From Isotopes to Images:
Accelerator Production of Radionuclides for Nuclear Medicine

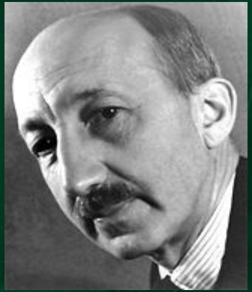
Suzanne Lapi, Associate Professor of Radiology
Director, UAB Cyclotron facility

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

What are isotopes used for?
The tracer principle

- In Nuclear Medicine and many areas of basic science, radioactive atoms are used tracers.
- Tracer behaves in a similar way to the components of the system to be probed.
- Tracer does not alter the system in any measurable fashion.
- Tracer concentration can be measured.

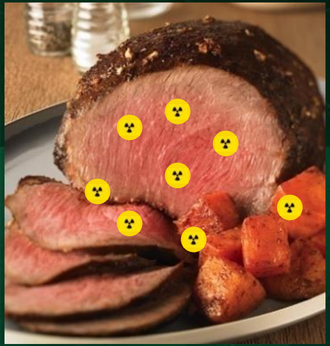
The first tracer experiment?



- George de Hevesy was a pioneer in radiochemistry
- While in Manchester in the early 1910's working with Rutherford, he suspected his landlady was serving recycled food

Sunday night roast

Radium



Wednesday hash

Radiopharmaceuticals

- A **radiopharmaceutical** is a drug labeled with a radionuclide to image a biological process or to deliver therapy to a specific disease site
  - the overall chemical structure determines biological properties
  - the radionuclide determines imaging or therapeutic properties

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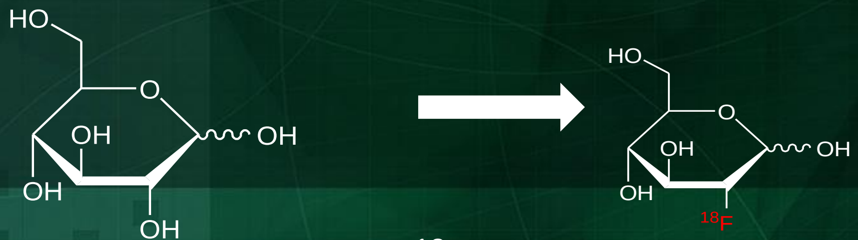
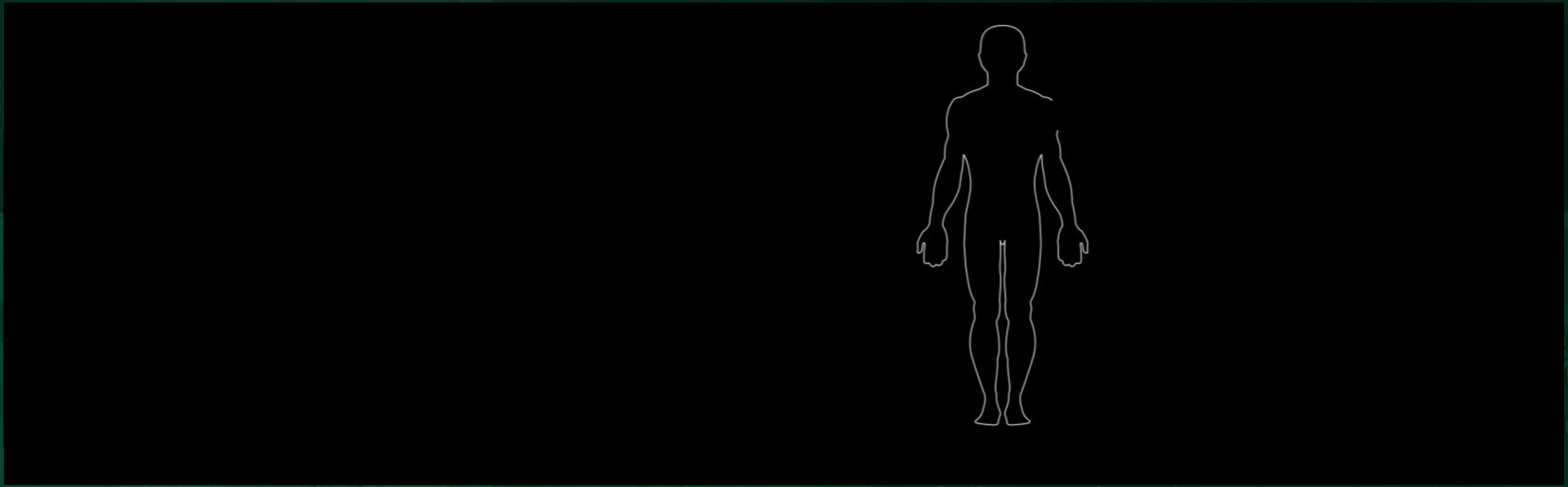


D-glucose

2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG)

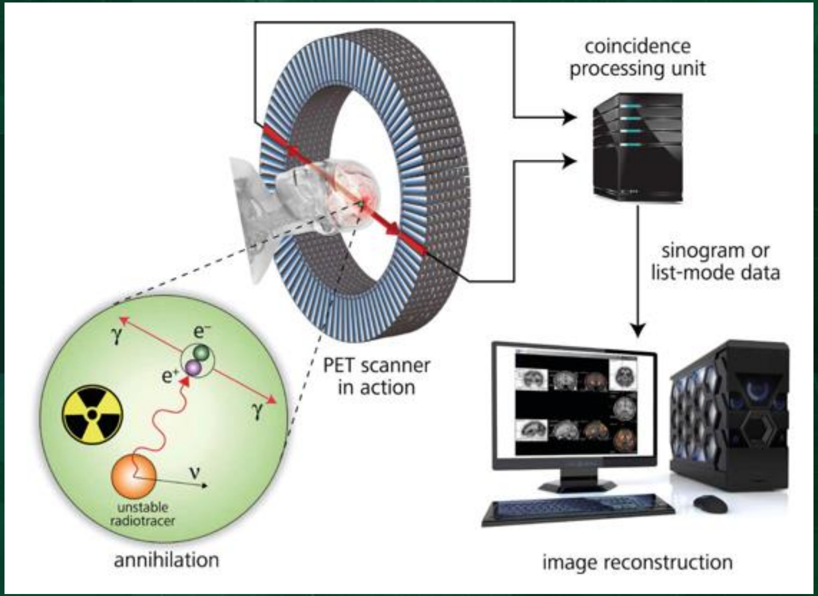
Radiopharmaceuticals

- Radiolabel compound of interest
- Use the radioisotope as a beacon to determine distribution over time

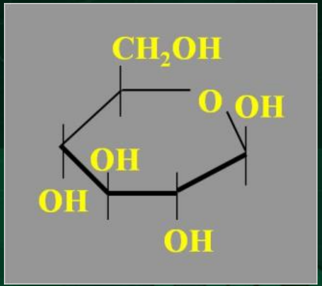


Positron Emission Tomography

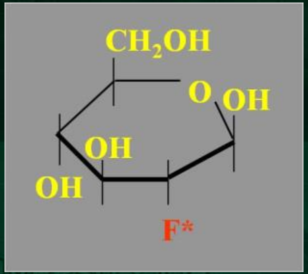
PET imaging is a very sensitive tool capable of providing quantitative information about biochemical and physiological processes in a non-invasive manner.



Glucose



Fluorodeoxyglucose (FDG)



59 year old woman with T-cell lymphoma

Initial study

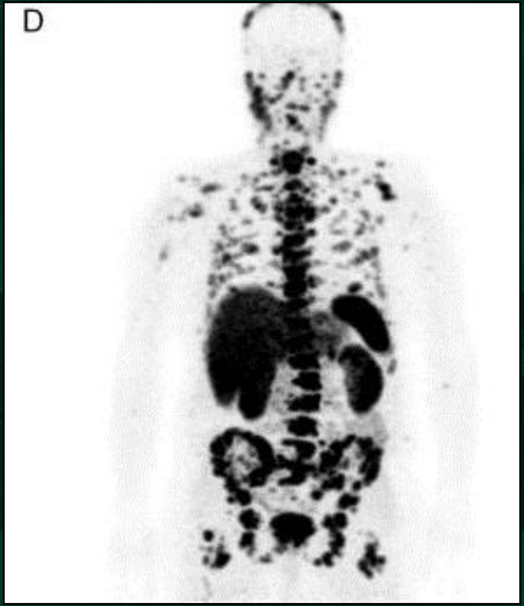
4 months later,
after chemotherapy

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

$^{14}N(p,\alpha)^{11}C$ $t_{1/2}$ = 20.3 min.

$^{18}O(p,n)^{18}F$ $t_{1/2}$ = 109.7 min.

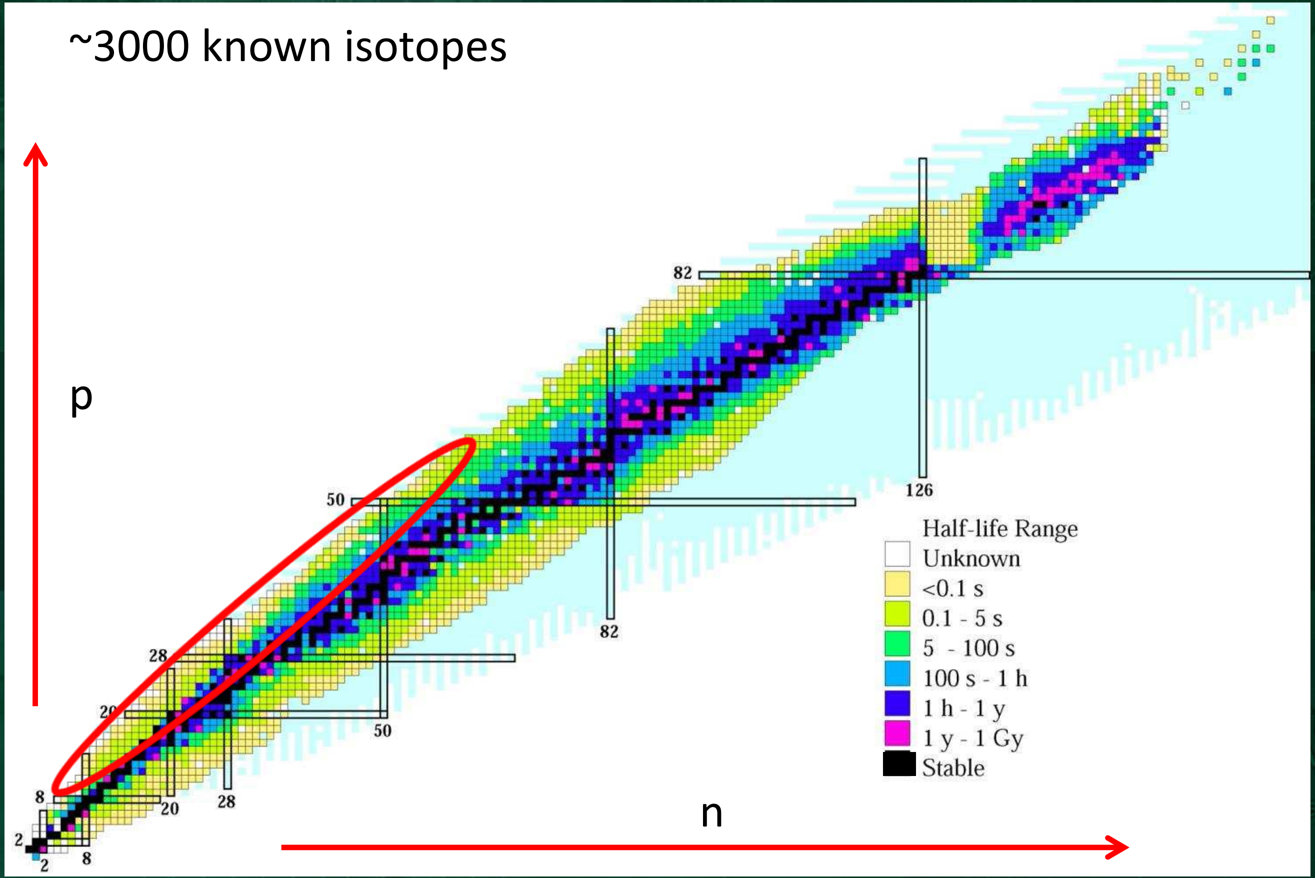
$^{16}O(p,\alpha)^{13}N$ $t_{1/2}$ = 9.97 min

$^{14}N(d,n)^{15}O$ $t_{1/2}$ = 2.0 min

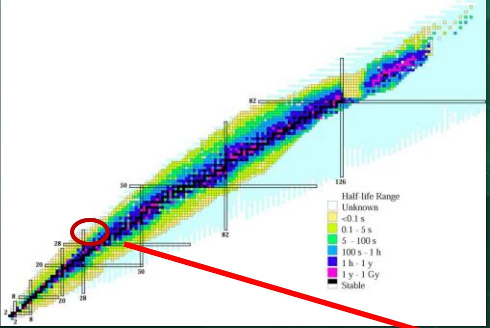
Radiometals

- 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



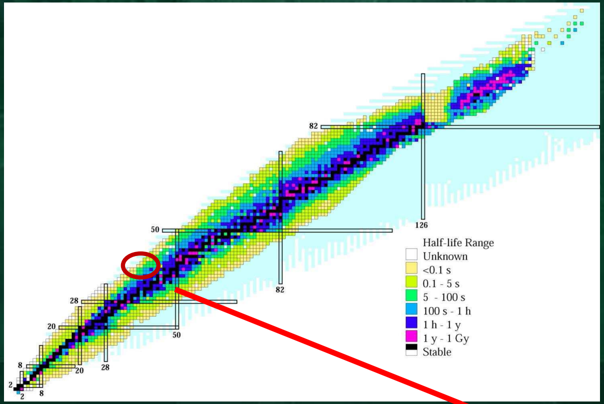
Radiometals?



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%

Radiometals?



Second row:

Z \ N	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%

Current Research

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

Cyclotron Production of Radionuclides

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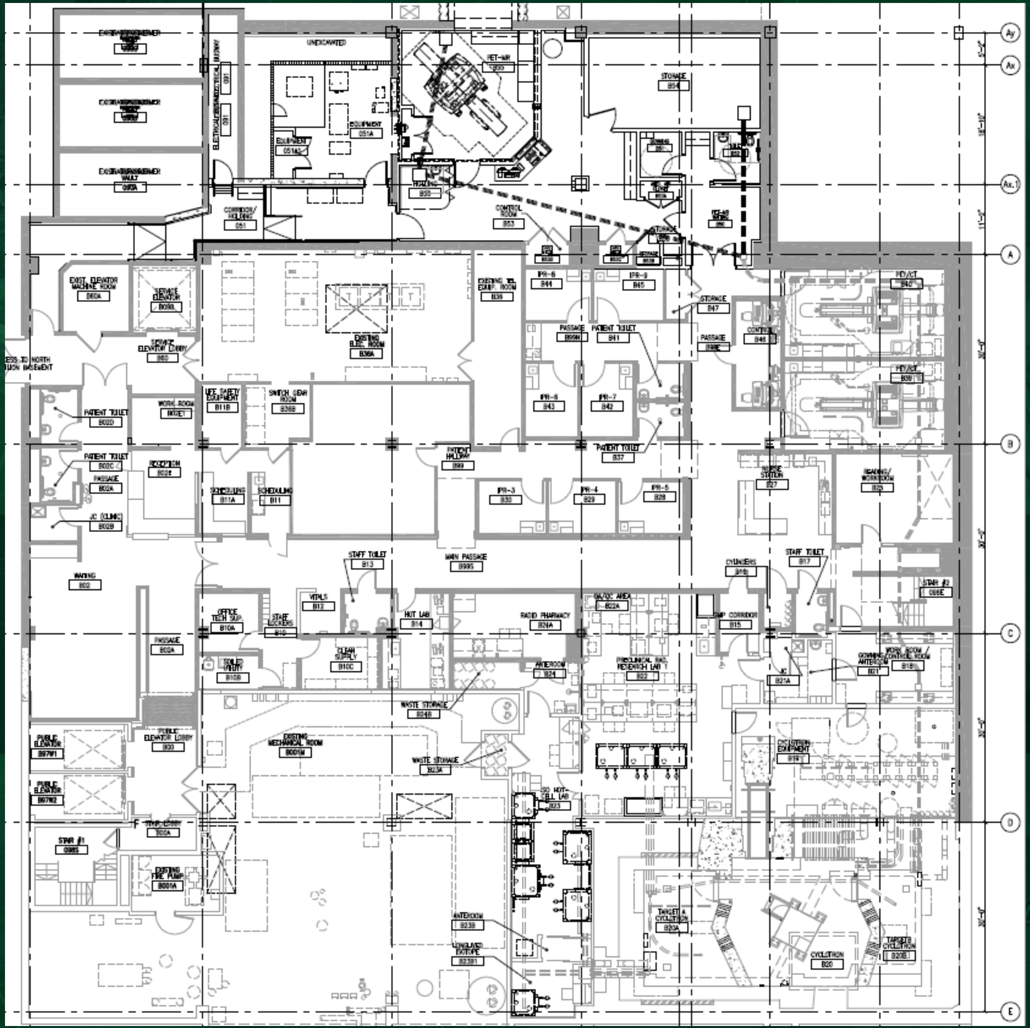
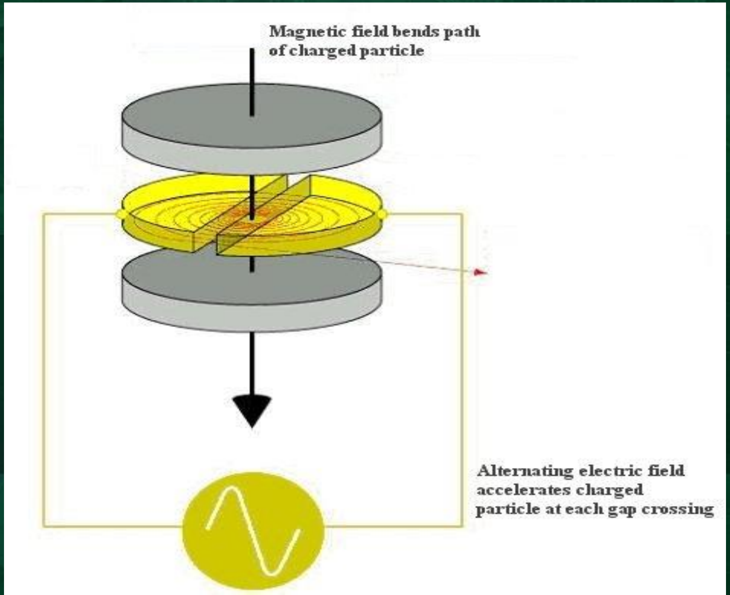
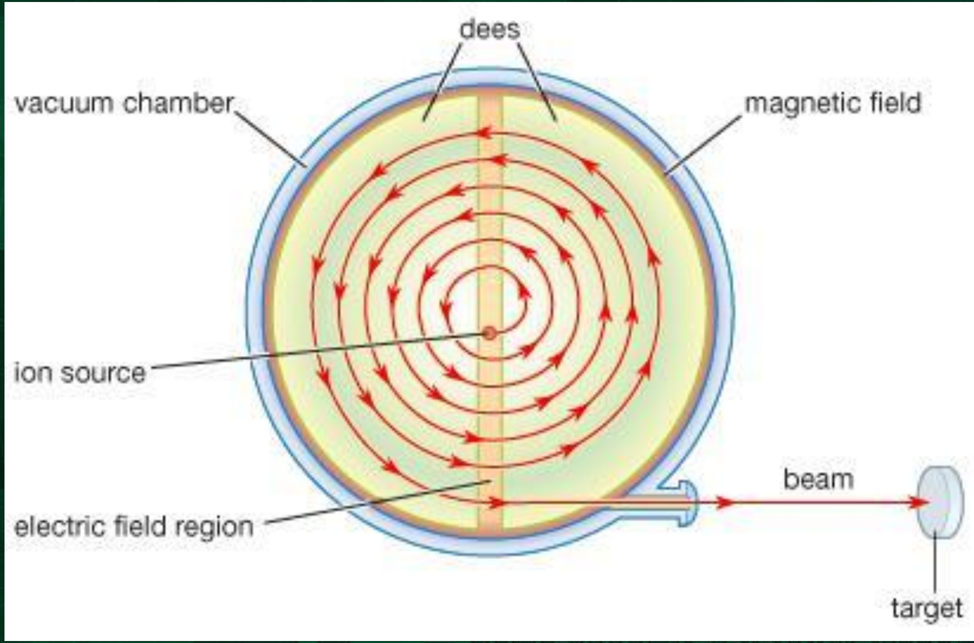
Knowledge that will change your world

University of Alabama: Wallace Tumor Institute



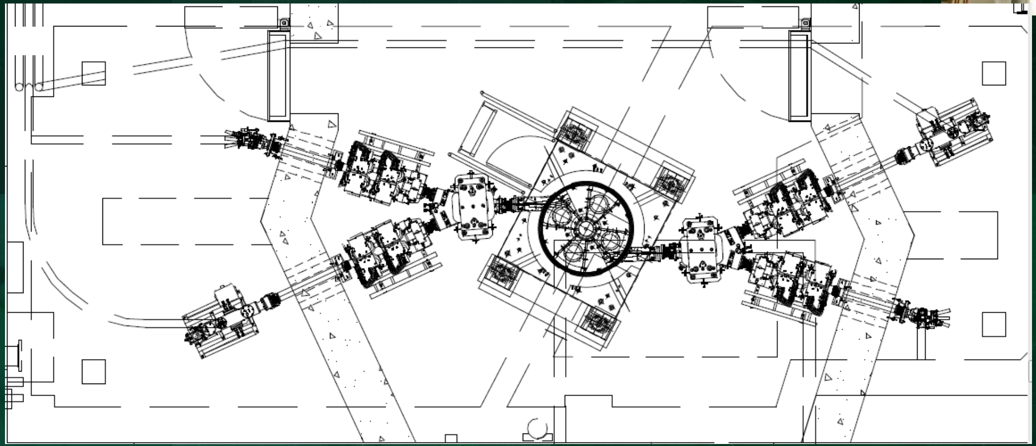
Cyclotrons

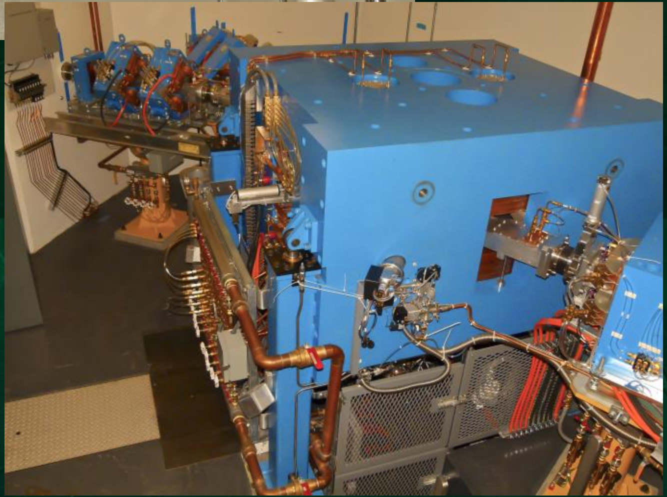

Magnetic field bends path
of charged particle
Alternating electric field
accelerates charged
particle at each gap crossing


dees
vacuum chamber
magnetic field
ion source
beam
electric field region
target

Cyclotrons (University of Alabama at Birmingham)

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





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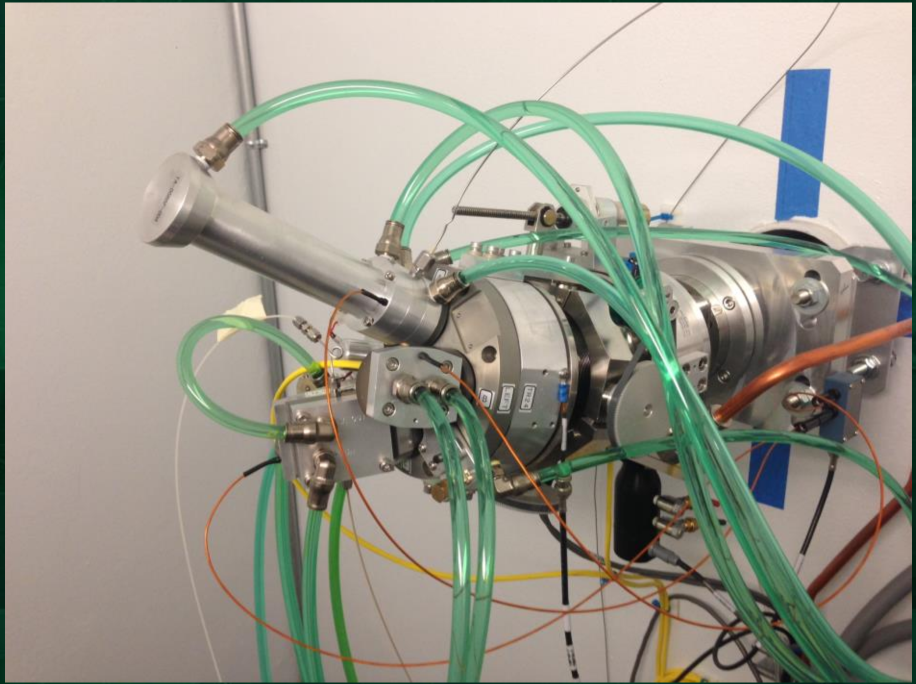
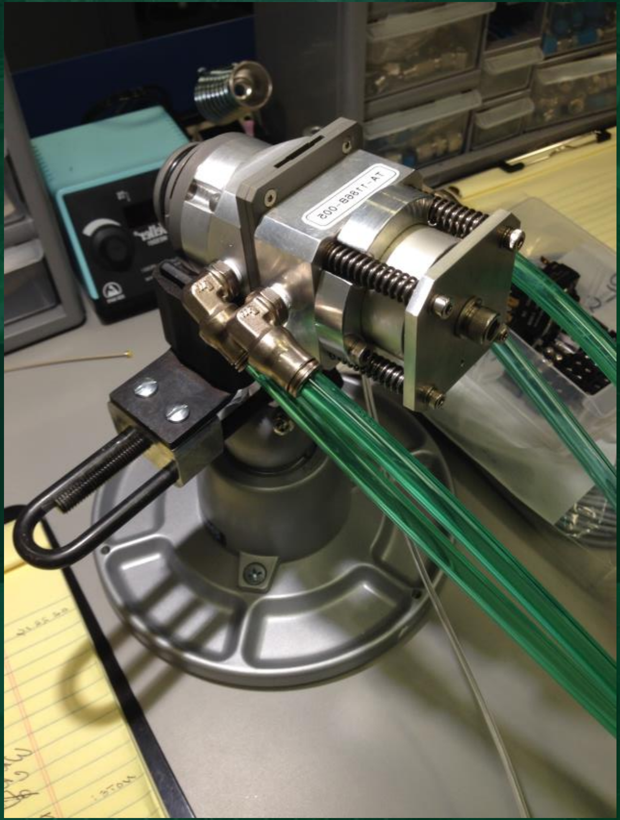
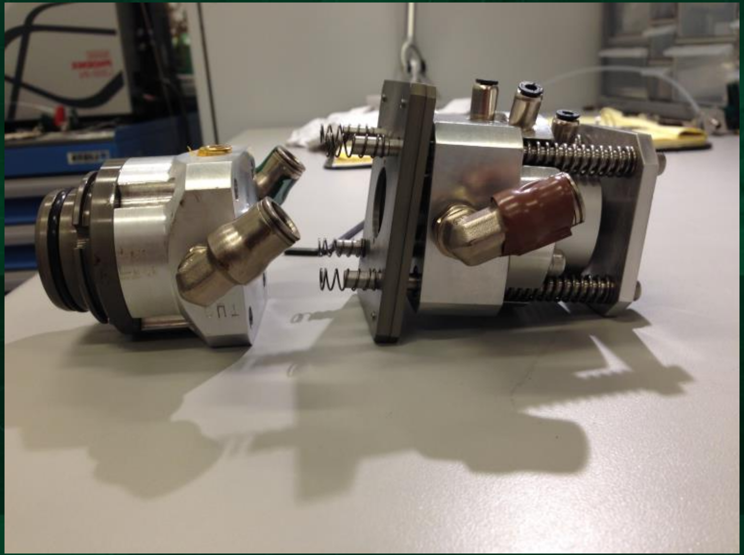


Targetry Systems (University of Alabama at Birmingham)



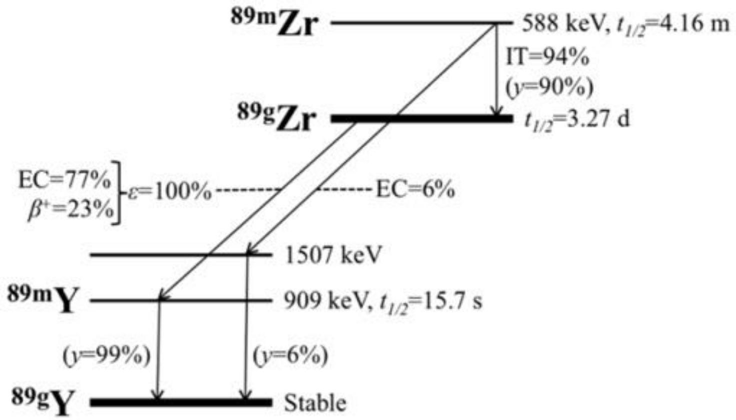


PET Radiometals

Isotope	Half-Life	Target Material
^{52}Mn	5.6 d	^{52}Cr
^{55}Co	17.5 h	^{58}Ni
^{64}Cu	12.7 h	^{64}Ni
^{86}Y	14.7 h	^{86}Sr
^{89}Zr	3.27 d	^{89}Y

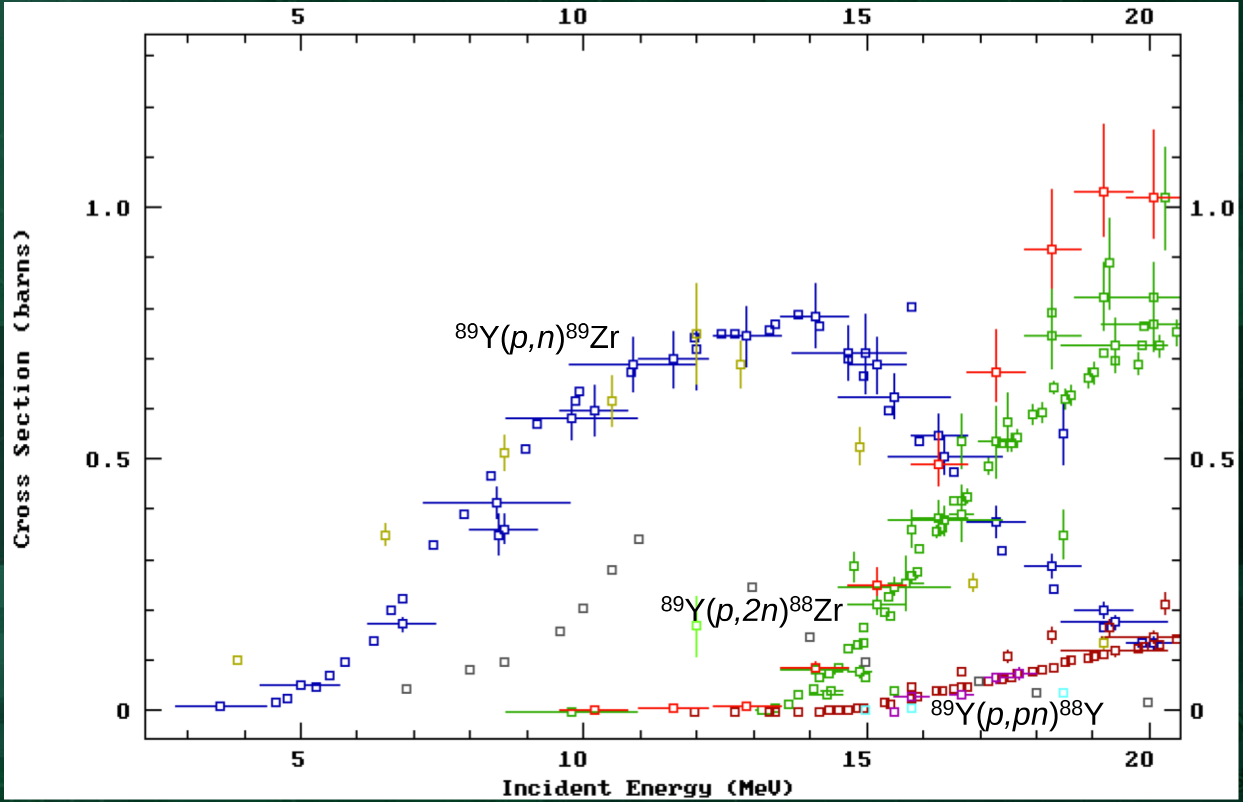
Zirconium-89

- 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

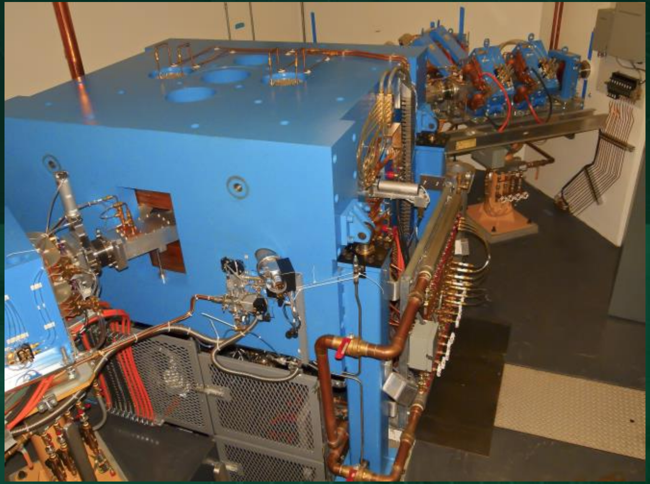
- $^{89}Y(p,n)^{89}Zr$

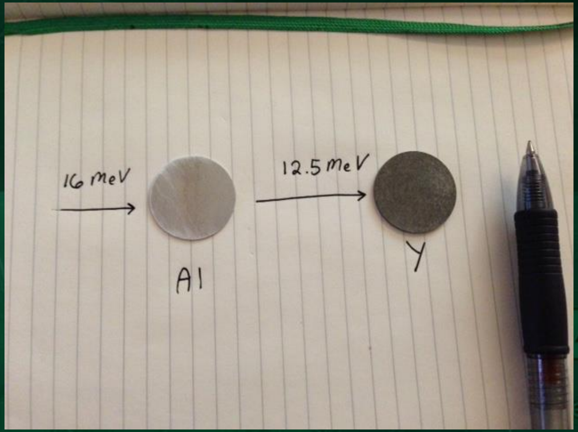


Zr-89 production

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

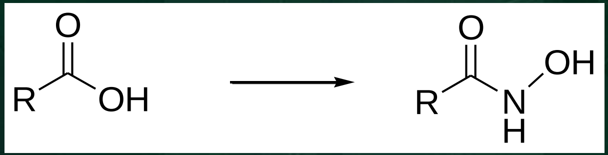
87Zr 1.68 H ϵ: 100.00%	88Zr 83.4 D ϵ: 100.00%	89Zr 78.41 H ϵ: 100.00%	90Zr STABLE 51.45%	91Zr STABLE 11.22%	92Zr STABLE 17.15%	93Zr 1.53E+6 Y β-: 100.00%
86Y 14.74 H ϵ: 100.00%	87Y 79.8 H ϵ: 100.00%	88Y 106.626 D ϵ: 100.00%	89Y STABLE 100%	90Y 64.053 H β-: 100.00%	91Y 58.51 D β-: 100.00%	92Y 3.54 H β-: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



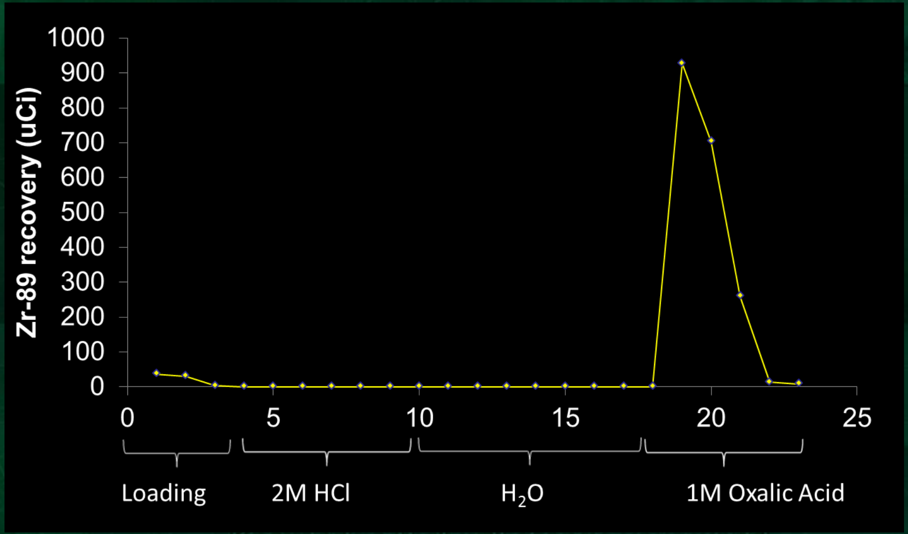


^{89}Zr purification

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

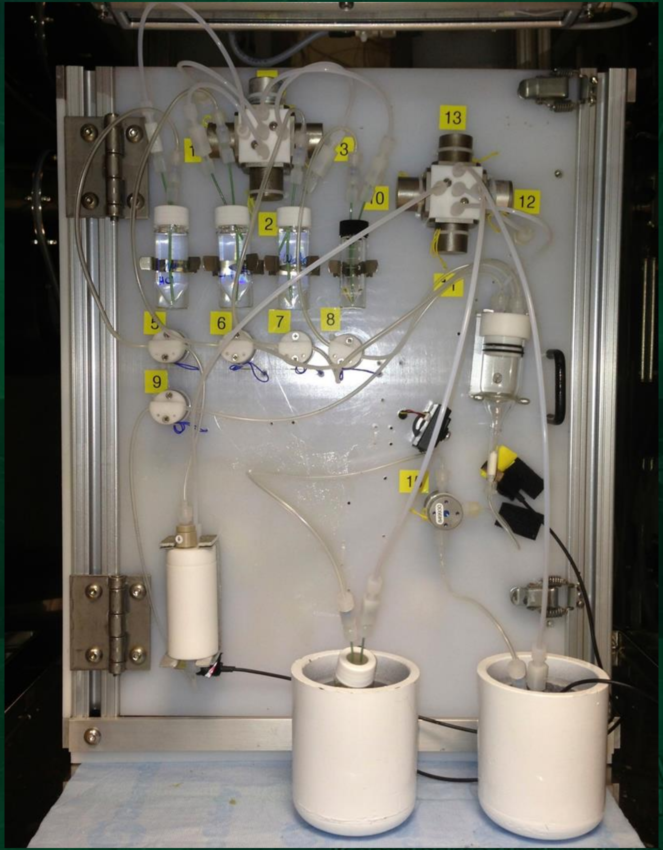


Accell resin Hydroxamate resin



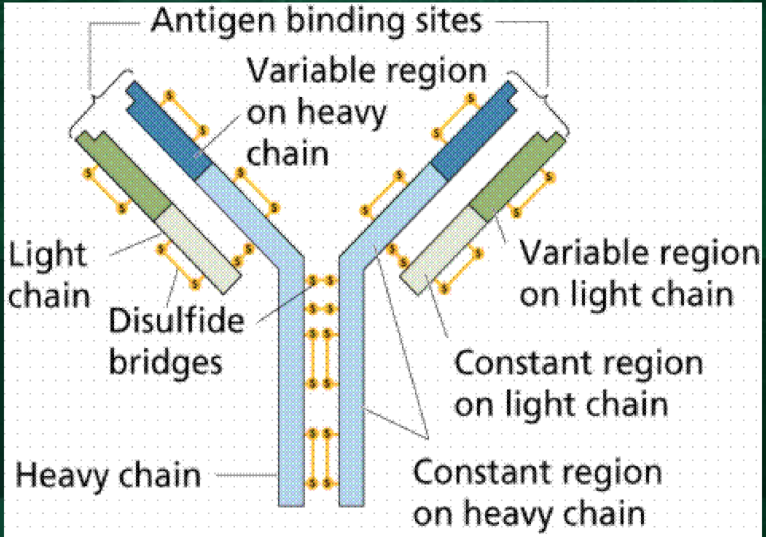
Verel et al J Nuc Med 2003

Scale Up and Automated Separation



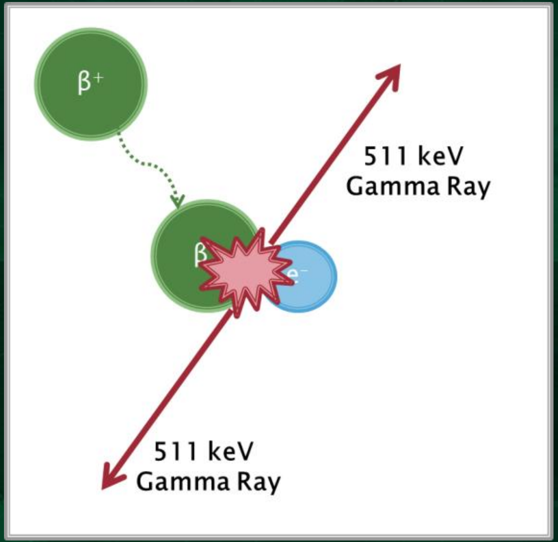
Wooten et al. App Sci 2013

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

Human Epidermal Growth Factor Receptor 2 (HER2)

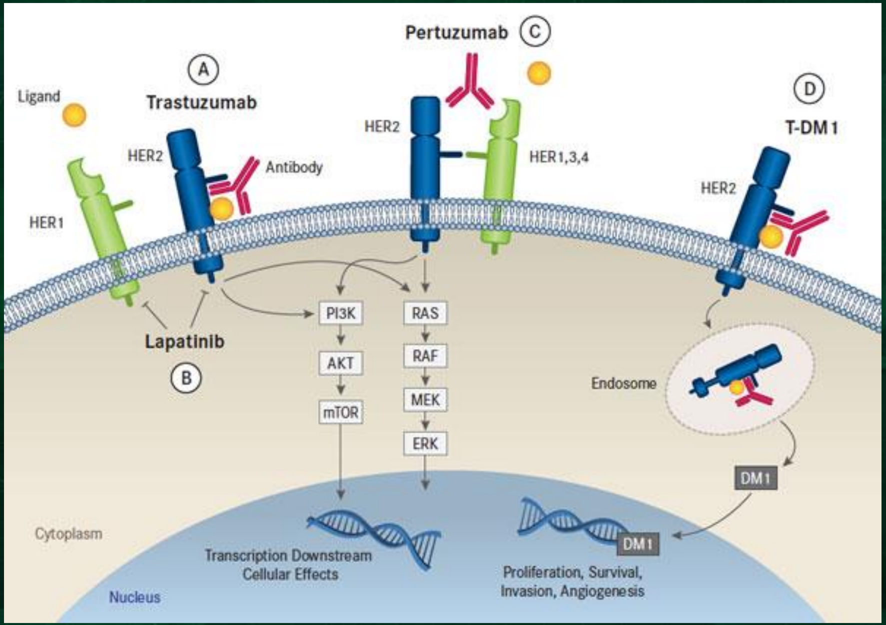
- Transmembrane receptor
- No known natural ligands
- Amplified in approximately 20 % of invasive breast cancers
- Associated with increased tumor aggressiveness, resistance to therapies, and increased mortality

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

Trastuzumab

- Clinically approved antibody

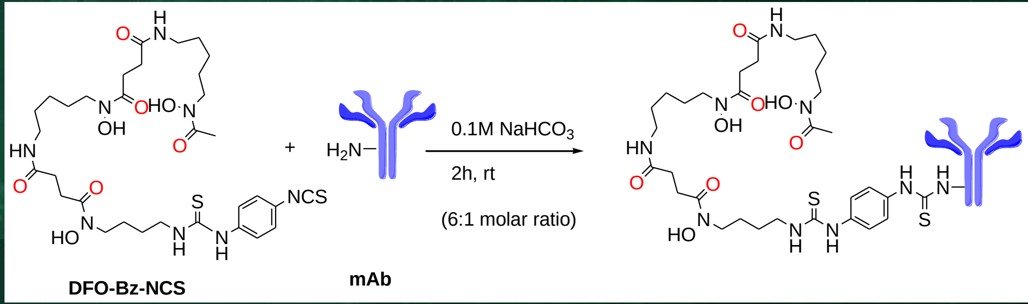
INDICATIONS AND USAGE

HERCEPTIN as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. HERCEPTIN in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease. HERCEPTIN should be used in patients whose tumors have been evaluated with an assay validated to predict HER2 protein overexpression (see PRECAUTIONS: HER2 Testing and CLINICAL STUDIES: HER2 Detection).

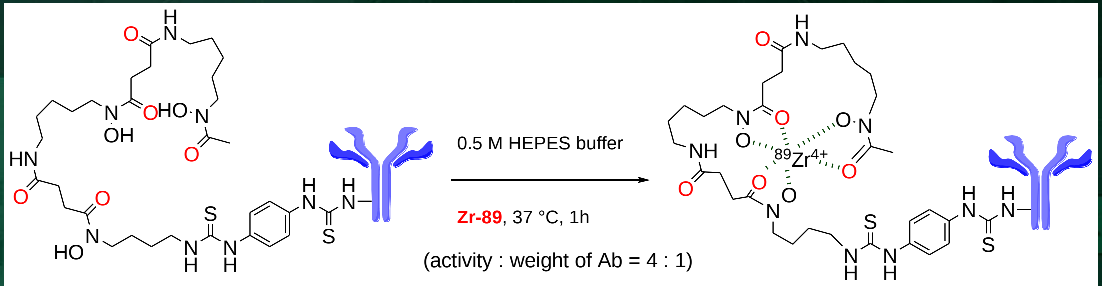
- Trastuzumab imaging agent may be useful for determining dosing strategies and for predicting response to Trastuzumab therapy

^{89}Zr: Conjugation and Labeling

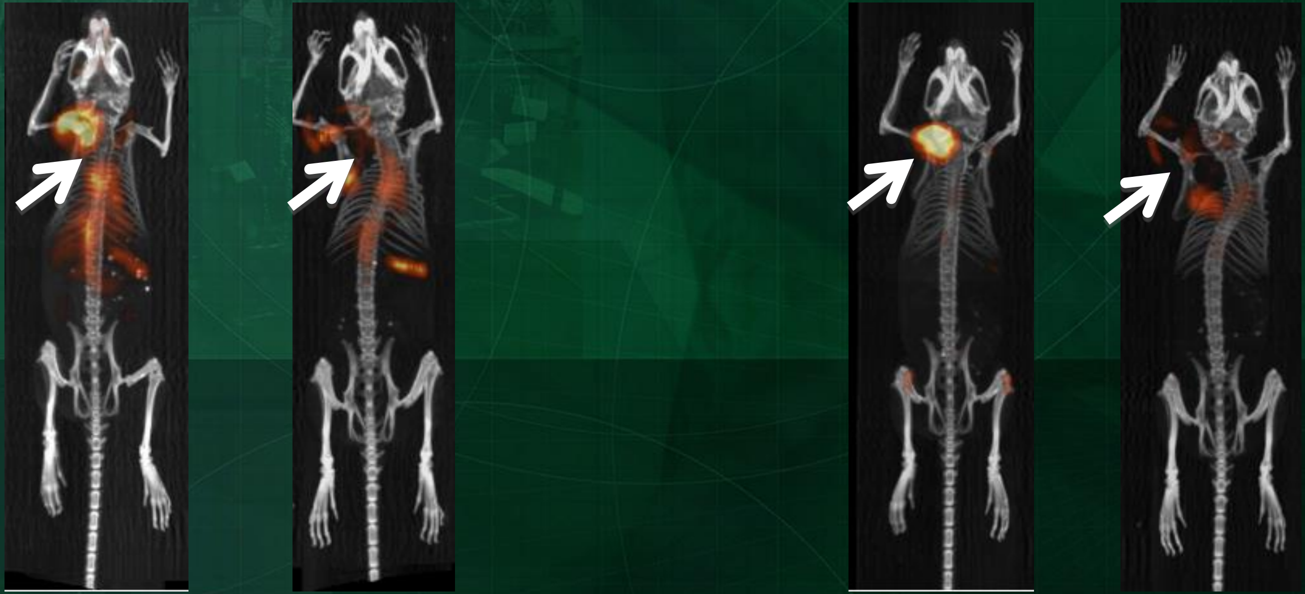
(a) mAb conjugation to DFO-Bz-NCS



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



^{89}Zr-DFO-Trastuzumab



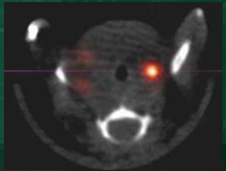
Her2+ Her2- Her2+ Her2-

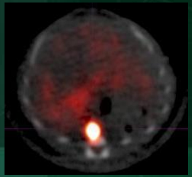
24 h 96 h

Chang et al, Pharmaceuticals, 2012

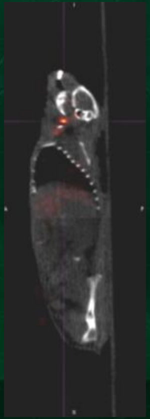
^{89}Zr-DFO-Trastuzumab Imaging Metastasis

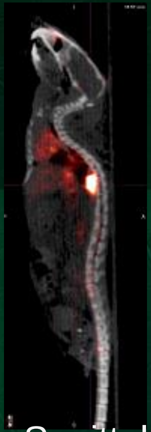
Bioluminescent Imaging



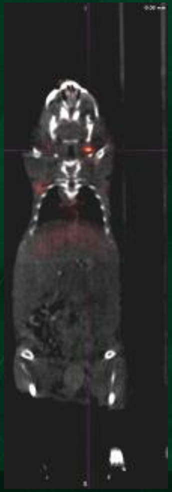


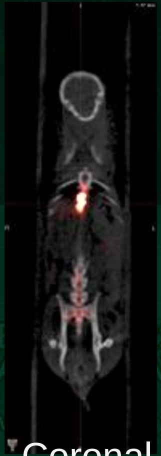
Axial





Sagittal





Coronal

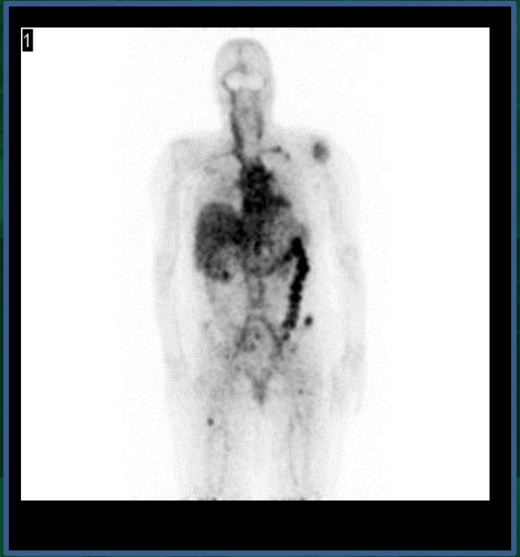
Chang et al, Pharmaceuticals, 2012

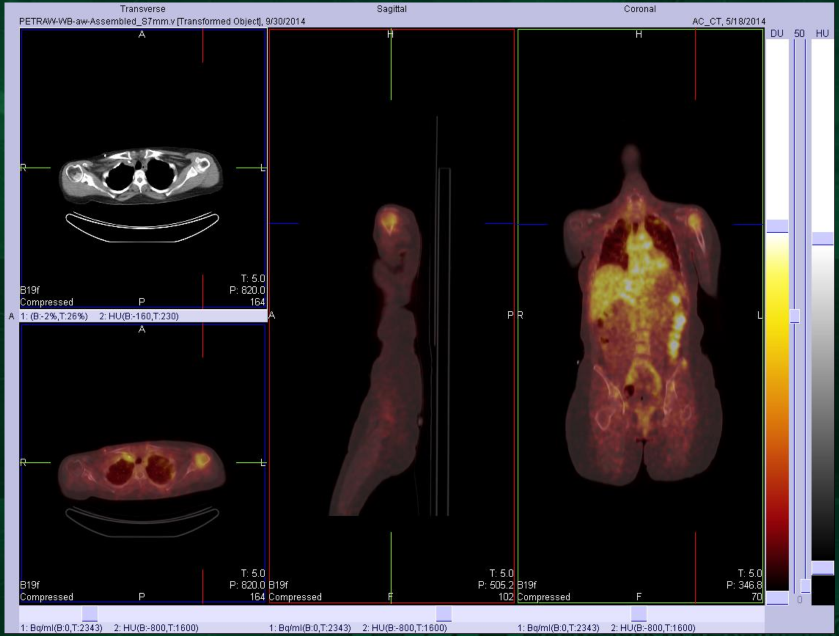
^{89}Zr-DFO-Trastuzumab
Washington University Clinical Trial

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

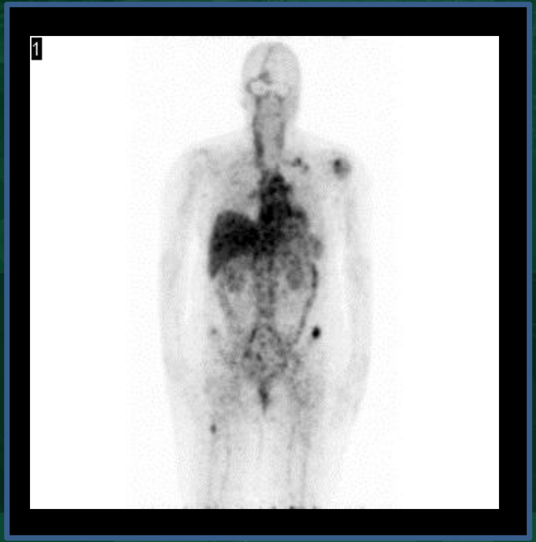
Arms	Assigned Interventions
Experimental: Cohort 1 ^{89}Zr-Trastuzumab Human Dosimetry and Safety	Drug: ^{89}Zr-Trastuzumab Human Dosimetry and Safety PET Imaging following administration of ^{89}Zr labeled Trastuzumab for calculation of human dosimetry and overall safety Drug: HER2 Positive Lesion Detection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

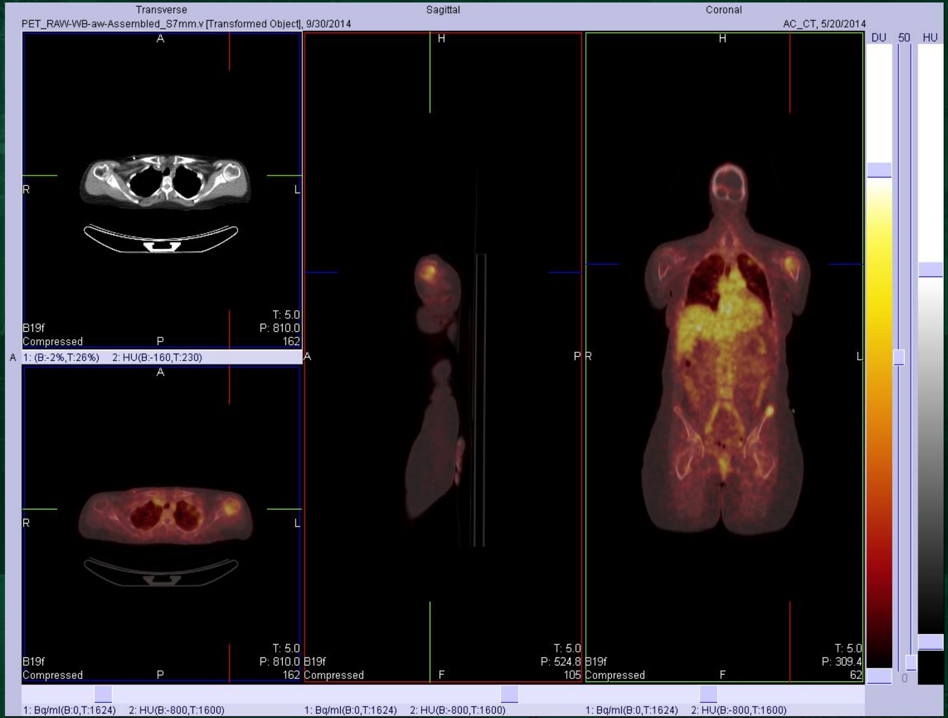
^{89}Zr-Trastuzumab Clinical Trial: Day 2





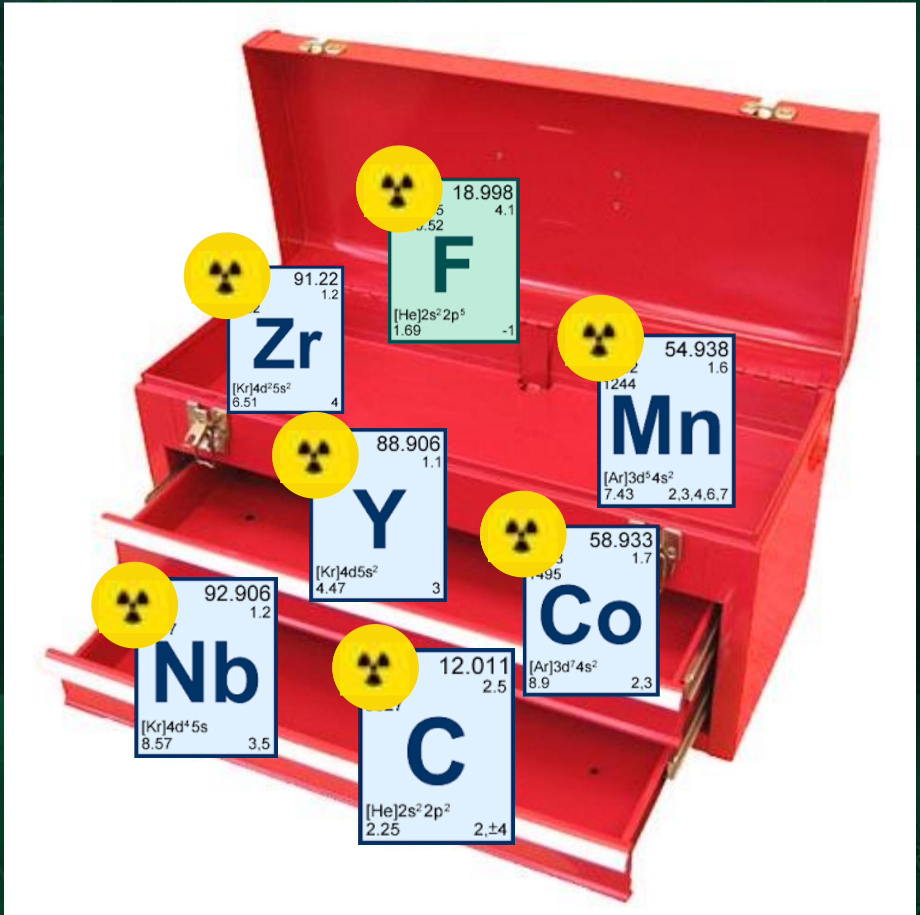
^{89}Zr-Trastuzumab Clinical Trial: Day 5





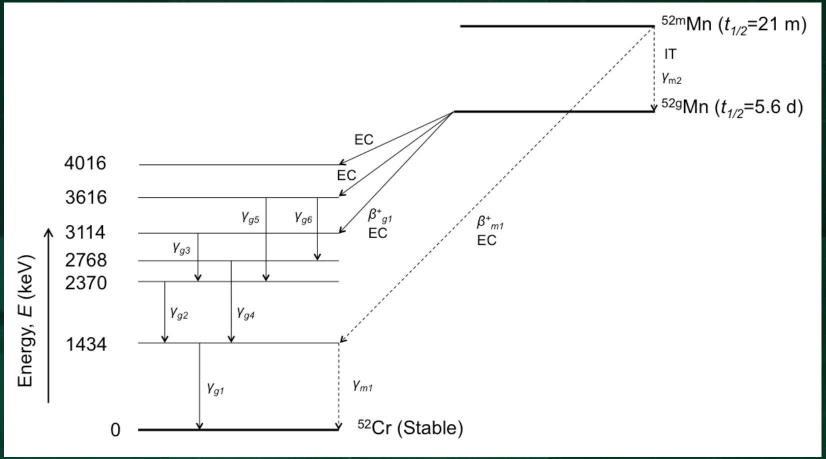
What's Next?

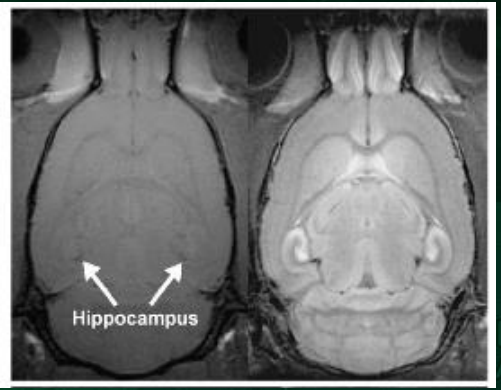
Expanding the Toolbox.

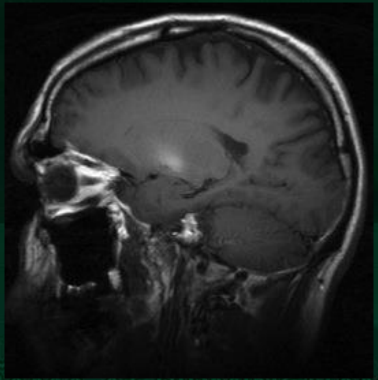


Development of Novel Radionuclides Examples: ^{52}Mn

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





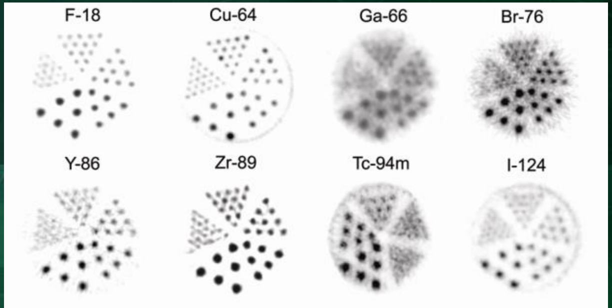


^{52}Mn Characteristics

		Production		Positron Emission		Gamma Radiation
	Half-Life	Most Common Target	Target Natural Abundance	Weighted Average Energy (keV)	Total Intensity	Gamma Factor ($R \cdot cm^2 \cdot mCi^{-1} \cdot h^{-1}$)
^{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.



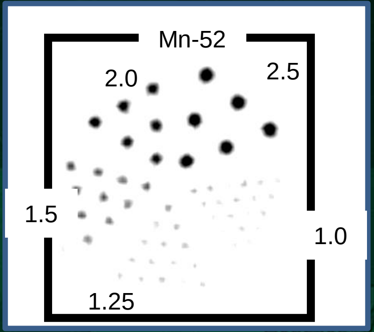
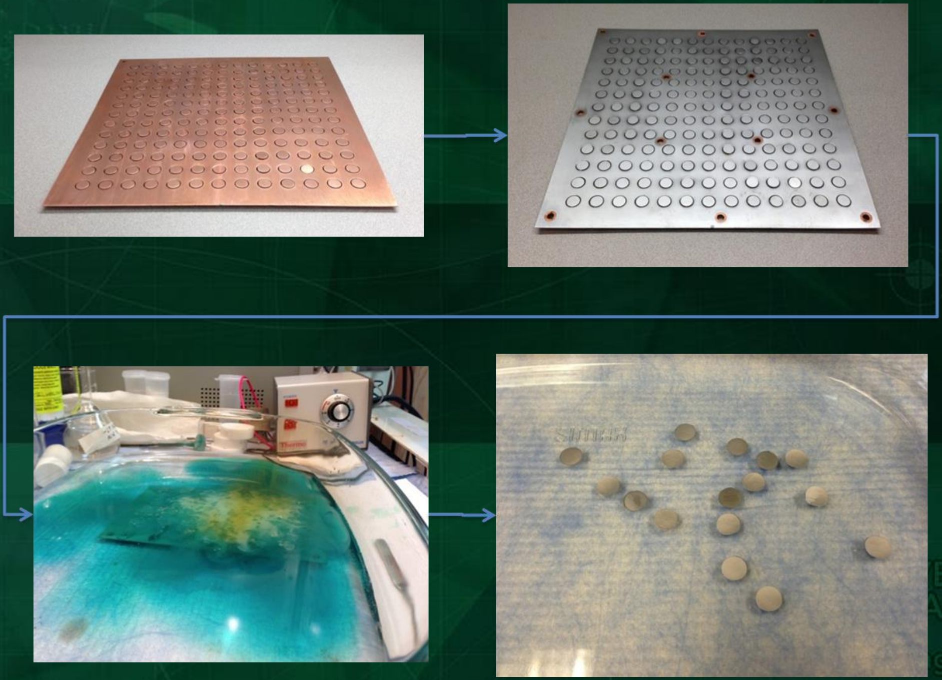


Image courtesy: Richard Laforest (WUSM/MIR).
(Cross-reference: Laforest, R.; Liu, X. *Q. J. Nucl. Med. Mol. Imaging* 2008.)

^{52}Mn Production

- Produced via $^{52}Cr(p,n)^{52}Mn$ reaction
- Targetry using natural composition Cr foils



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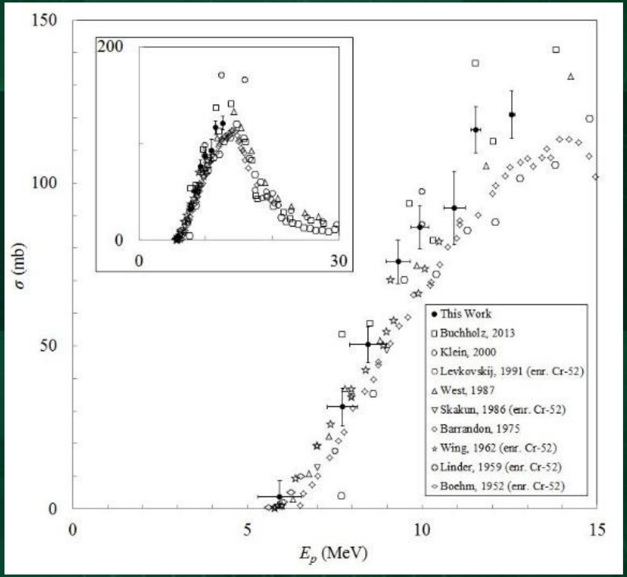
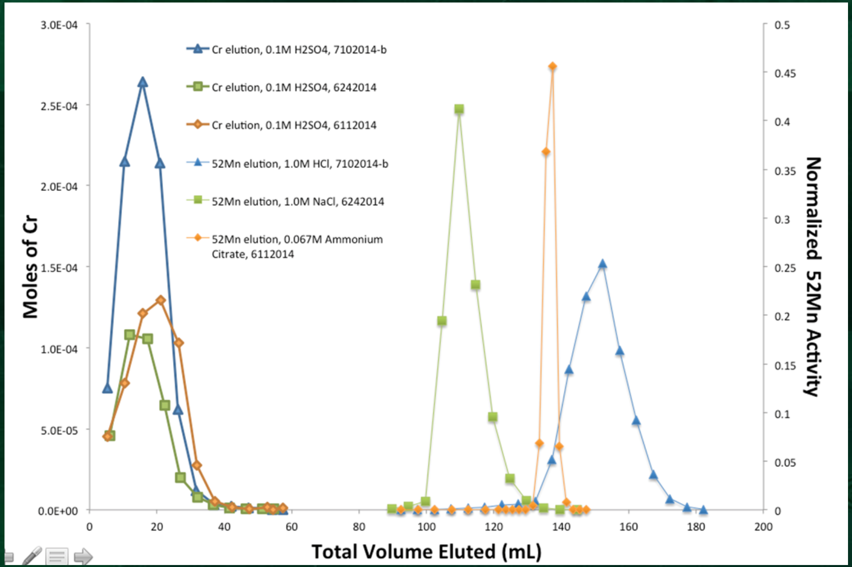
^{52}Mn Targets, Bombardment and Purification

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





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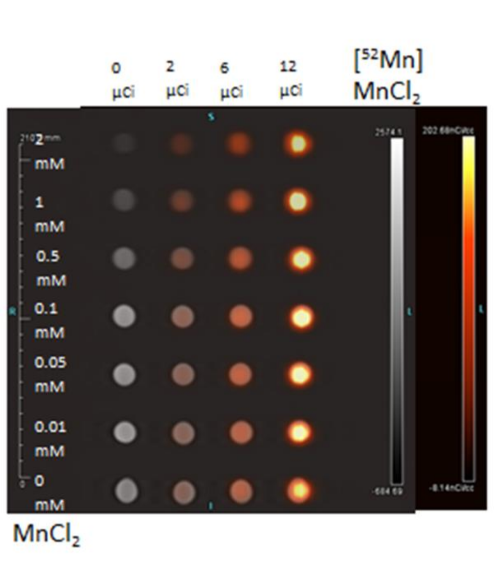
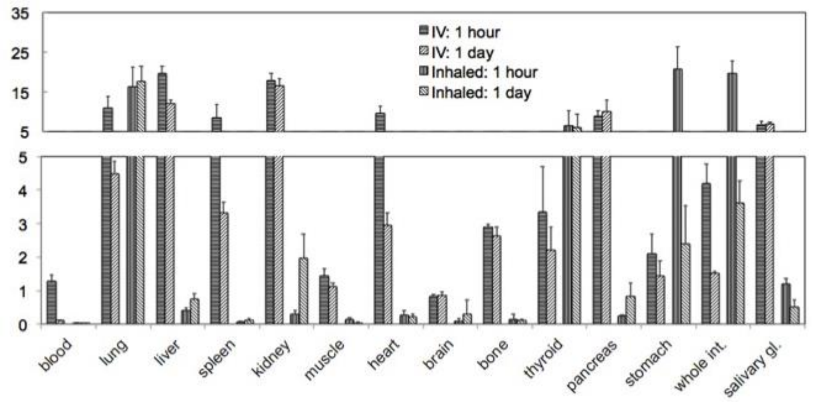
^{52}Mn Characterization

- Imaging characteristics and preliminary animal studies

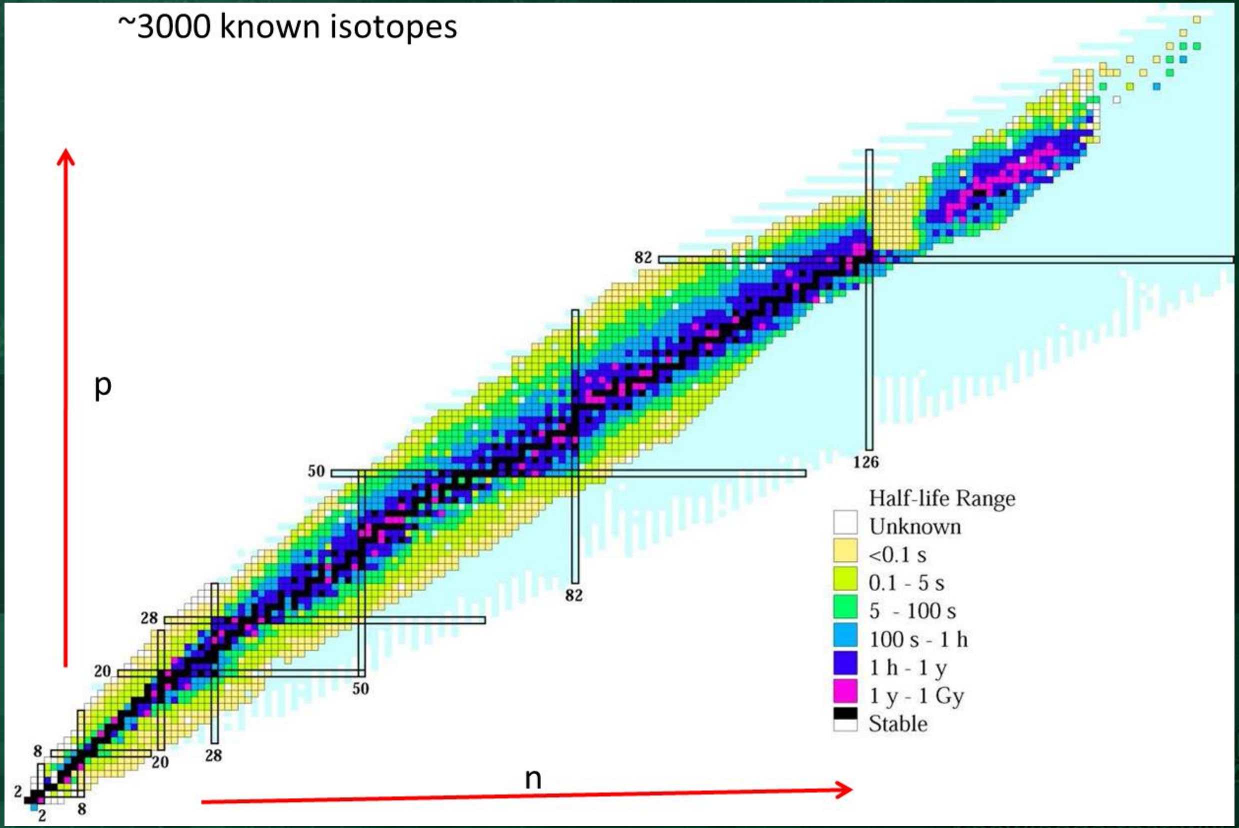




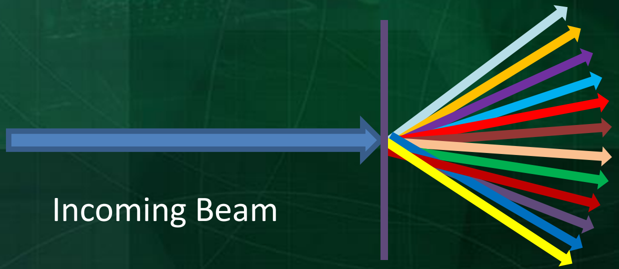
Cyclotron Production of Isotopes:

- Similar machines in many hospitals and academic centers.
- Small number of accessible nuclear reactions:
  - (p,n), (p2n), (p,α)
  - Produce high purity isotopes in high yield
  - Some desirable isotopes are inaccessible – other routes?

Other Isotopes?



Production of Radionuclides by Heavy Ion Fragmentation



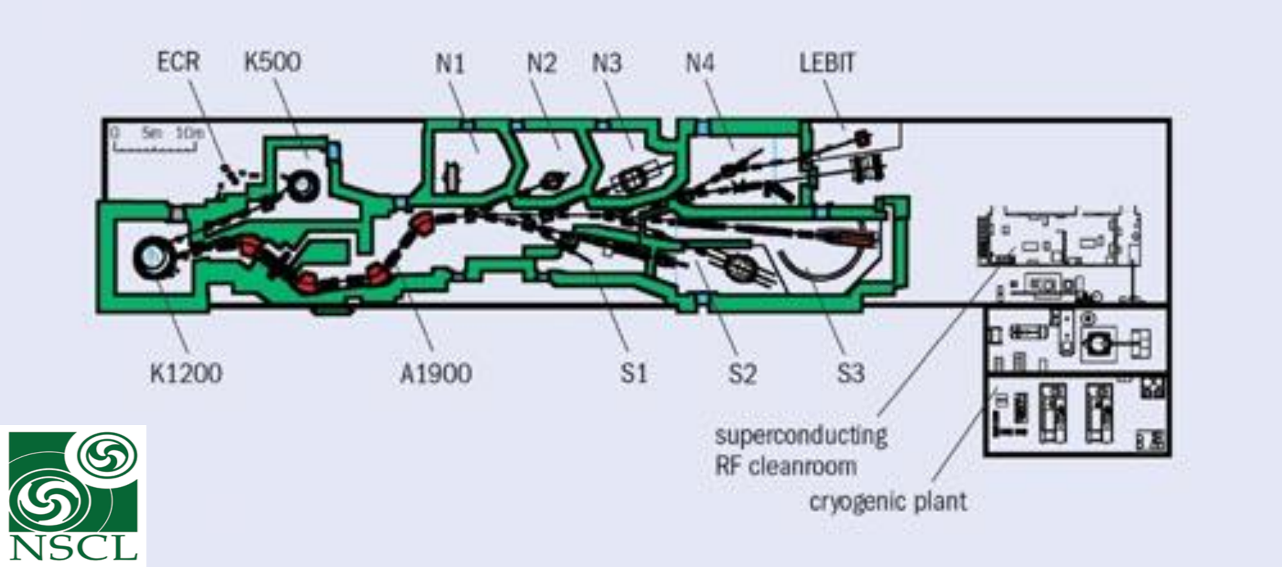
Potential Isotopes of Interest

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.

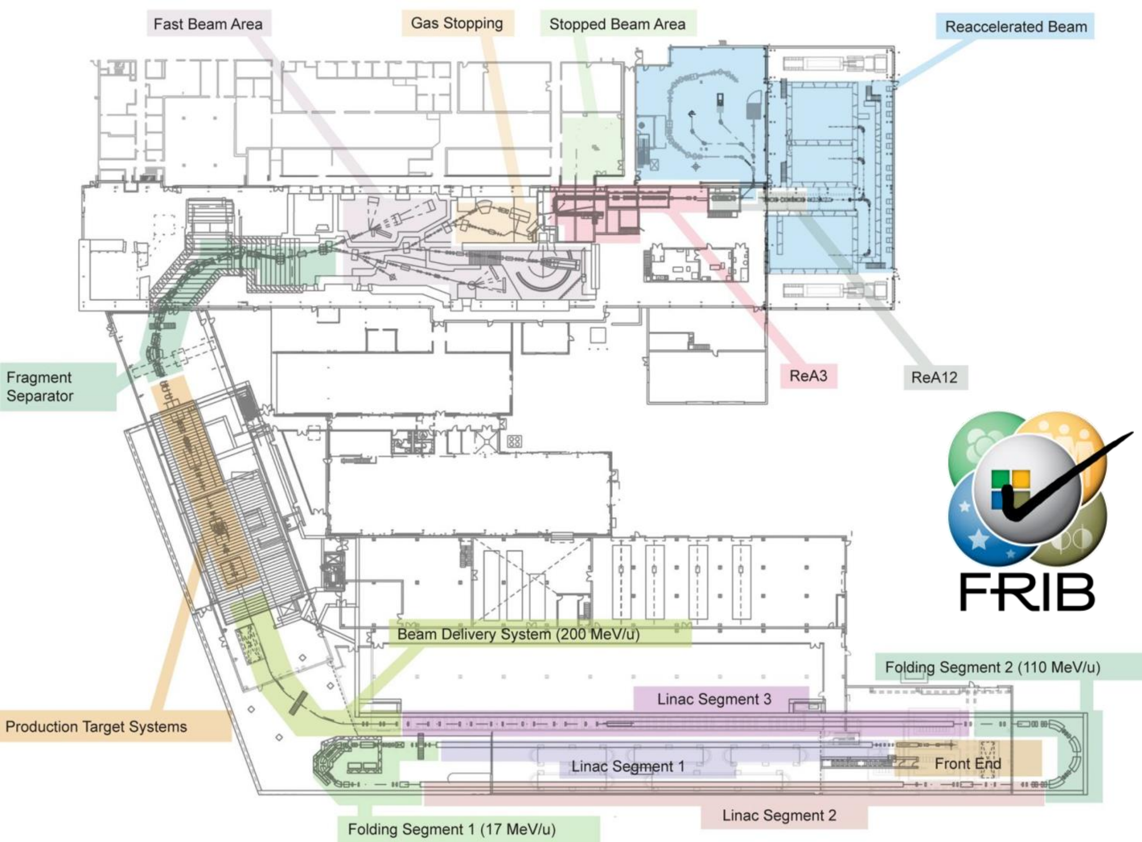
National Superconducting Cyclotron Laboratory (NSCL)

Located at Michigan State University

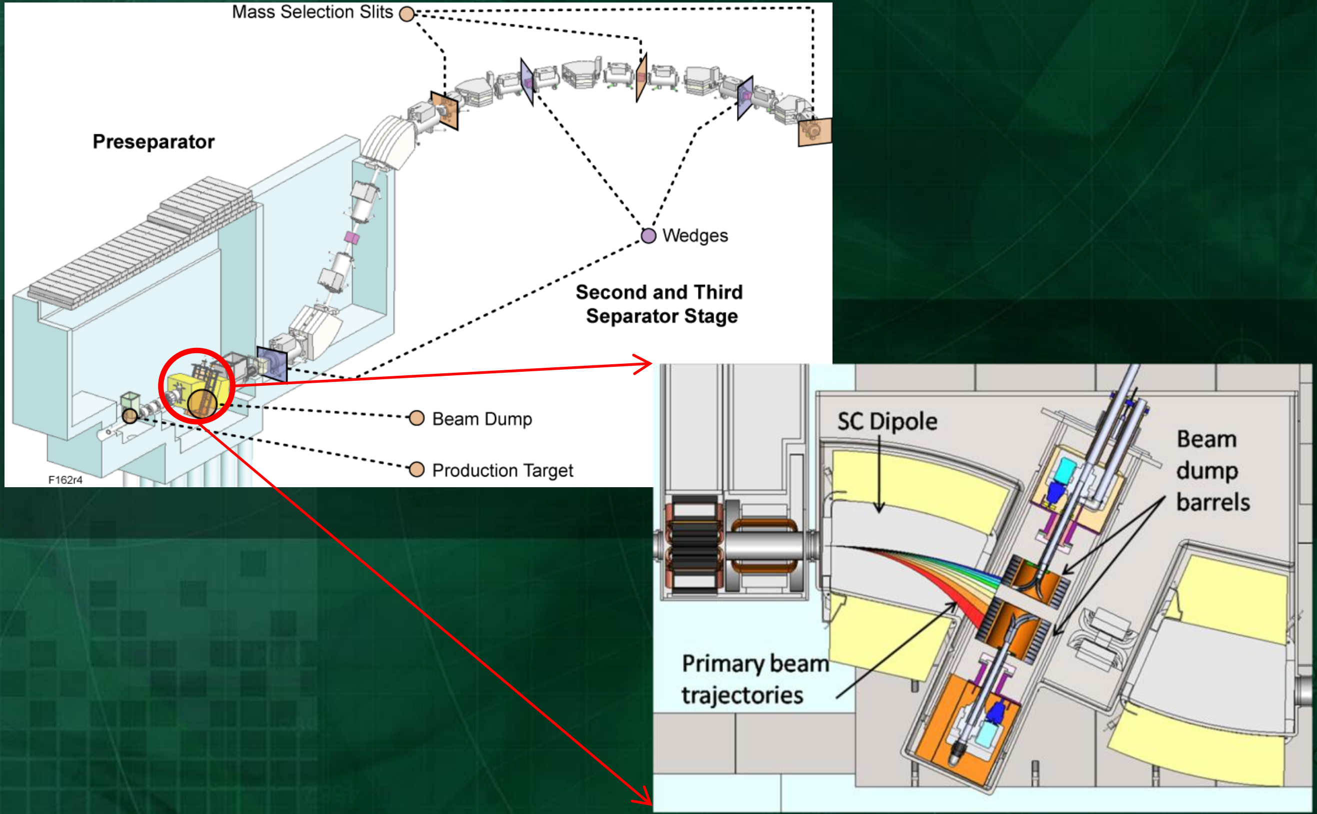


Upgrade of NSCL to FRIB

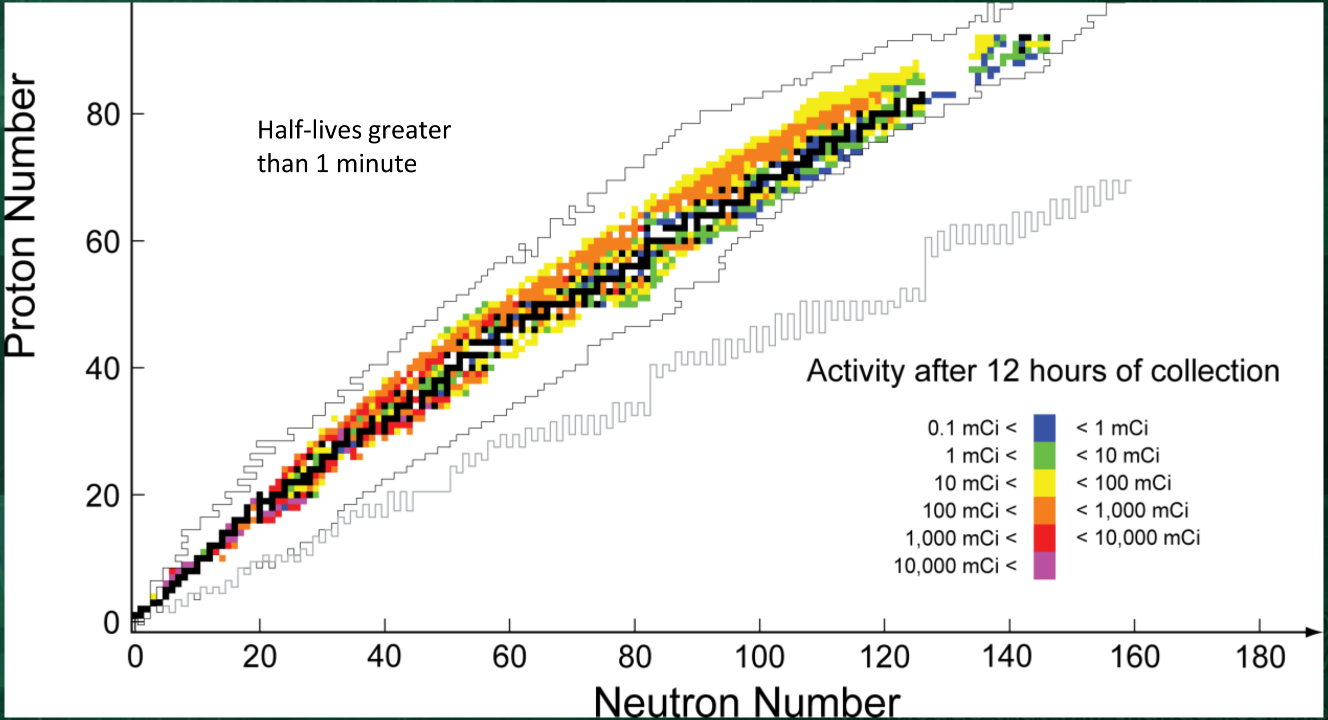
(Facility for Rare Isotope Beams)



Schematic of Proposed Secondary Beam Separator and Beam Dump at FRIB

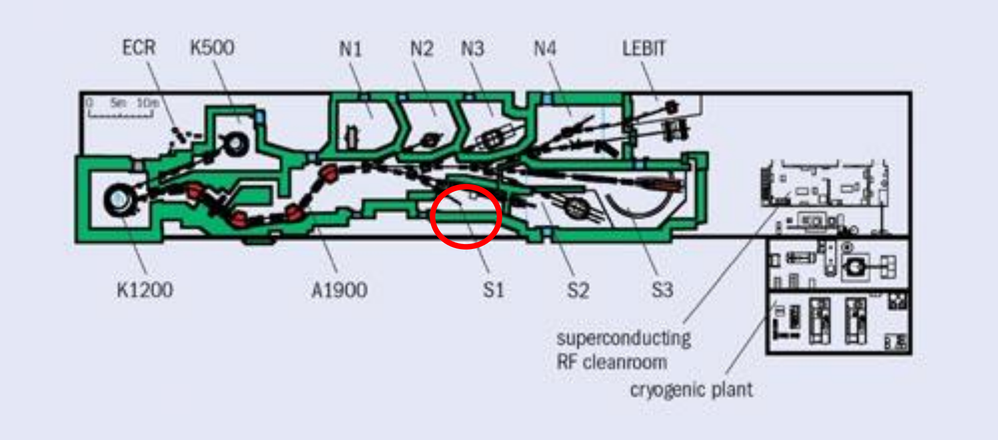


Why is Isotope Harvesting Important?



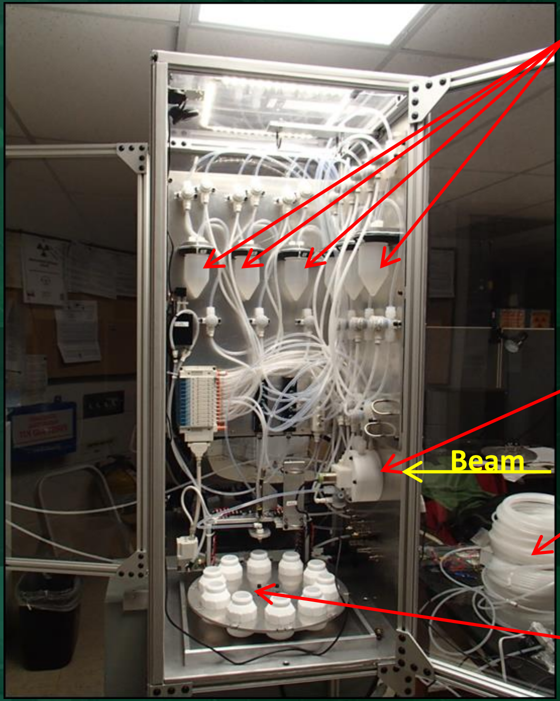
Preliminary experiments performed at the national superconducting cyclotron laboratory (NSCL)

- 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)



Multiple containers of water purged with He

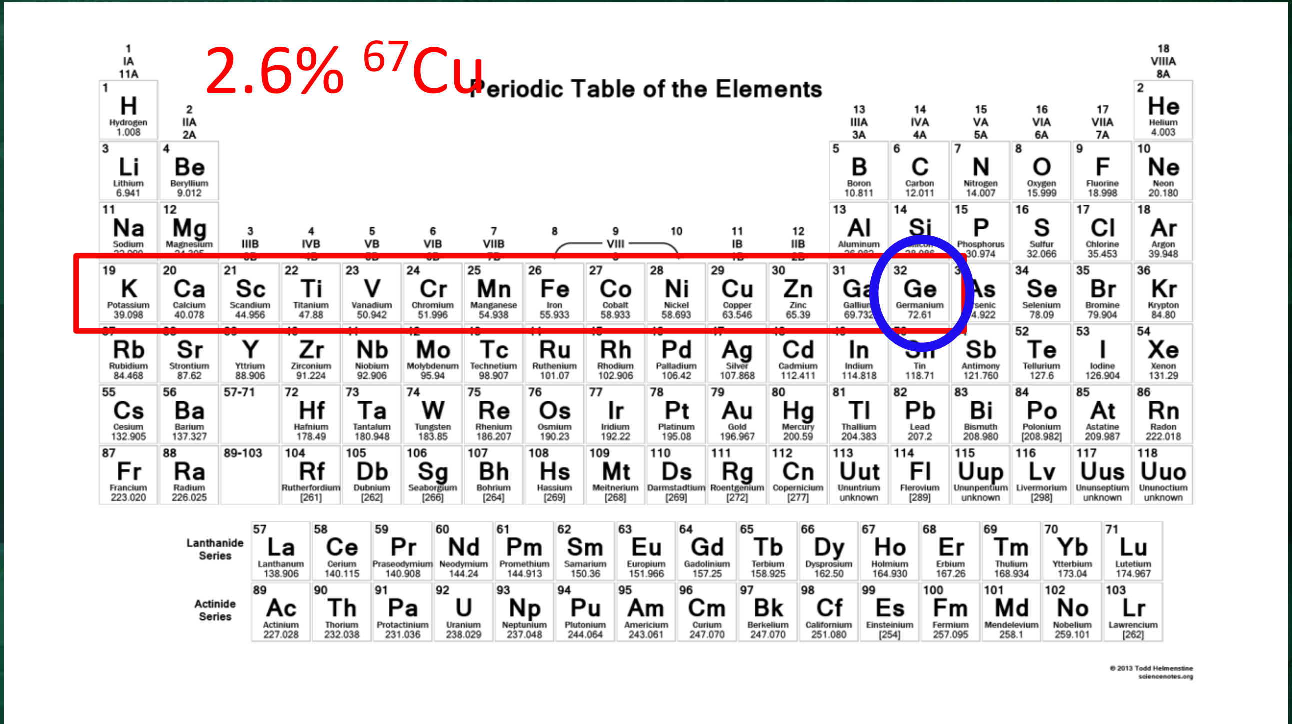
Water Cell w/ 8µm kapton window

Gas exit manifold

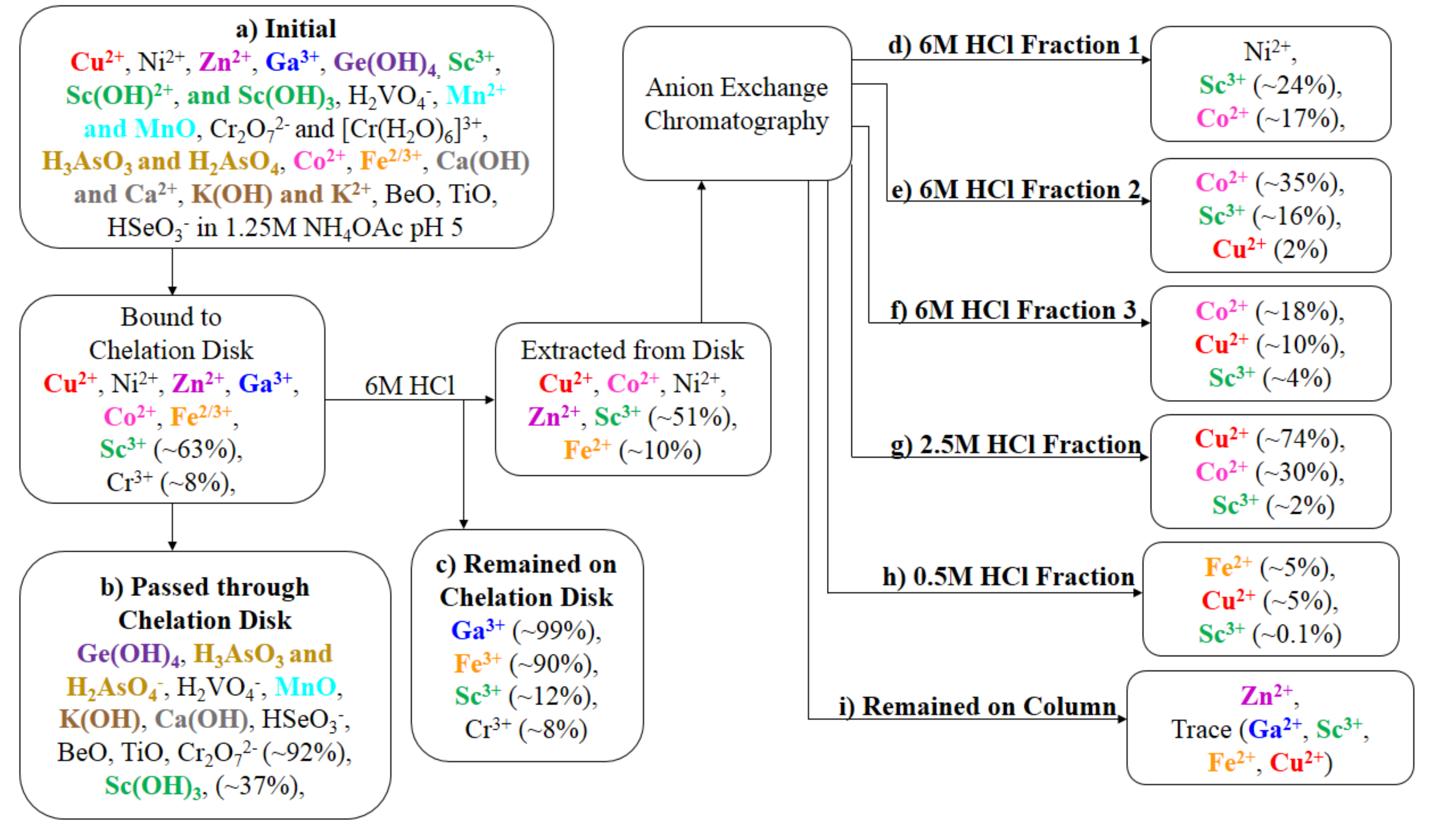
Collection Bottles on rotating carousel

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

^{76}Ge Beam Fragmentation Products without Wedge

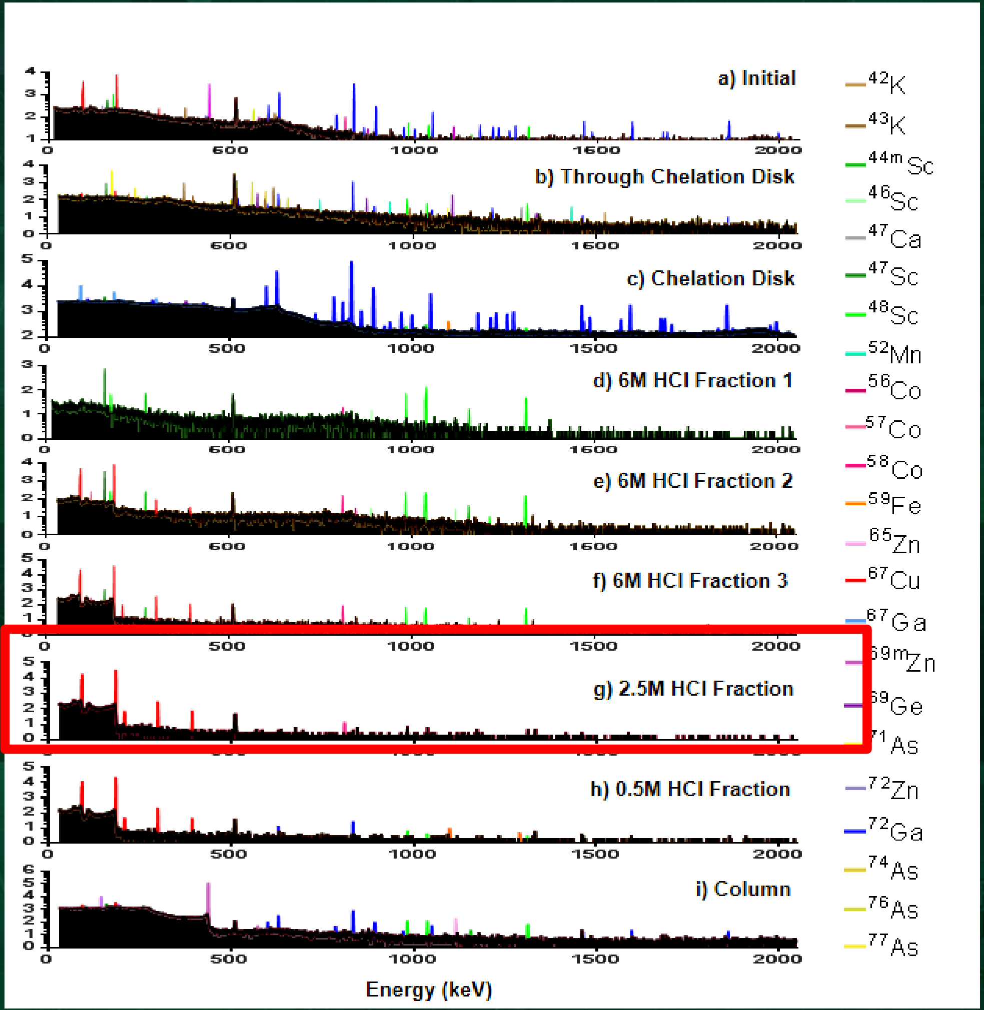


Separation Schematic



Mastren et al, Scientific Reports, 2014

HPGe Spectra of Different Points Throughout the Separation



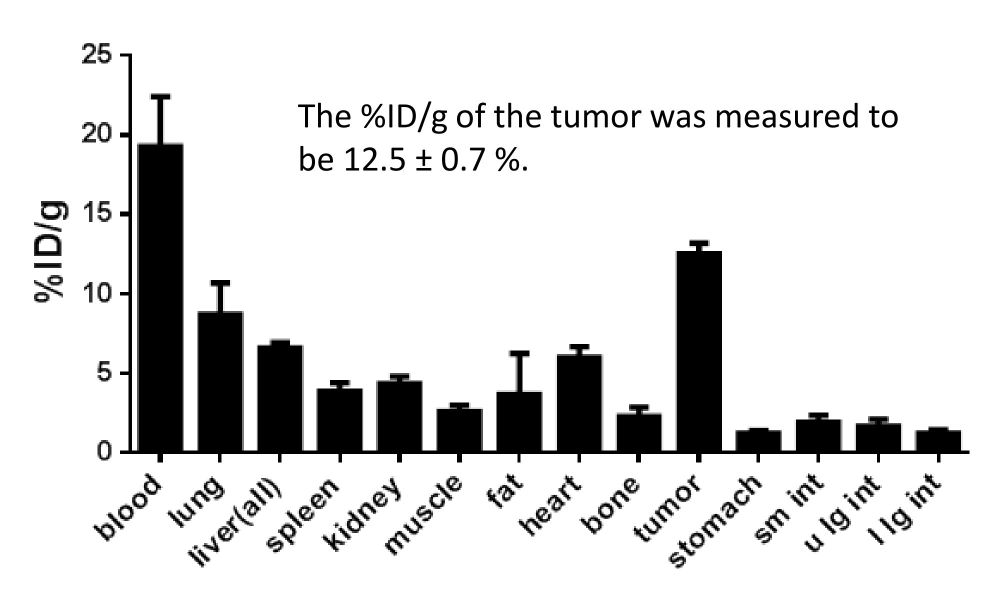
Mastren et al, Scientific Reports, 2014

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

Summary

- Radioisotopes continue to play an important role in medicine.
- 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, physicists, biologists and physicians.

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