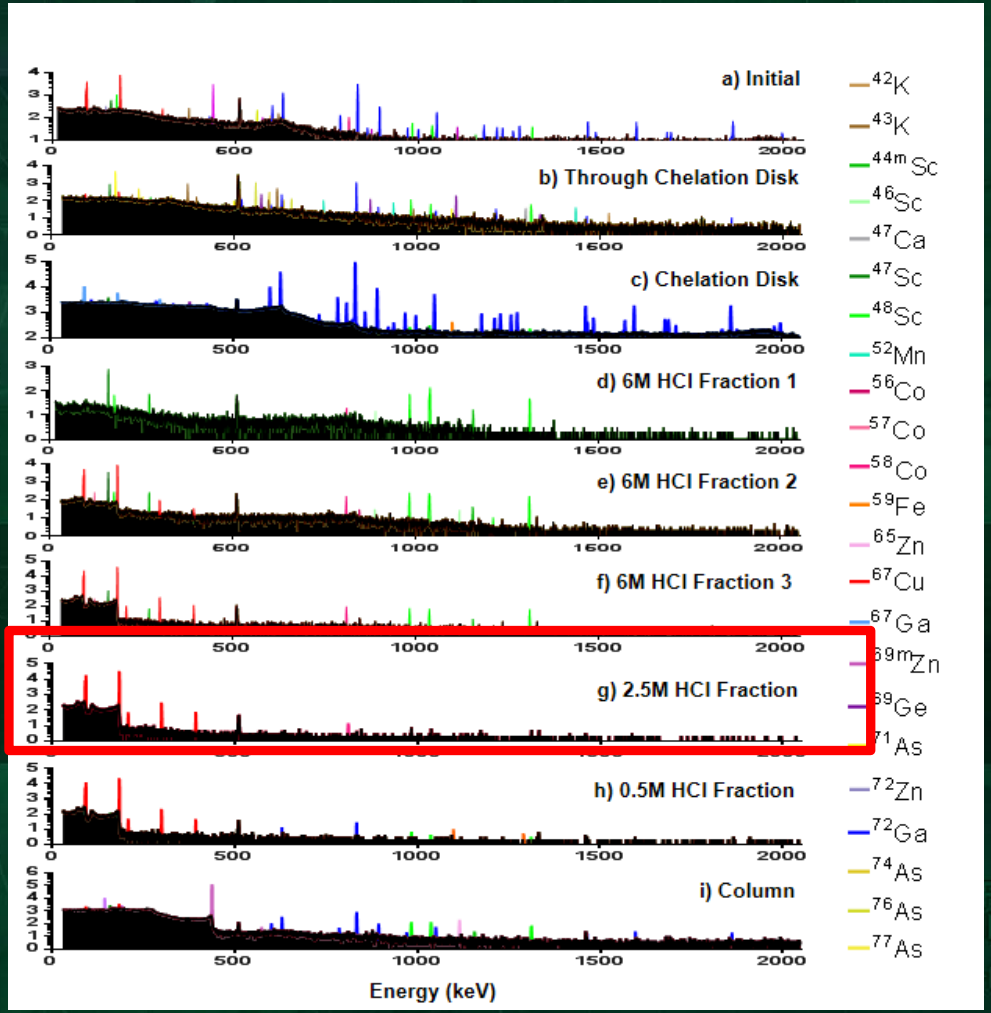


Separation Schematic



Mastren et al, Scientific Reports, 2014

HPGe Spectra of Different Points Throughout the Separation



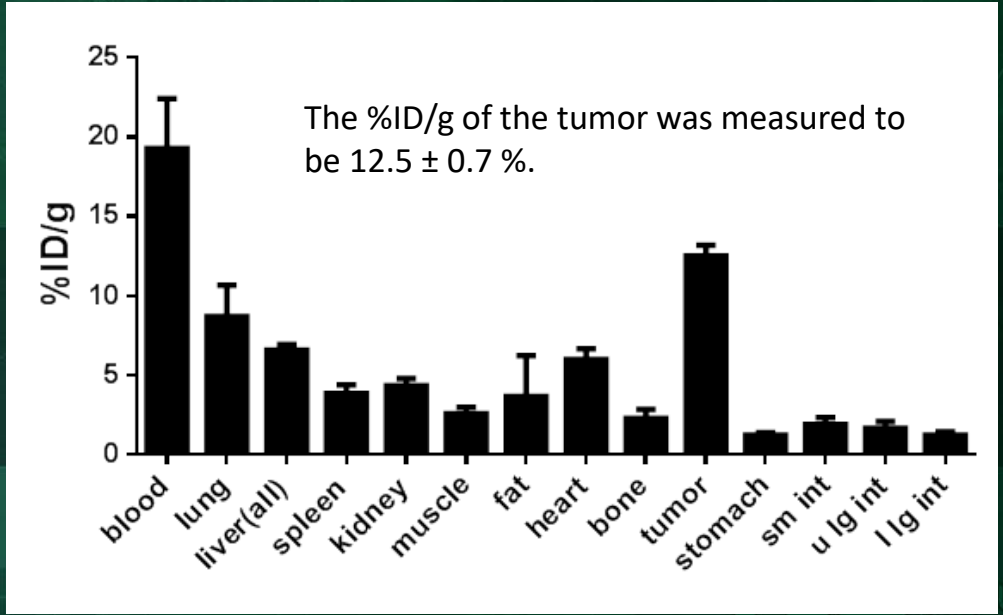
Mastren et al, Scientific Reports, 2014

Separation Results

Contaminating Element	Identifying Isotopes	Initial Contaminant to ^{67}Cu Ratio	Final Contaminant to ^{67}Cu Ratio
Ge	^{69}Ge	30	0
As	^{74}As	24	0
Ga	^{72}Ga	5.48	0.1096
Zn	^{69m}Zn	5.48	0
Ni	^{57}Ni	3.55	0
Fe	^{59}Fe	2.58	0
Cu	^{67}Cu	1.87	1.87
Cr	^{51}Cr	1.13	0
K	^{43}K	0.81	0
Ca	^{47}Ca	0.81	0
V	^{48}V	0.42	0
Sc	^{46}Sc, ^{47}Sc, ^{48}Sc	0.39	0.0078
Mn	^{52}Mn	0.32	0
Se	^{75}Se	0.13	0
Co	^{58}Co	0.06	0.018

74 ± 4% of the ^{67}Cu was obtained in the 2.5M fractions with a radiochemical purity of >99%. The other contaminants present in the ^{67}Cu fractions measured by HPGe for 12 hours and decay corrected to end of bombardment were ^{58}Co (0.07%), ^{48}Sc (0.06%), ^{47}Sc (0.06%), and ^{72}Ga (0.30%).

Biodistribution of ^{67}Cu-NOTA-Bz-Panitumumab



Mastren et al, Scientific Reports, 2014

Next Up: ^{48}V

- $t_{1/2}$ = 15.97 d, β^+_{avg} = 290 keV (49.9%)
- Goal: Harvest bulk quantity of ^{48}V (mg) from the beam dump at FRIB allowing for production of a ^{48}V target for an in-beam measurement of the $^{48}V(n,p)^{48}Ti$ reaction[3]
- Alternate production routes

  Accelerator: $^{nat}Ti(d,xn)^{48}V$, $^{nat}Ti(p,n)^{48}V$[1]
- Nuclear data from such a measurement will help better our understanding of nuclear reaction networks important to the mission of the Stockpile Stewardship Program[4]
- ^{48}V will be the fourth isotope harvested in a series of a proof-of-principle experiments (including ^{24}Na, ^{67}Cu, and ^{85}Kr)

[1]Cohen, I. M.; Siri, S.; Iljadica, M. C. F. *Adv. Chem. Engineer. Sci.* **2014**, 4, 300-307 [2]Siri, S.; Cohen, I. M. *Radiochim. Acta*. **2009.** 97, 543–546
[3]Mark Stoyer, personal communication, May **2016** [4]NSAC Rare-Isotope Beam (RIB) Task Force Report. **2007**.

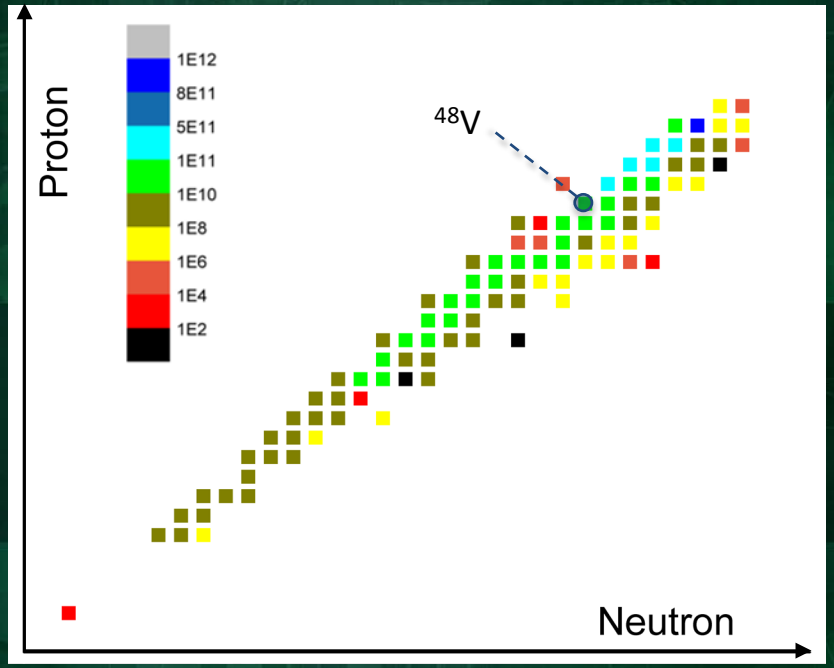
^{48}V - Modeling

- ^{58}Ni (160 MeV/u) on ^{9}Be (0.5 mm) stopped in a 100 mL water cell (~300 isotopes)
- Fragmentation products corrected for decay and ingrowth of daughters at 72 h after end of beam (~40 isotopes)

Element	N (atoms)	Fractional %	Oxidation	Element	N (atoms)	Fractional %	Oxidation
Co	1.03E+12	36.5	+2, +3	Cl	4.42E+10	1.6	-1, +1, +3-7
Fe	4.47E+11	15.8	+2, +3	S	4.65E+10	1.6	-2, +2, +4, +6
Cr	2.41E+11	8.5	+2, +3, +6	Si	3.18E+10	1.1	-4, +4
Mn	2.62E+11	8.0	+2-4, +5, +6	P	2.40E+10	0.8	-3, +3, +5
V	1.55E+11	5.5	+2-4, +5	Al	1.33E+10	0.5	+3
Ca	1.97E+11	6.9	+2	Mg	1.36E+10	0.5	+2
Ti	1.52E+11	5.4	+2, +3, +4	Na	7.83E+09	0.3	+1
K	7.16E+10	2.5	+1	C	1.37E+09	0.04	-4, +2, +4
Sc	5.10E+10	1.8	+3	Ni	4.84E+07	0.002	+2

[1]Predicted fragmentation products simulated using LISE++ (*http://lise.nscl.msu.edu/*)

^{48}V – Separation Chemistry



100 mL

dH_2O

Separation Chemistry

- Isotopic "Zoo"
- Selectively target vanadium
- Adjust sample to 0.01 M H_2SO_4
- Mixture of di-, tri-, and tetravalent cations

^{48}V – Separation Chemistry

- At H^+ concentrations above 0.01 M, vanadium(V) in low concentrations exists only as the VO_2^+ cation[1]
- The VO_2^+ cation reacted with H_2O_2 forms a mono- and diperoxoyvanadate shown below

$$VO_2^+ + H_2O_2 \leftrightarrows V(O_2)O^+ + H_2O \quad (K_1)$$

$$VO_3^+ + 2H_2O_2 \leftrightarrows VO_5^- + 2H_2O \quad (K_2)$$

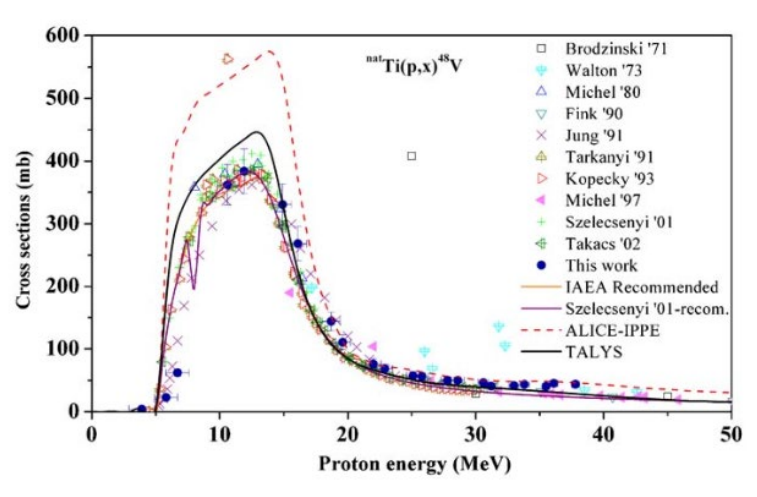
- Equilibrium constants have been reported in the literature (I = 1.0 M, t = 25.0°C)

Secco, F. (**1979**)[2]	Dean, G. A. (**1961**)[3]	Ohranovic, M. & Wilkins, R. G. (**1967**)[4]
$K_1 = 3.7 \pm 0.4 \times 10^4\ M^{-1}$	$K_1 = 8.2 \pm 0.0 \times 10^4\ M^{-1}$	$K_1 = 3.5 \pm 0.0 \times 10^4\ M^{-1}$
$K_2 = 0.6 \pm 0.1\ M$	$K_2 = 2.2 \pm 0.2\ M$	$K_2 = 1.3 \pm 0.0\ M$

[1]Fritz, S. J.; Abbink, J. E. *Anal. Chem.* **1962**, 34, 9 [2]Secco, F. *Inorganic Chemistry*. **1980**, 19, pp 2722-2726
[3]Dean, G. A. *Can. J. Chem.* **1961**, 39, pp. 1174-1183 [4]Orhanovic, M.; Wilkins, R. G. *J. Am. Chem. Soc.* **1967**, 89(2), pp 278-282

^{48}V – Cyclotron Production

- ◊ 127 micron ^{nat}Ti foil target (0.005”)
- ◊ dE/dx = 2.3 MeV (SRIM/TRIM 2013)
- ◊ 361-381 mb (IAEA recommended data set, CSISRS)



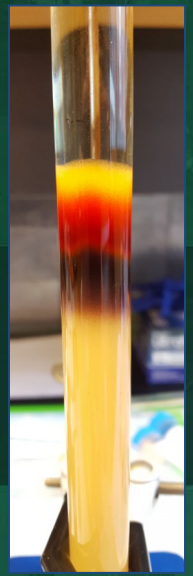
Target

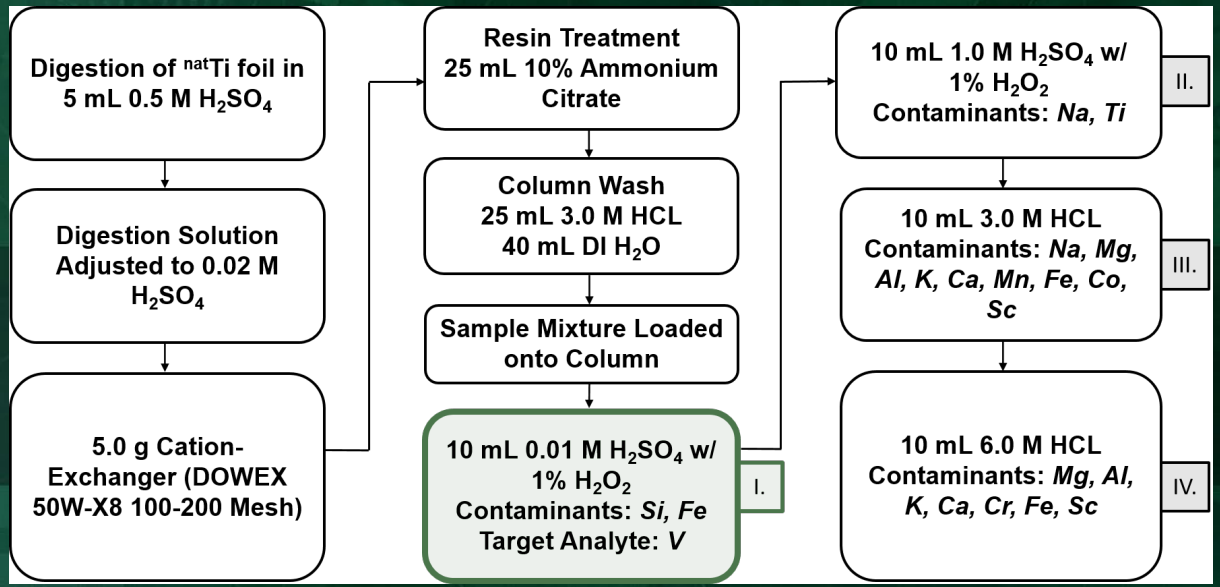
Reflux Digestion

[1]Khandaker, M. U. et al. *Appl. Radiat. Isot.* **2009**, 67, 1348-1354 [2]Wooten, A. L. et al. *Appl. Radiat. Isot.* **2015**, 96, pp. 154-161

^{48}V – Separation Chemistry

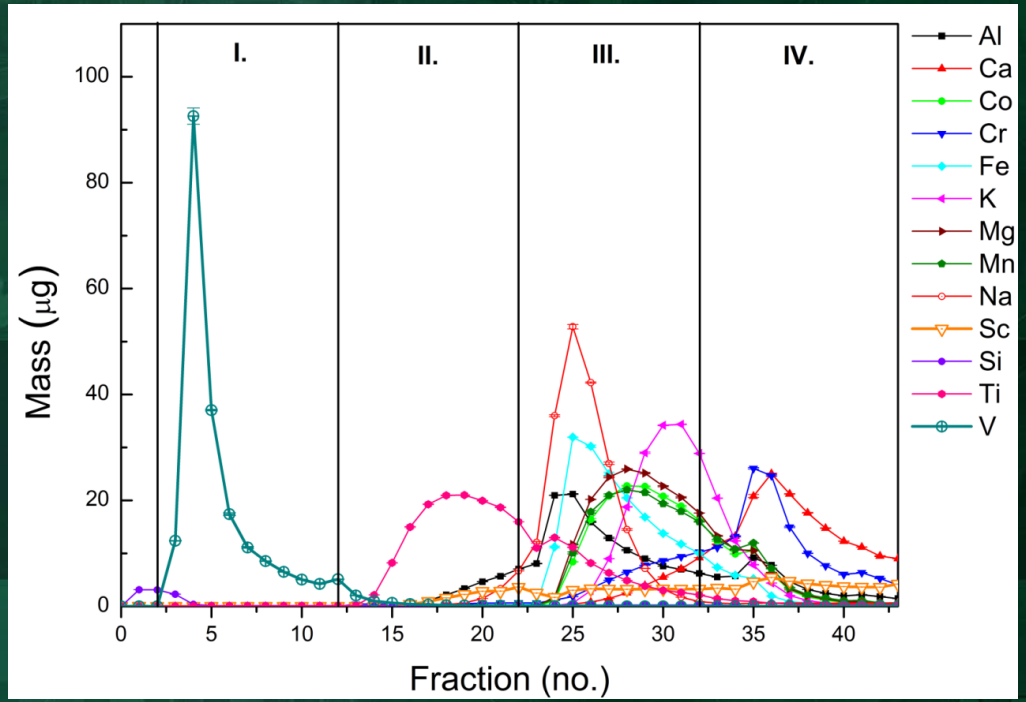
◊ Cation exchange method adapted from Fritz & Abbink[1]





[1]Fritz, S. J.; Abbink, J. E. *Anal. Chem.* **1962**, 34, 9

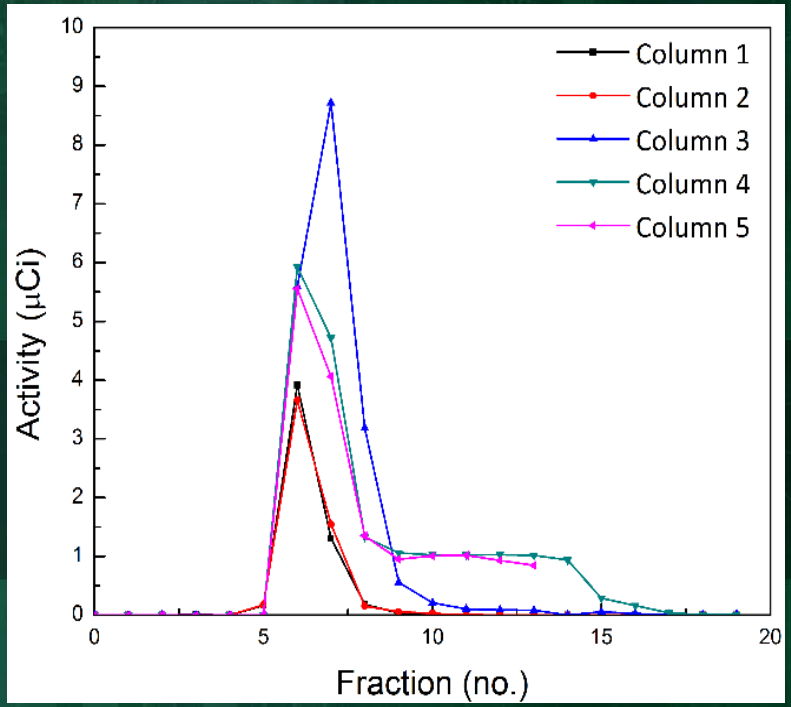
^{48}V – Separation Chemistry (cold)



Recovery		
Element	**Mass**	**%**
Al	189.7	95
Ca	198.1	99
Co	194.9	97
Cr	188.2	94
Fe	197.6	99
K	207.7	104
Mg	220.1	110
Mn	200.2	100
Na	217.3	109
Sc	89.3	45
Si	13.3	7
Ti	214.4	107
V	205.4	103

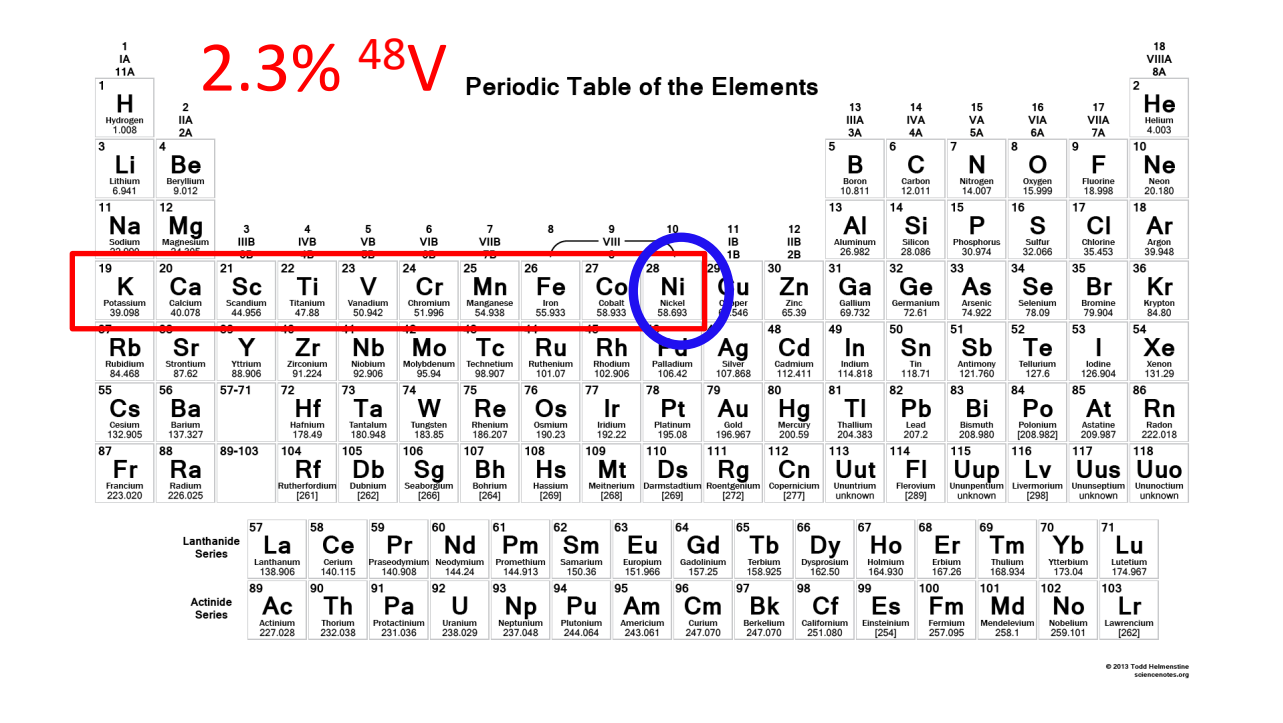
[a]Initial Mass = 200 µg

^{48}V – Separation Chemistry (tracer)



Percent Recovery for ^{48}V (n=5)					
Column	1	2	3	4	5
Initial (μCi)	6	6	18	18	19
Final (μCi)	6	6	19	20	18
Recovery (%)	100	100	106	111	95

^{48}V – ^{58}Ni Fragmentation run



- Identified ^{48}V, ^{44}Sc, ^{52}Mn,
- Separation chemistry and many gamma spectra under analysis

Summary

- Radioisotopes continue to play an important role in medicine.
- Complementary techniques can produce a wide variety of half-lives, imaging characteristics and chemistries leading 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, physicists, biologists and physicians.

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