From Antimatter to Images: The Use of Radioisotopes in Medical Imaging

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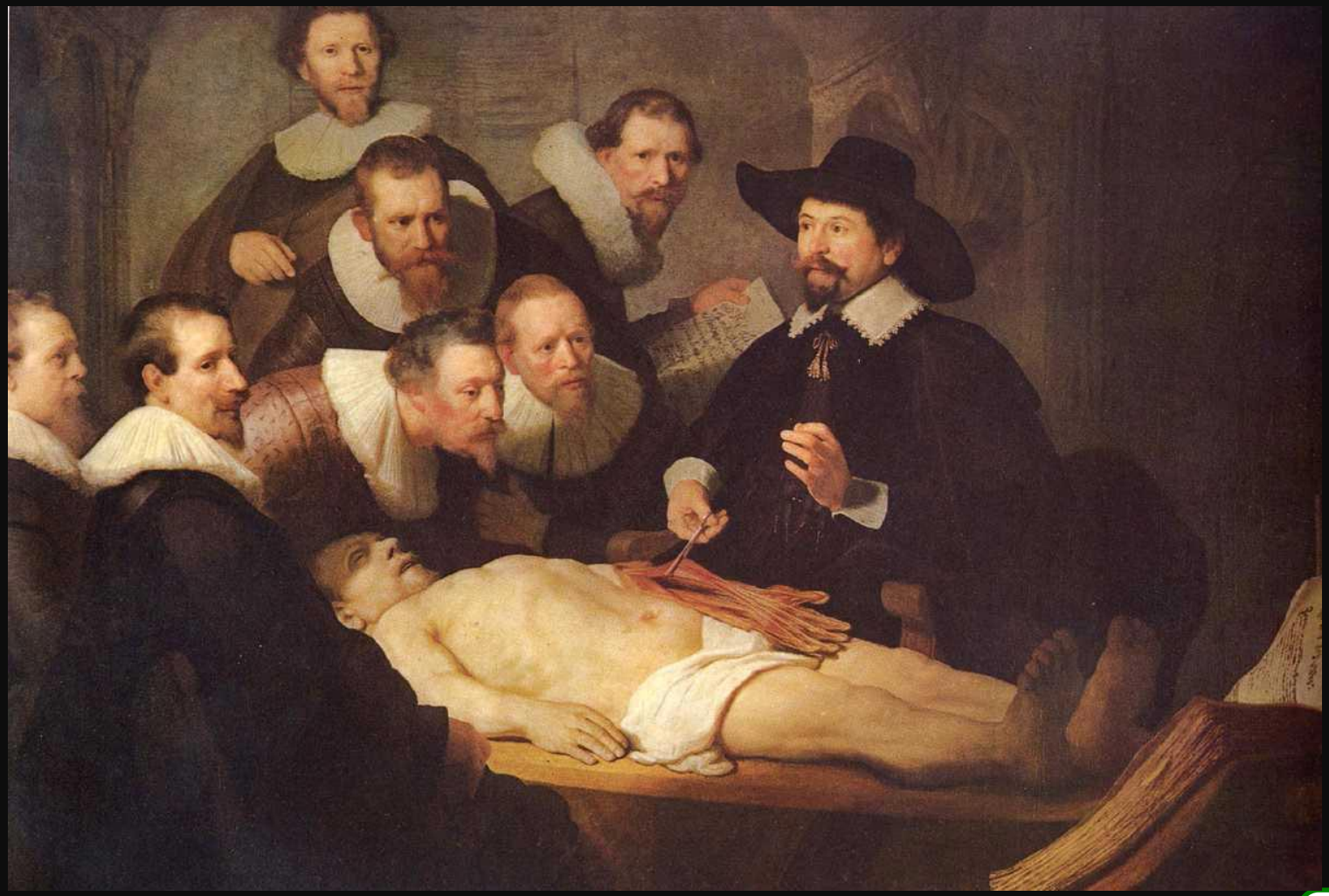
Washington University School of Medicine

Diagnostic Medicine: Past



Rembrandt - anatomy lesson

How can we probe the human body without a knife?

Basics of Nuclear Medicine

- Nuclear medicine encompasses most of the medical uses of radioactive substances
  - diagnostic tests
  - imaging studies
  - therapy for certain diseases

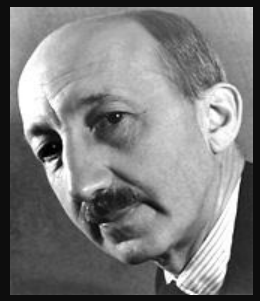
Radiotracers

- A substance that is radioactive used as a tracer.
- The radioactivity makes it possible to determine where it is and how much is present, an extremely sensitive tool.

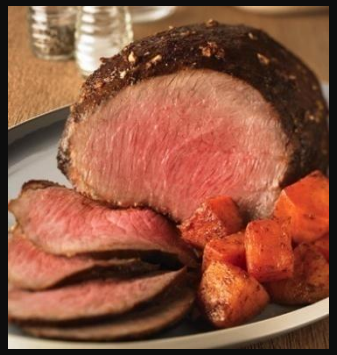
Tracer Principle

- 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?

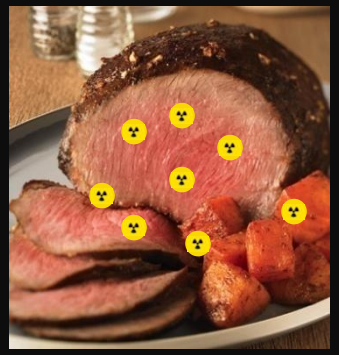


- George de Hevesy was a pioneer in radiochemistry
- While in Manchester in the early 1910's working with Rutherford, he suspected his landlady was serving recycled food



Sunday night roast

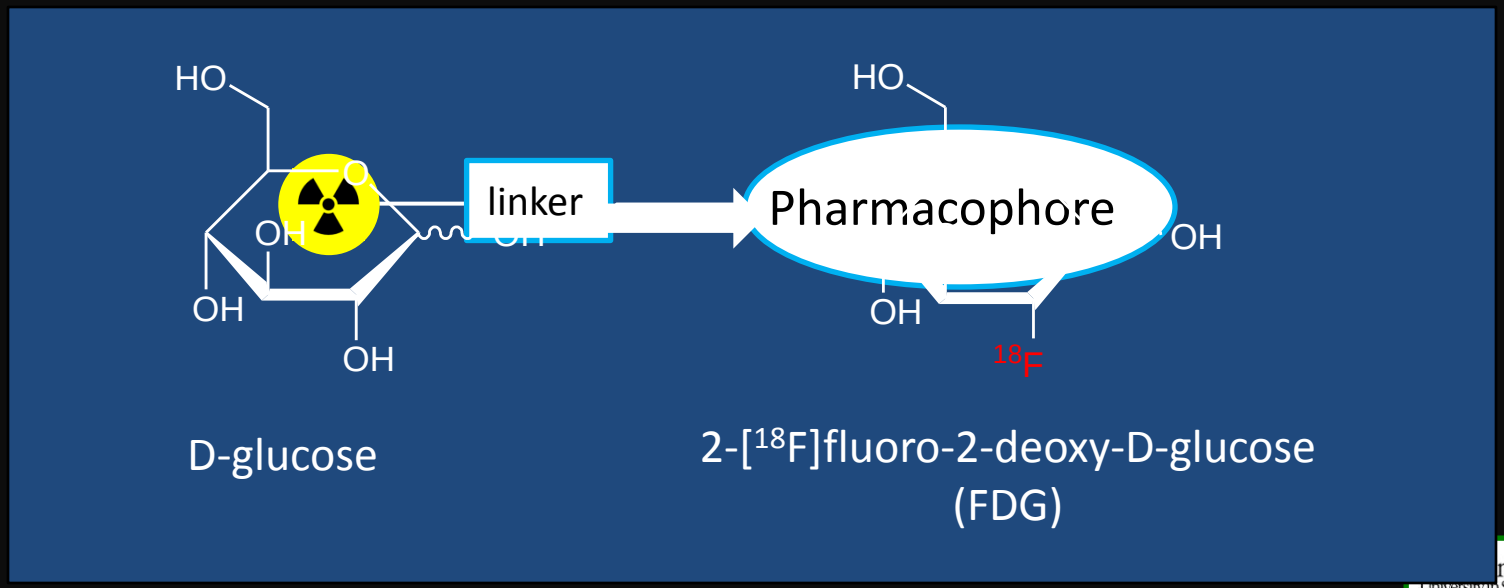
Radium



Wednesday hash

Radiopharmaceuticals

- A **radiopharmaceutical** is a drug labeled with a radionuclide to image a biological process
  - the overall chemical structure determines biological properties
  - the radionuclide determines imaging properties

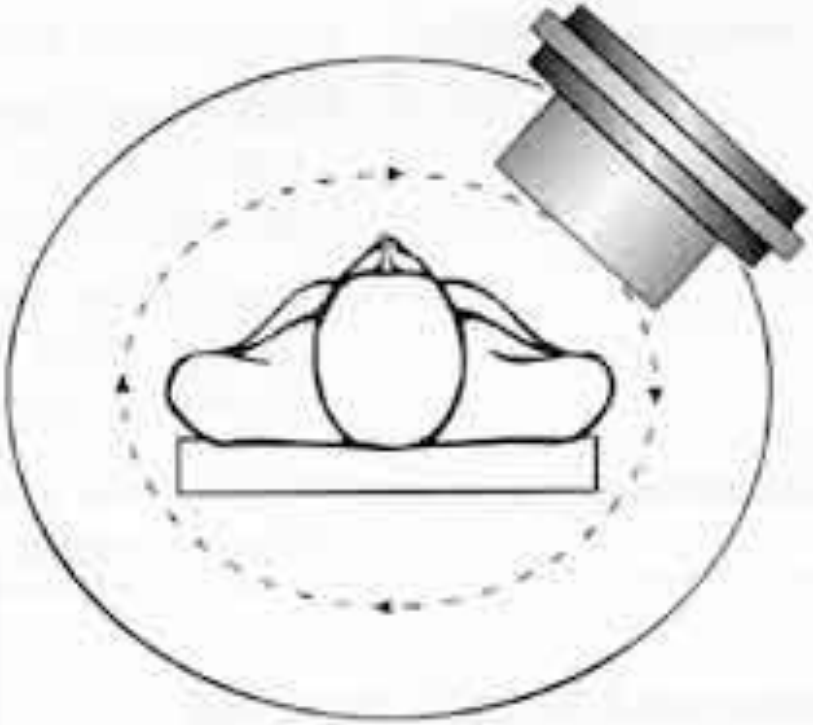


Nuclear Imaging

SPECT: Single Photon Emission Computed Tomography

PET: Positron Emission Tomography

In planar imaging, the camera records an image from one perspective



In SPECT imaging, the camera rotates around the patient, recording multiple images that are then reconstructed into a three-dimensional data set by a computer

Gamma camera imaging

Gamma cameras are used for planar and SPECT imaging

^{99m}Tc-radiopharmaceuticals are imaged with gamma cameras

From http://www.upo.com.mx/img/imagenologia/cardiodiagnostico/e_cam3.jpg

Tc - Backgroud

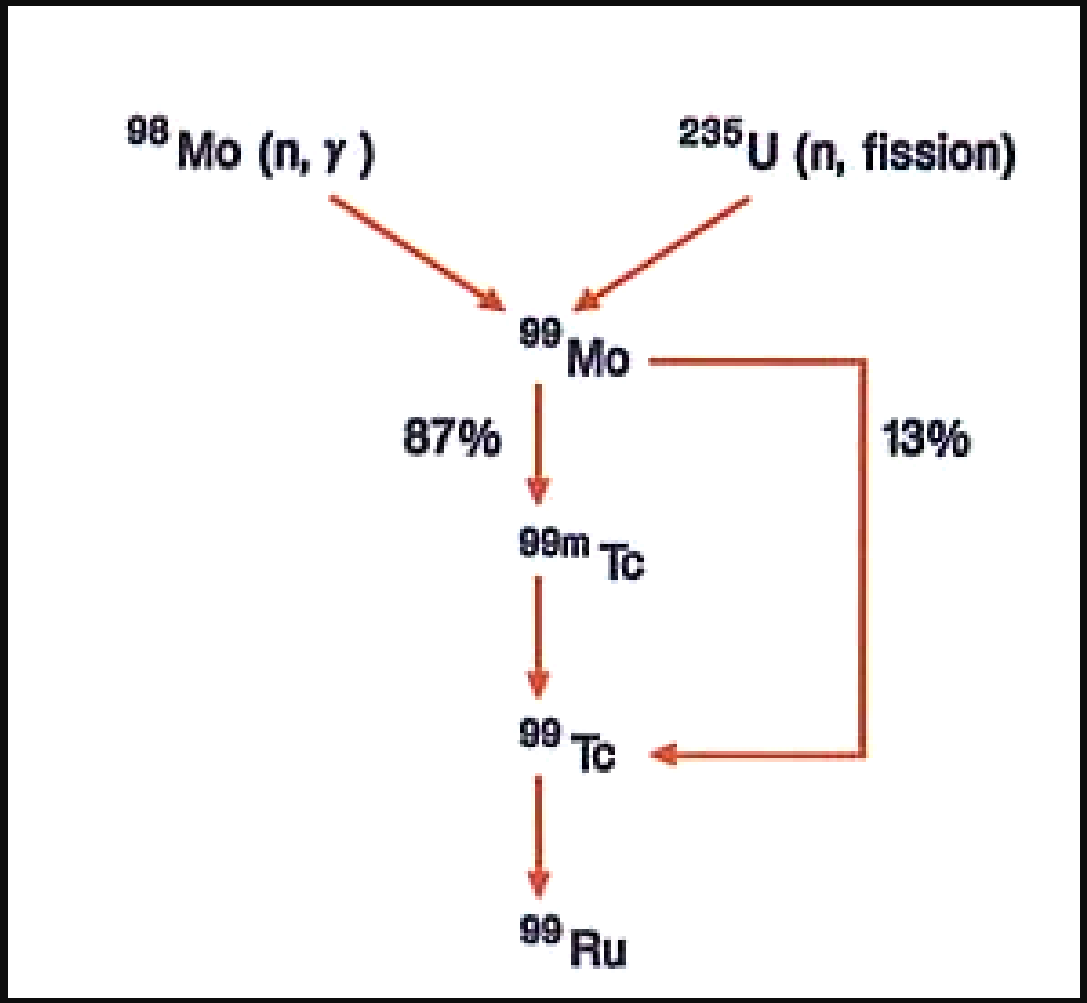
- Tc discovered in 1937 by Perrier and Segré, who separated it from a Mo deflector plate after years of deuteron irradiation in the Berkeley cyclotron
- 17 known isotopes of Tc - all radioactive
  - ^{99m}Tc ($T_{1/2}$ = 6.03 h) is most widely used in Nuclear Medicine - discovered in 1938 by Seaborg and Segré
  - ^{99}Tc ($T_{1/2}$ = 2.1 x 10^5 y) is produced by U fission; used to establish chemistry of the element under conventional chemical concentrations

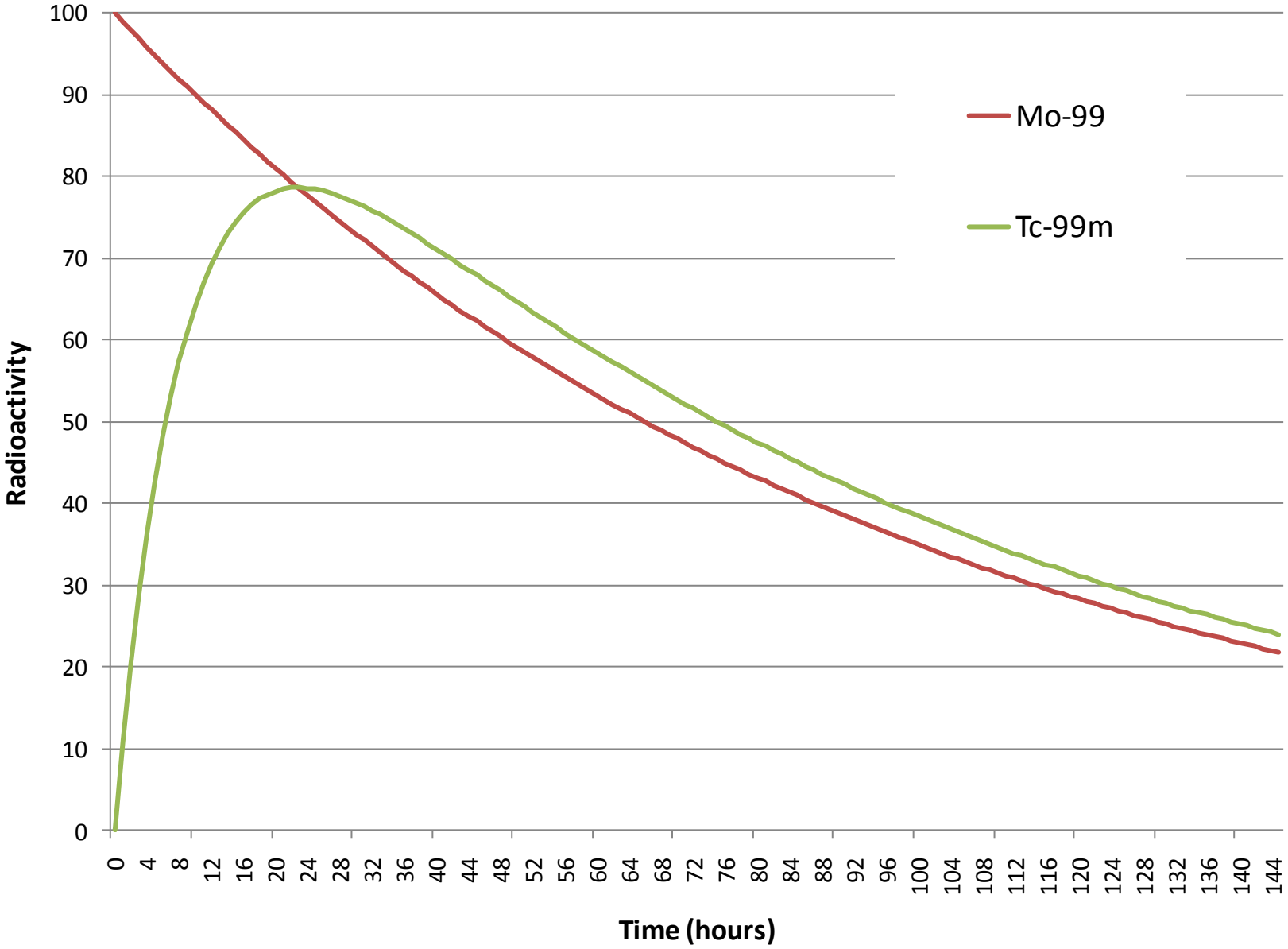
Radionuclide Generator

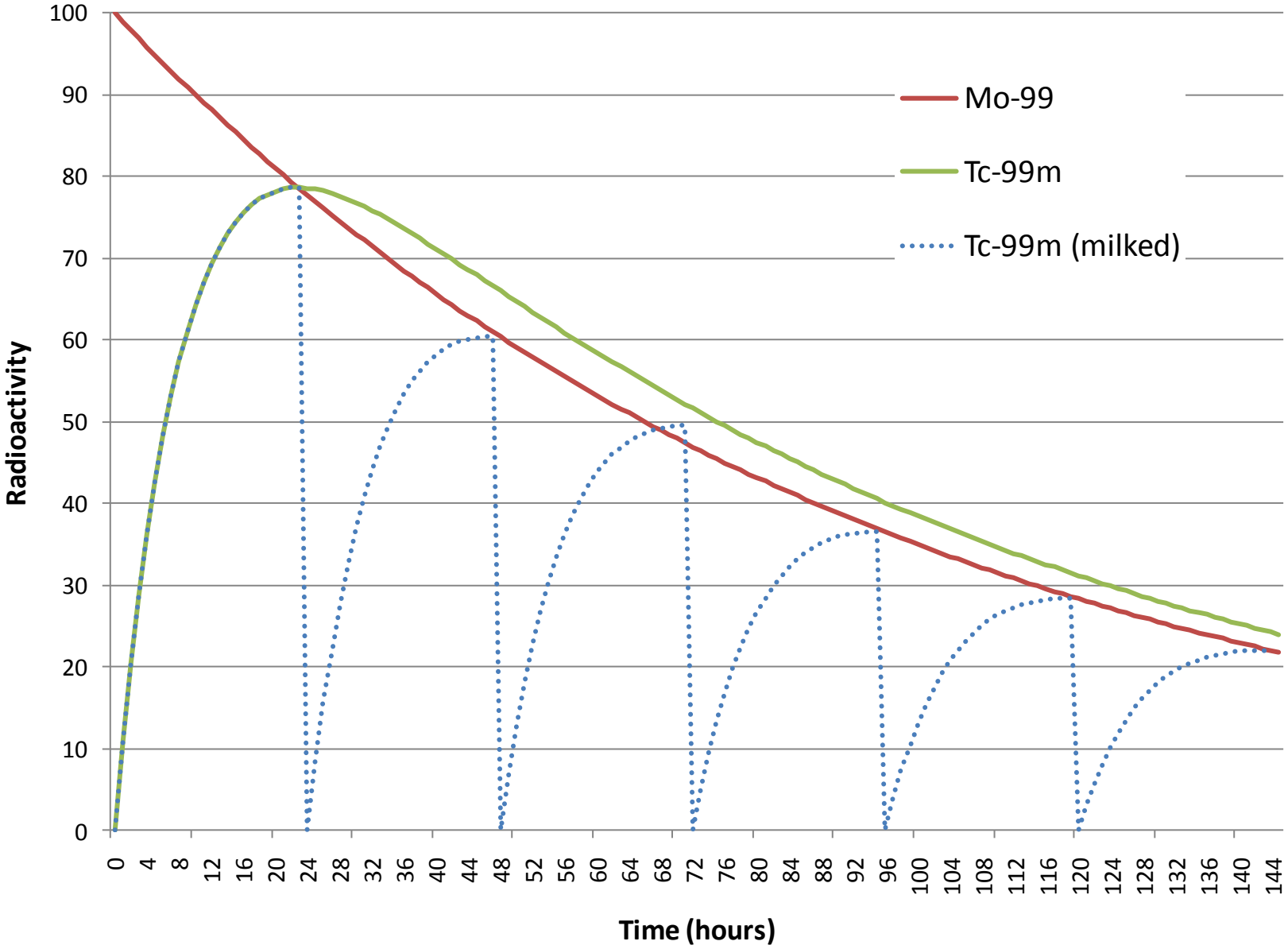
A device that separates a daughter radionuclide from a parent radionuclide

- Typically a chromatographic separation based on the different chemical properties of the parent and daughter radionuclides
- The daughter radionuclide is the desired radionuclide used for nuclear medicine applications

^{99}Mo Decay




Mo-99
Tc-99m
Radioactivity
Time (hours)
0
10
20
30
40
50
60
70
80
90
100
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96 100 104 108 112 116 120 124 128 132 136 140 144


Mo-99
Tc-99m
Tc-99m (milked)
Radioactivity
Time (hours)
0
10
20
30
40
50
60
70
80
90
100
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96 100 104 108 112 116 120 124 128 132 136 140 144

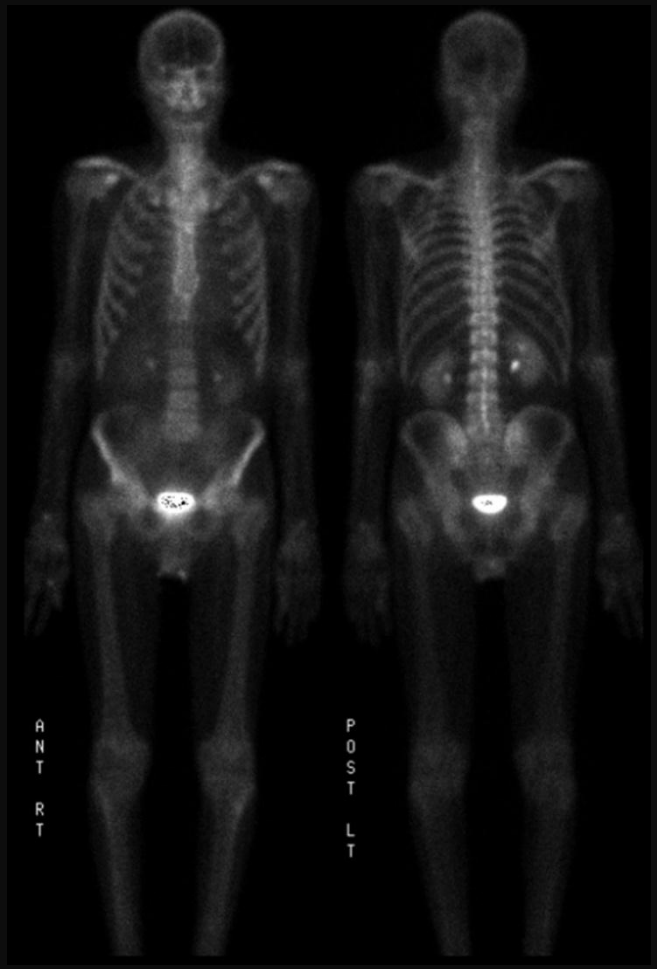
$^{99}Mo/^{99m}Tc$ Generator

- Comments on patent application of Green, Richards and Tucker in 1958 for $^{99}Mo/^{99m}Tc$ generator:
  - "While this method is probably novel, it appears the product will probably be used mostly for experimental purposes in the laboratory. On this basis no further patent action is believed warranted…" Atomic Energy Commission
  - "We are not aware of a potential market for ^{99m}Tc… We would recommend against filing…" Research Corporation for Associated Universities, Inc.
- First injection of $^{99m}TcO_4^-$ into a human was made in 1961, following development of the BNL generator
- By 1970, it was estimated that more than 2000 daily diagnostic procedures were carried out in the U.S.
- By 1985 market for ^{99m}Tc was >$30 million
- Diagnostic radiopharmaceutical market was $1.69 billion in 2005 ($259 million for FDG)

Example: Skeletal imaging

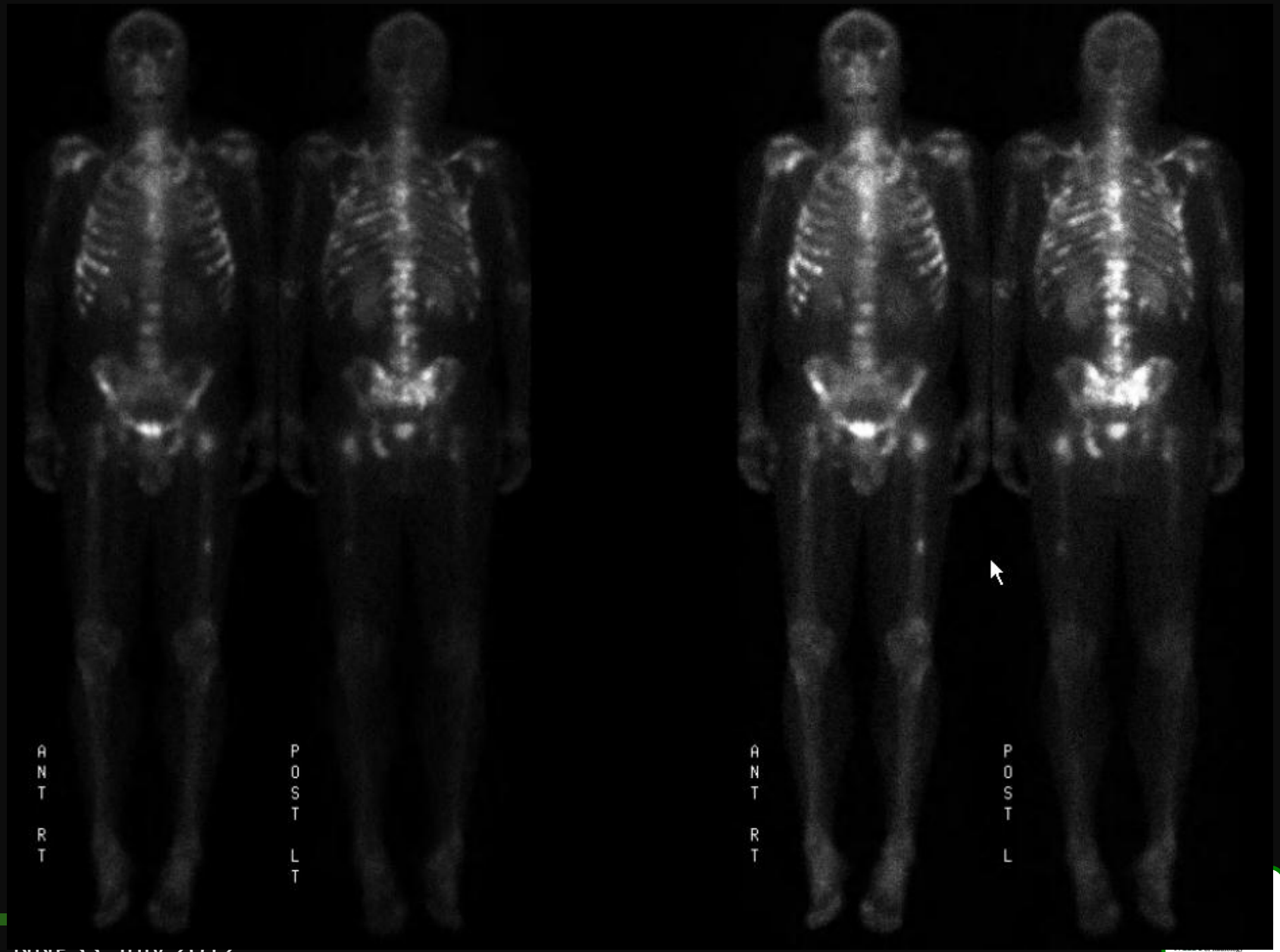
- Used to detect osseous metastases, fractures and infection
- Often called a bone scan
- Common radiopharmaceuticals:
  - ^{99m}Tc-MDP binds to calcium matrix
  - ^{18}F-fluoride can be used for PET skeletal imaging
- Non-specific marker of increased bone matrix turnover

Normal ^{99m}Tc-MDP bone scan



Images acquired about 3 hours after injection

58 year old man with prostate cancer



RF

Looming Isotope Shortage Has Clinicians Worried

By Michael Smith, North American Correspondent, MedPage Today
Published: February 16, 2010

Medical isotope shortage reduces tests

Last Updated: Wednesday, June 16, 2010 | 6:58 PM ET CBC News

Isotope shortage to get worse with closing of more reactors

GLORIA GALLOWAY
Ottawa— From Thursday's Globe and Mail
Published Wednesday, Feb. 17, 2010 10:57PM EST

Worldwide Shortage of Isotopes for Medical Imaging Could Threaten Quality of Patient Care

ScienceDaily (Aug. 22, 2010) — Twenty million medical scans and treatments are done each year that require radioactive isotopes and scientists are now describing a global shortage of these life-saving materials that could jeopardize patient care and drive-up health care costs.

^{99m}Tc Availability Issues: "The Isotope Crisis"

- Tc-99m is most widely used radionuclide for nuclear medicine procedures in the world and accounts for >80% of all procedures
- Many radiopharmaceuticals to assess
  - Cardiac function
  - Blood flow
  - Bone metastases
- Half life & chemical properties of Mo-99 and Tc-99m are exploited to separate them in generator
  - Mo-99/Tc-99m generator invented at Brookhaven National Laboratory
  - Mo-99 half life is 66 hours, Tc-99m has a half life of 6 hours
- Generators sent around the world

The simplicity of the $^{99}Mo/^{99m}Tc$ generator

Developed at BNL in 1958 it was never patented.

Where does the ^{99}Mo come from?
→ Fission

Reactor	*In-service date*	*Target uranium enrichment type*
NRU (Canada)	**1957**	**HEU**
BR2 (Belgium)	**1961**	**HEU**
HFR (Netherlands)	**1963**	**HEU**
SAFARI (South Africa)	**1965**	**HEU**

Notes:
- Other smaller suppliers: RA-3 (Argentina) is a domestic supplier and OSIRIS (France) provides some back-up to BR2 and HFR.
- OPAL (Australia): commissioned in 2008, in early stages of operation.

Issues

- Chemistry is performed on targets resulting in a Mo-99 solution
- Solution shipped to companies for purification and placement into column
- Mo-99 is eluted (extracted with a solvent) from the column
- Produced eluate is conditioned and ^{99}Mo re-extracted
- Meeting US demand requires about 34,000–46,000 Curies/week at the reactor

Other Issues

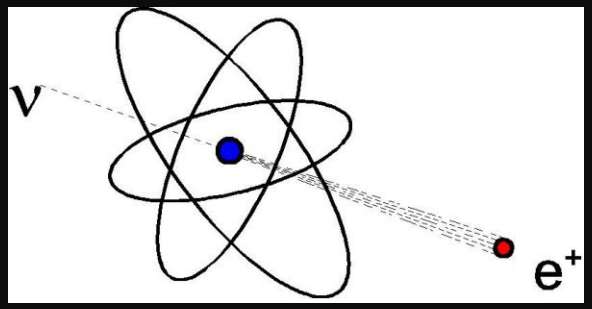
- US production was halted in 1989
  - Foreign subsidies were claimed to be the cause for lower costs abroad
  - Deemed “not worth it” to continue in US
- US demand shared by Canada + The Netherlands
- HEU has significant security issues; future will likely require use of something else
- Stay tuned….

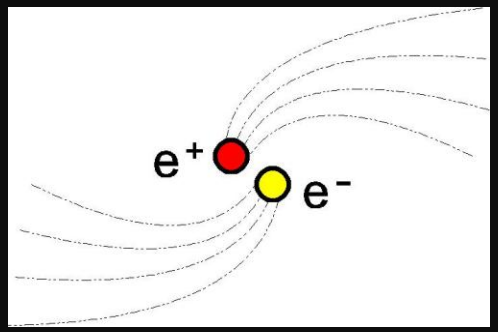
Positron Emission Tomography (PET)

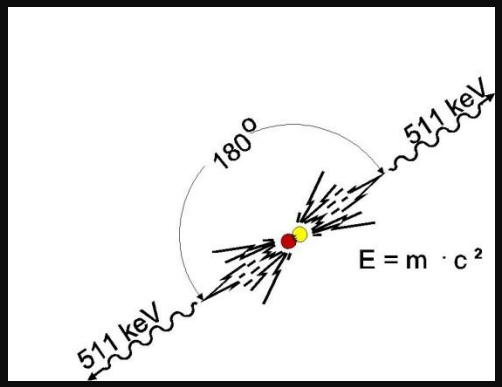
PET imaging is a very sensitive tool capable of providing quantitative information about biochemical and physiological processes in a non-invasive manner.

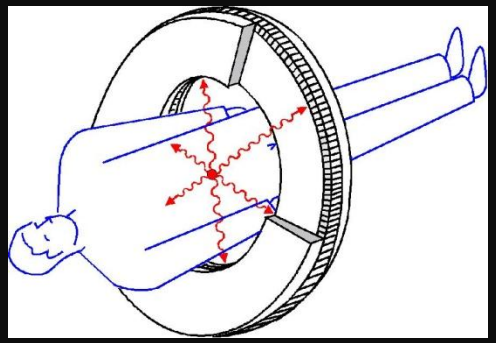
Principles of Positron Emission Tomography (PET)

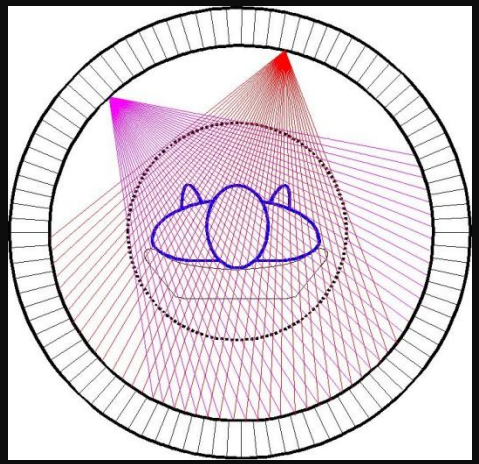
- Based on tracer principle
- Tracer labeled with positron emitting radioisotope
- Positron decay
- Coincidence detection of annihilation radiation

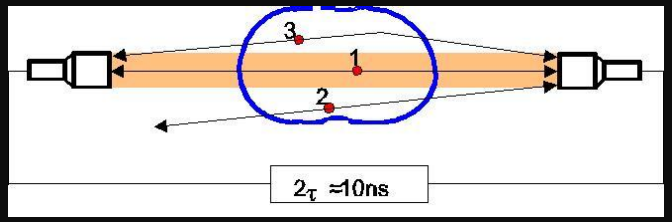




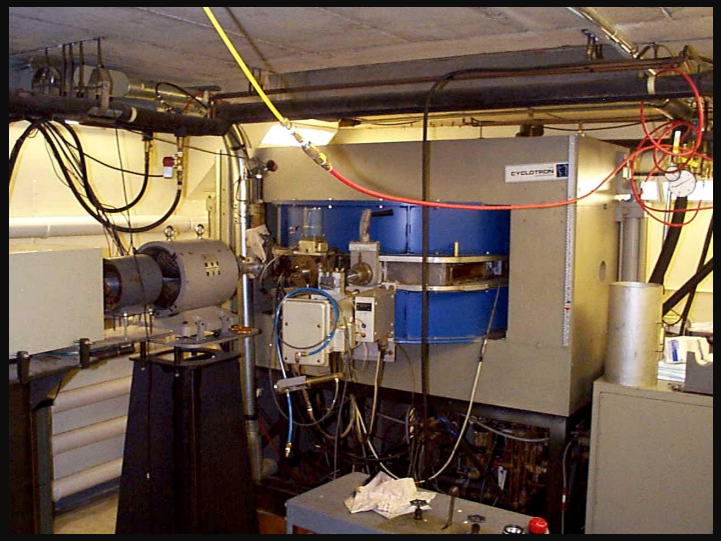


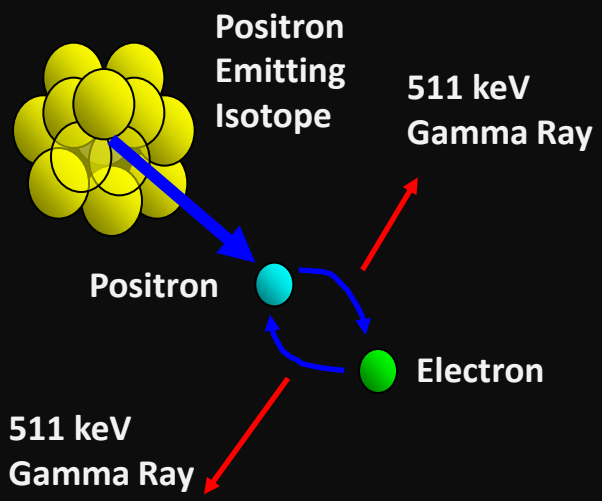






Principles of PET Imaging





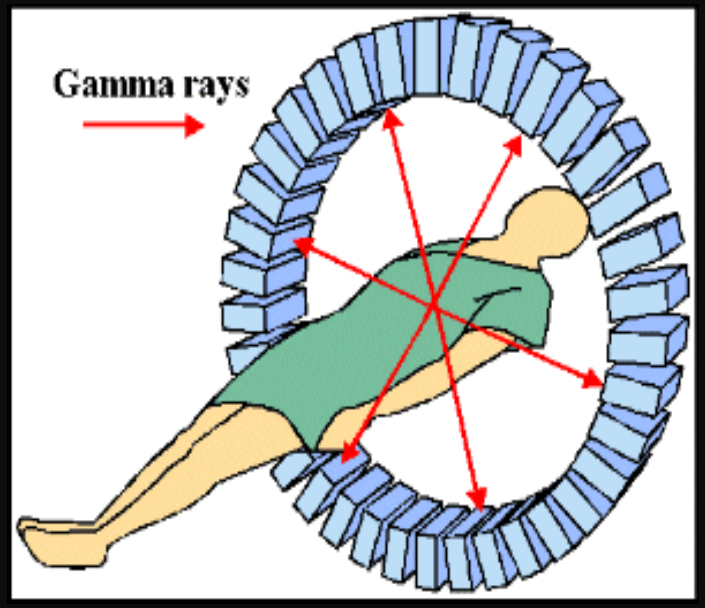
Positron-emitting isotopes produced on cyclotrons or generators

Injection of a tracer compound labeled with a positron-emitting radionuclide

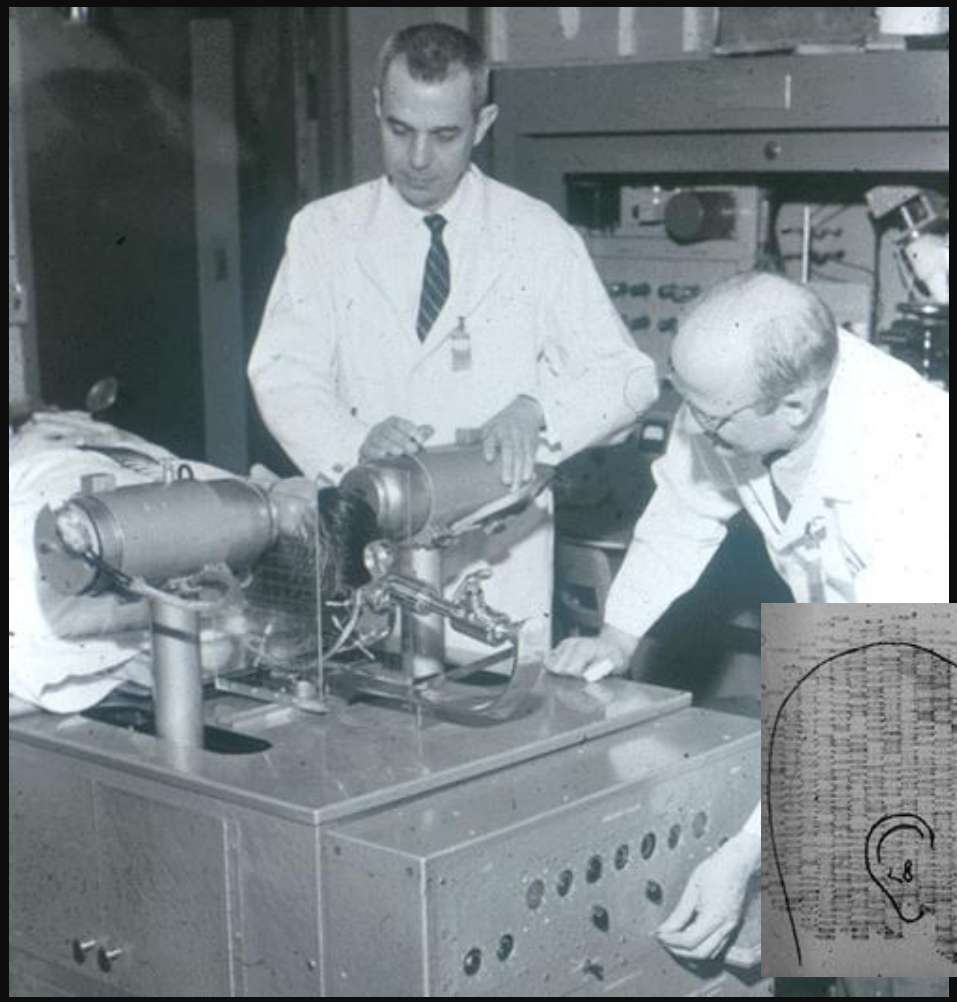
The radionuclide in the radiotracer decays and the resulting positrons subsequently annihilate on contact with electrons after traveling a short distance (~ 1-10 mm) within the body

Principles of PET Imaging

Each annihilation produces two 511 keV photons traveling in opposite directions (180^{O}) which are detected by the detectors surrounding the subject

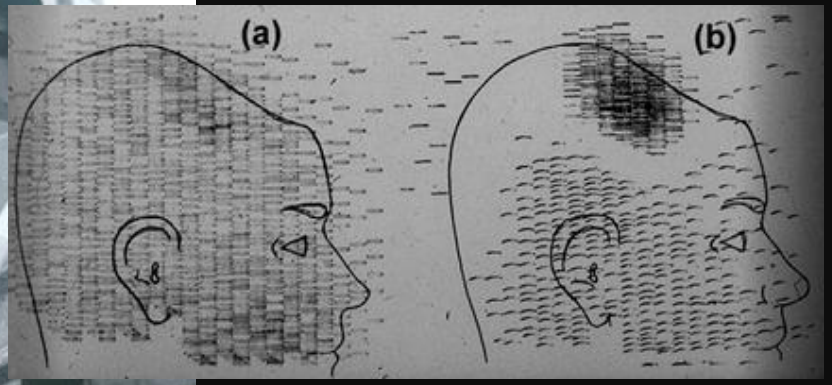


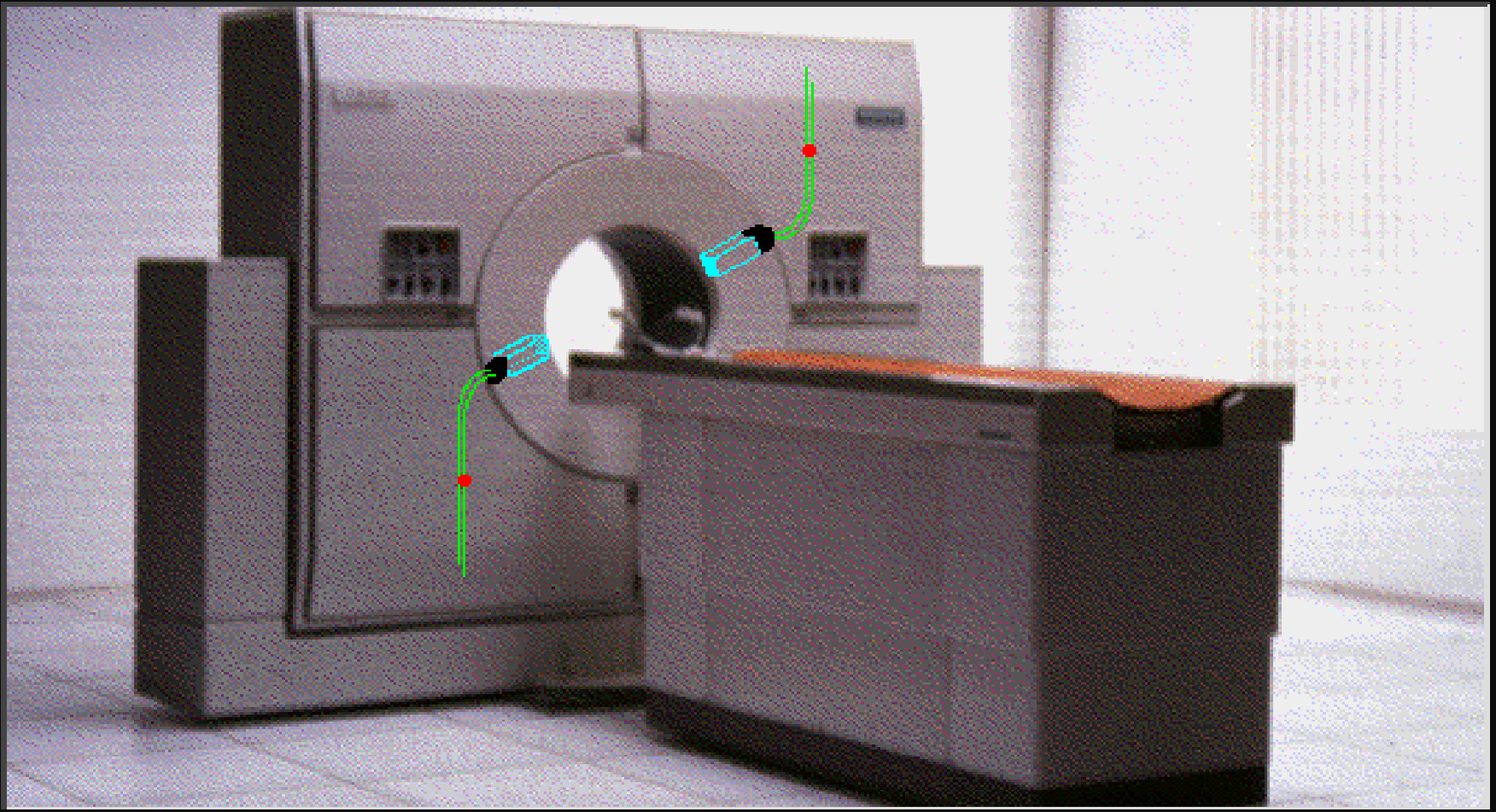
Early PET Imaging



1951:

Gordon L. Brownell and colleagues at the Massachusetts General Hospital

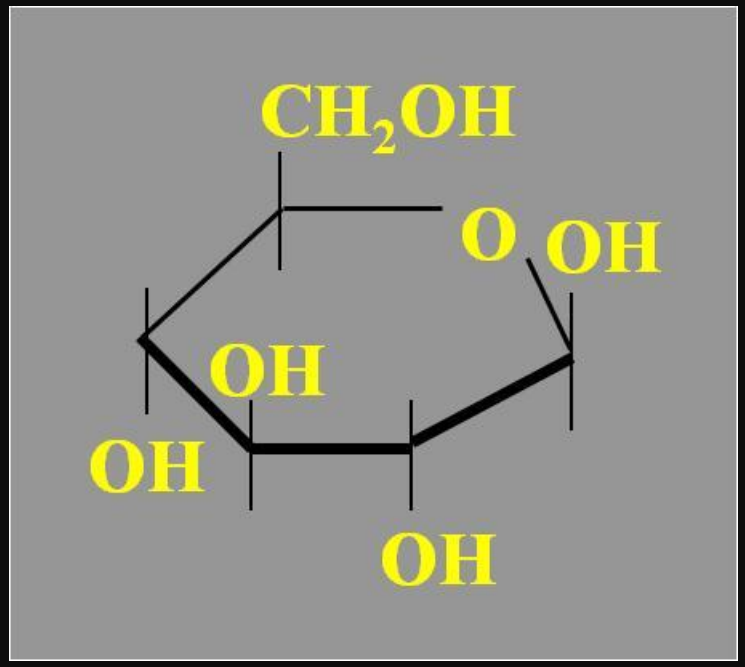




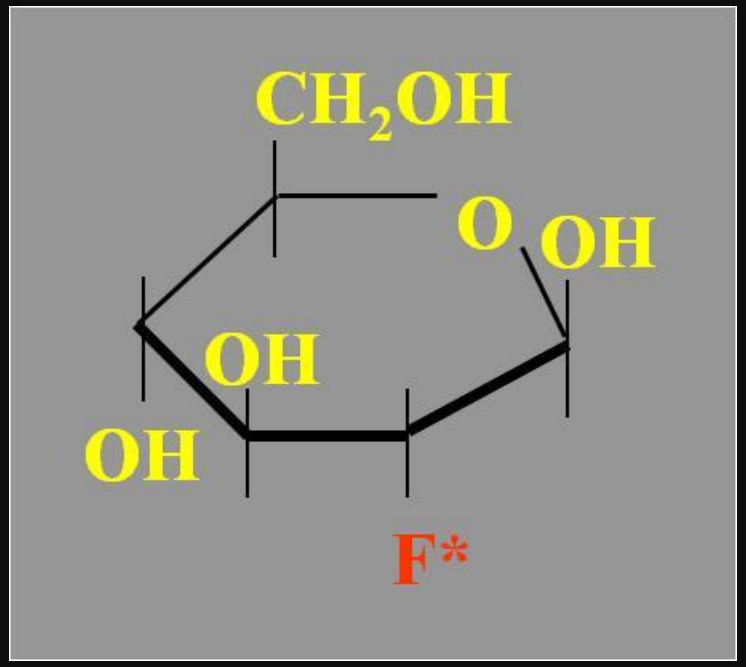
Preclinical Imaging

PET Radiopharmaceutical: FDG

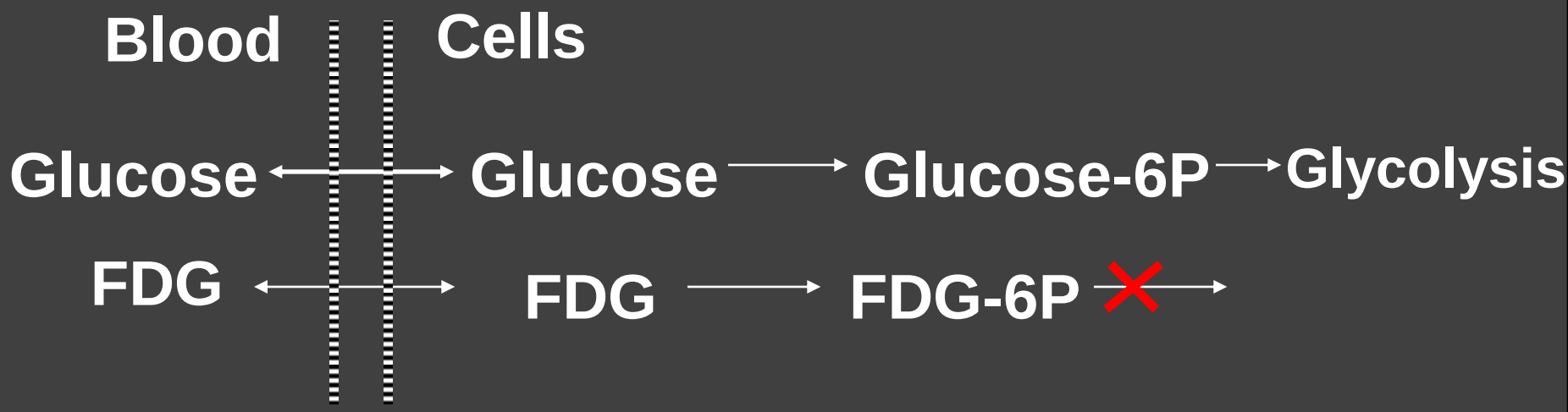
Glucose



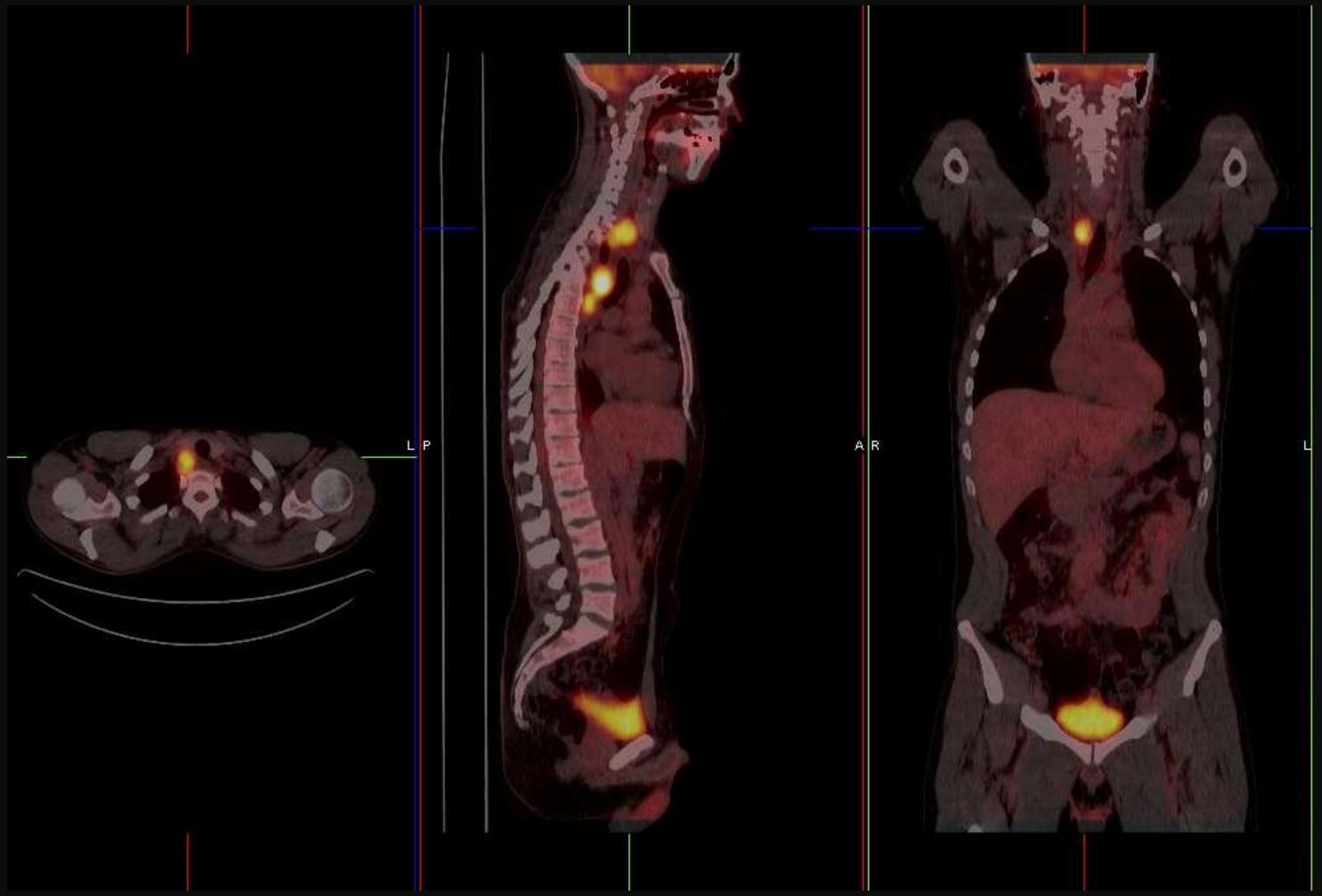
Fluorodeoxyglucose (FDG)



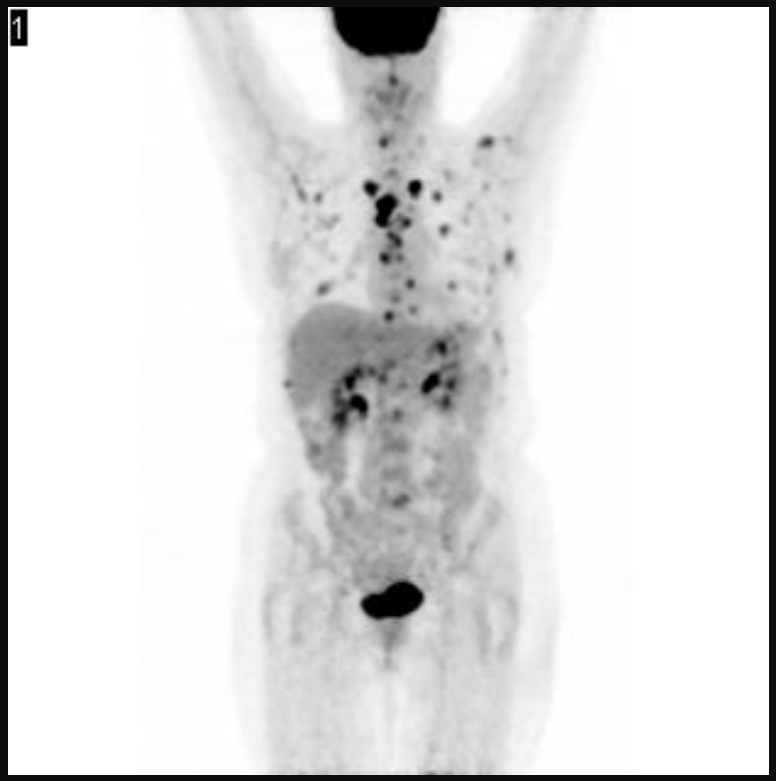
FDG Uptake and Retention



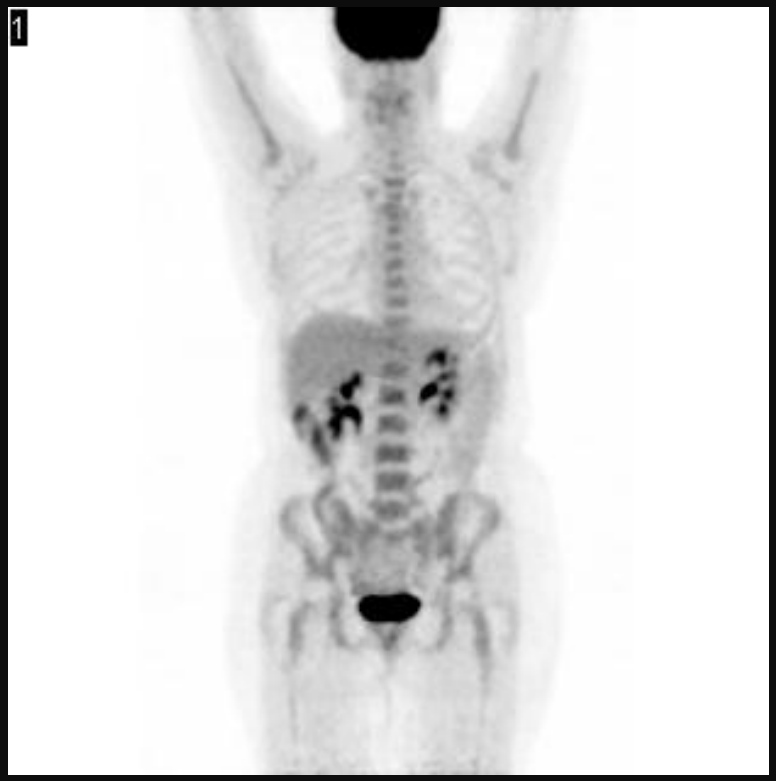
Diagnostic Medicine: Present



59 year old woman with T-cell lymphoma

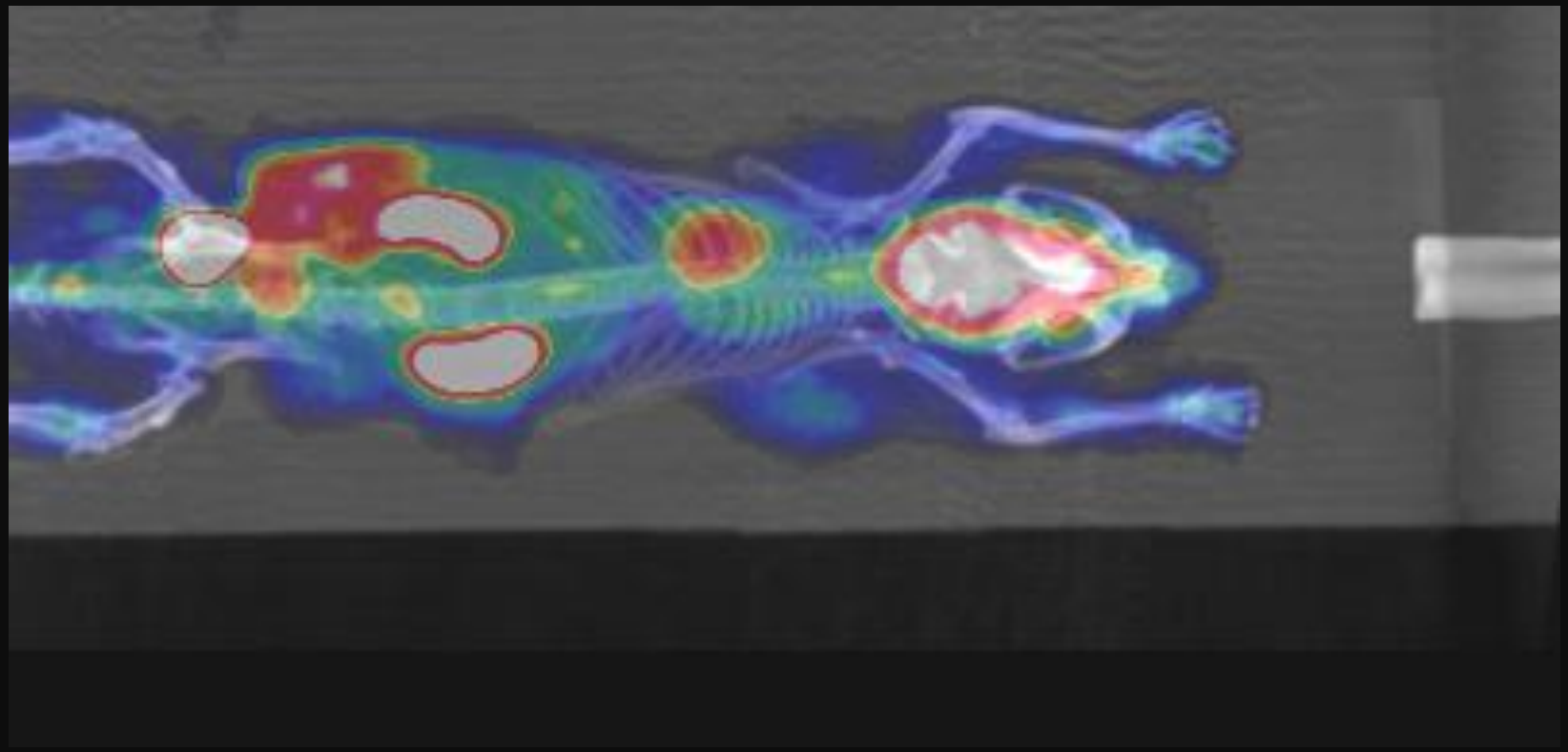


Initial study



4 months later,
after chemotherapy

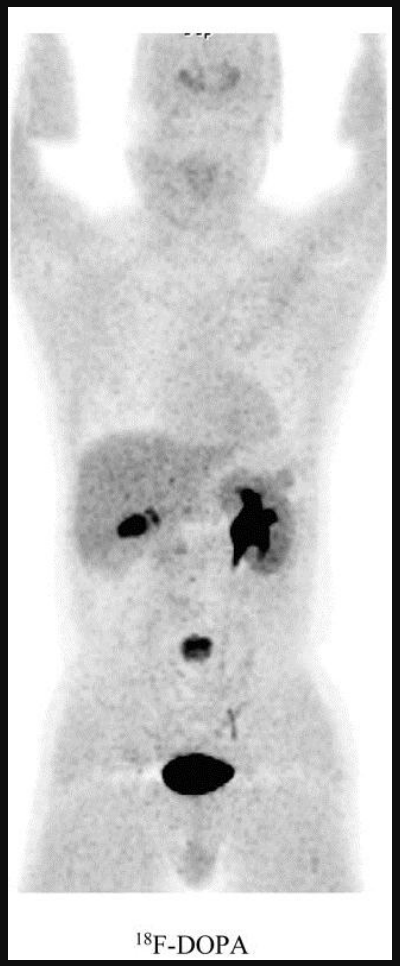
^{18}FDG - micro PET/CT

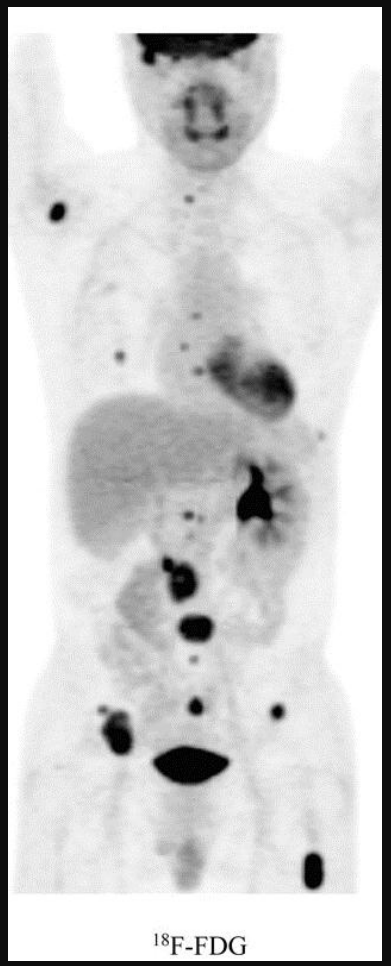


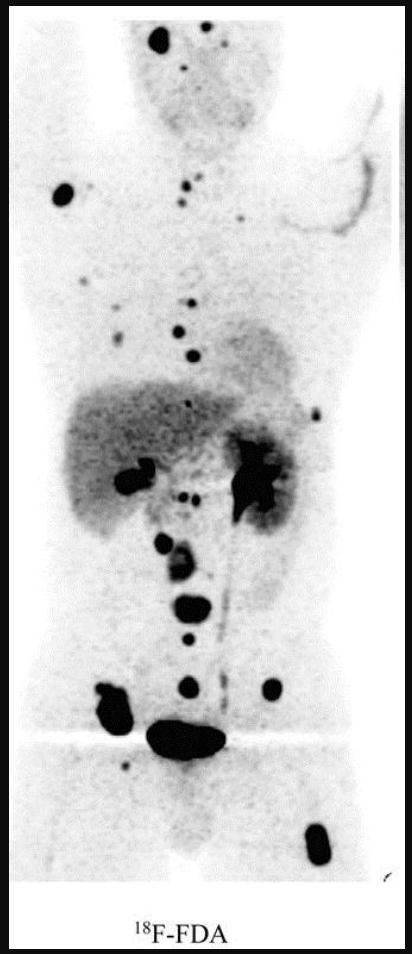
Why develop new imaging agents?

- 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

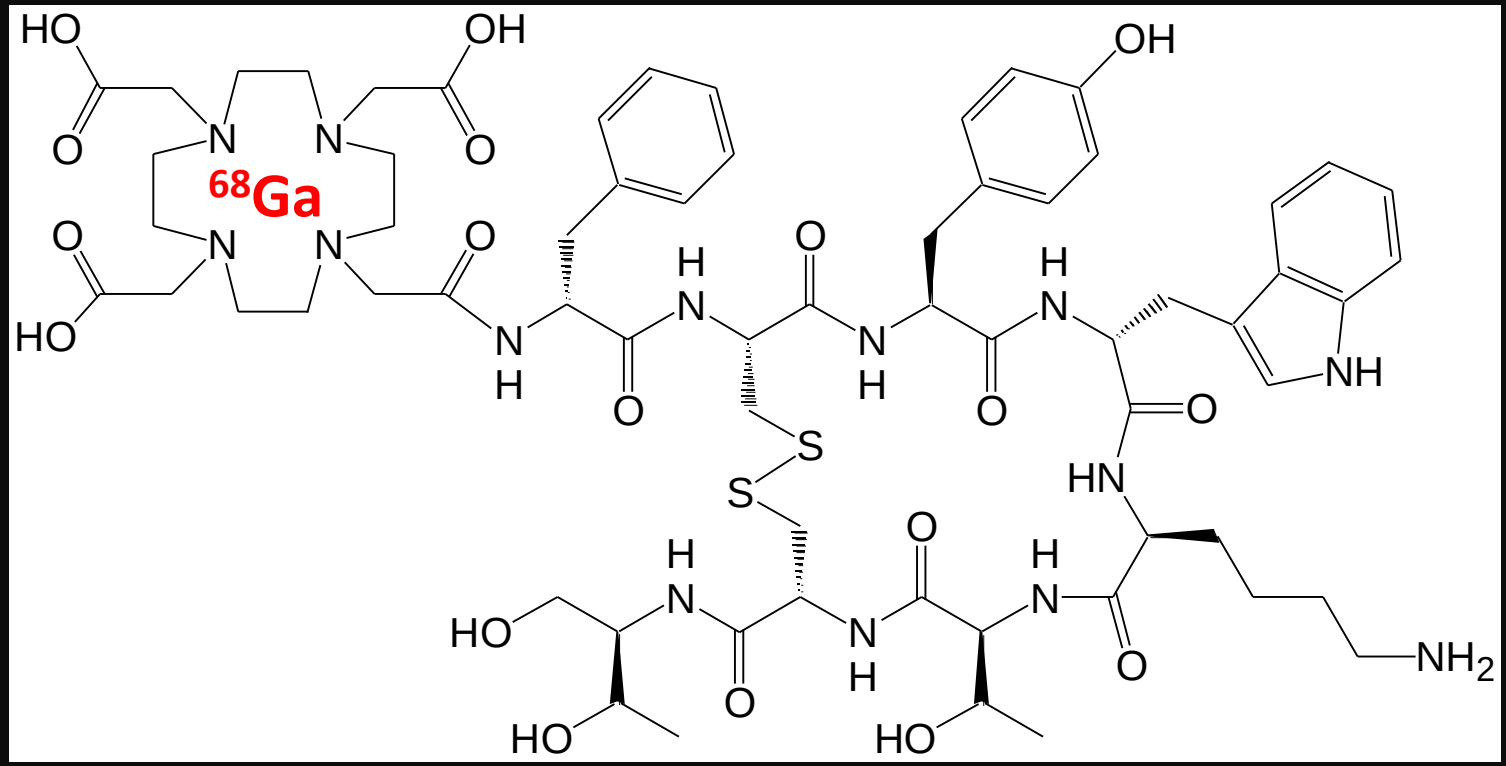






J Clin Endocrinol Metab. 2009 Dec;94(12):4757-67. Epub 2009 Oct 28.

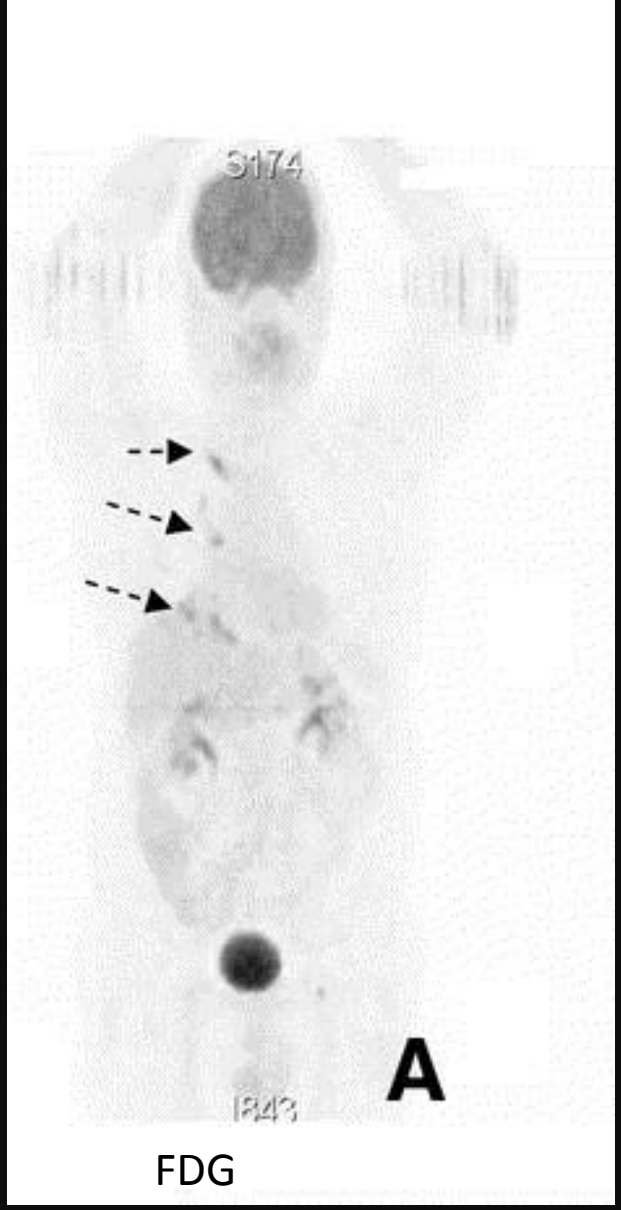
Octreotide and DOTATOC



Targets somatostatin receptors (sstr) overexpressed on neuroendocrine tumors

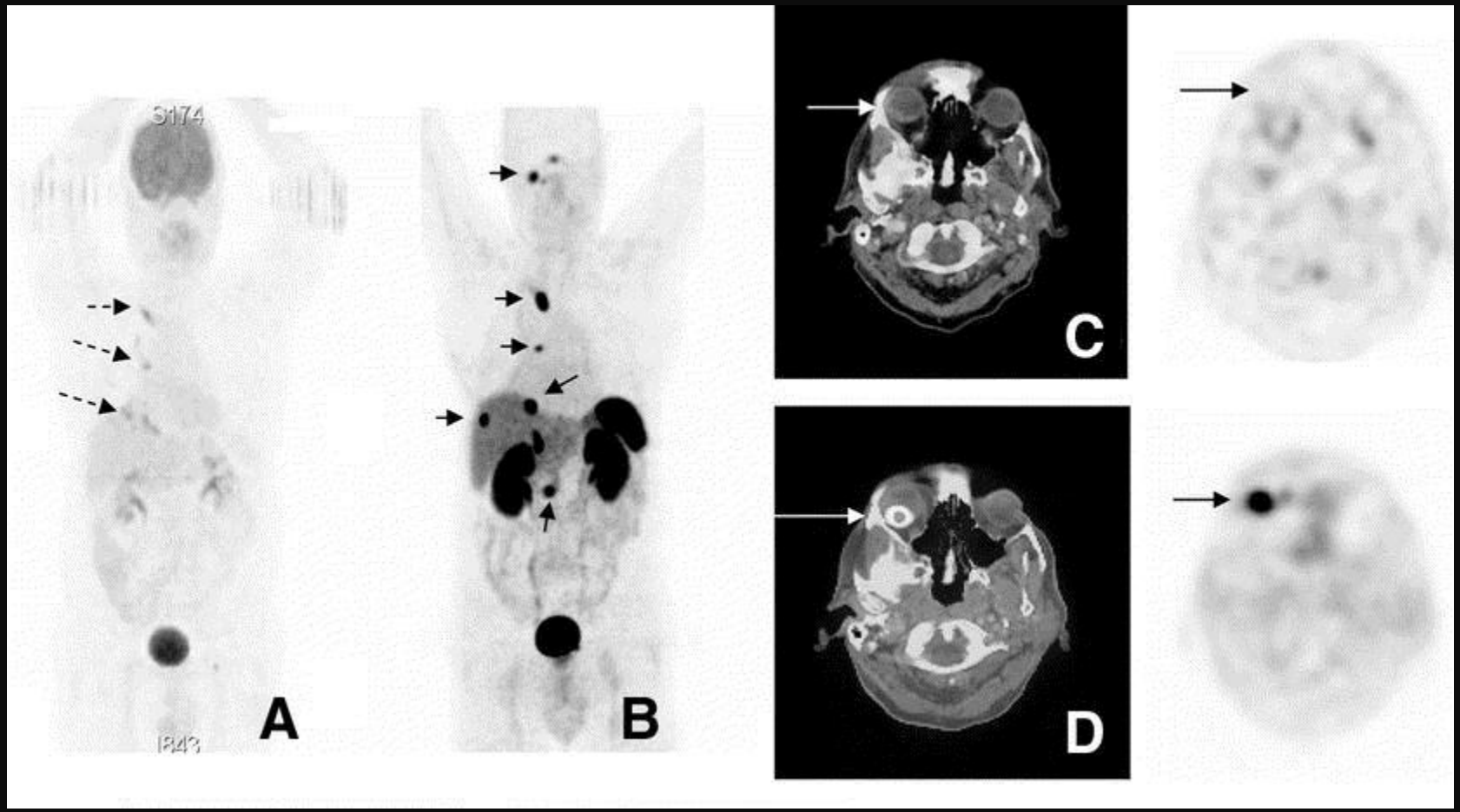
Case Study

- A 61-year-old man presented with the sudden onset of vision problems of the right eye
- Ophthalmoscopy and MRI were suspicious for a choroidal melanoma
- A subsequent FDG PET showed no FDG accumulation



FDG

Van Riet: Clin Nucl Med, Volume 34(1).January 2009.27-28



FDG ^{68}Ga-DOTATOC

Van Riet: Clin Nucl Med, Volume 34(1).January 2009.27-28

PET in Oncology

- diagnosis
  - location and extent of disease
  - general (FDG) or tumour-specific probes
- prognosis
  - size, stage, grade of disease
  - proliferation (FLT) and/or hypoxia (EF5, etc)
- "real-time" therapy evaluation
  - customizing treatment could increase efficacy, decrease toxicity, and improve economics

How to pick a radioisotope?

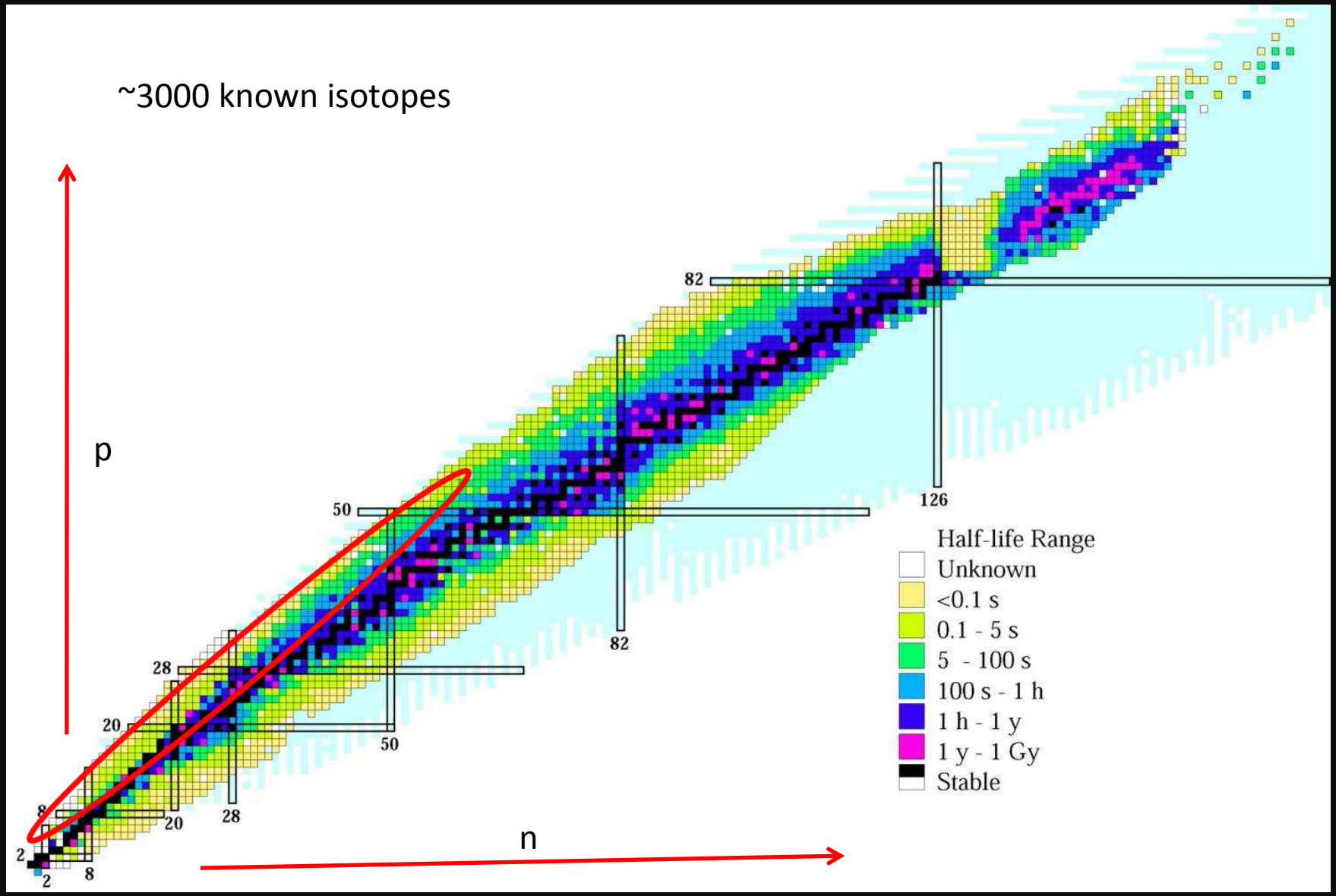
- Chemistry
- Half-life
- Decay Properties
- Availability
- Purity
- Specific Activity (amount of radioactivity per mass)

Common PET isotopes

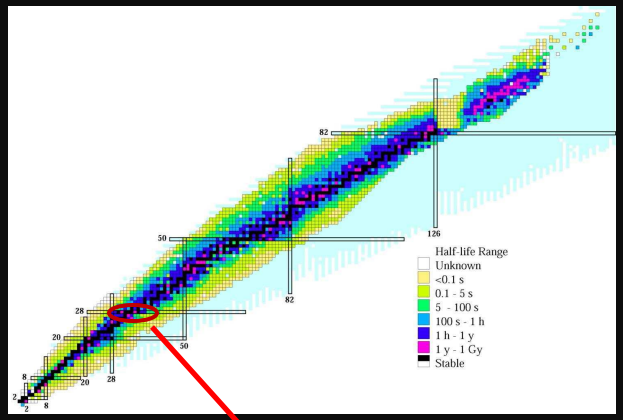
$^{14}N(p,\alpha)^{11}C$	$t_{1/2}$ = 20.3 min.
$^{18}O(p,n)^{18}F$	$t_{1/2}$ = 109.7 min.
$^{16}O(p,\alpha)^{13}N$	$t_{1/2}$ = 9.97 min
$^{14}N(d,n)^{15}O$	$t_{1/2}$ = 2.0 min

The Toolbox

~3000 known isotopes

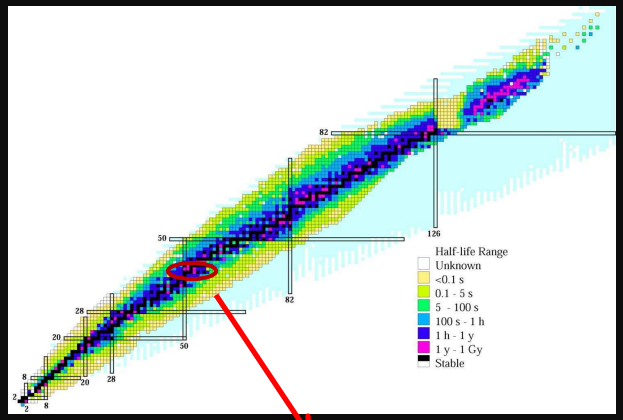


Radiometals?



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:

	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%

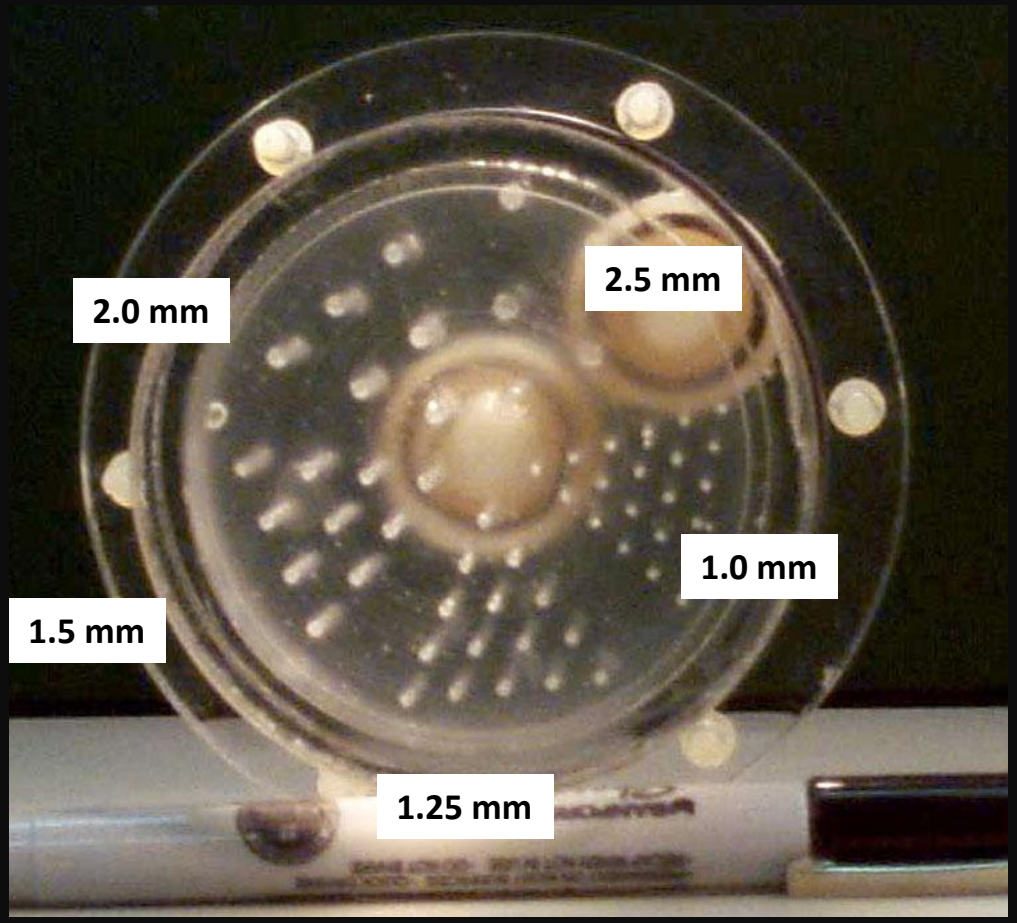
Radiometals

- 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.

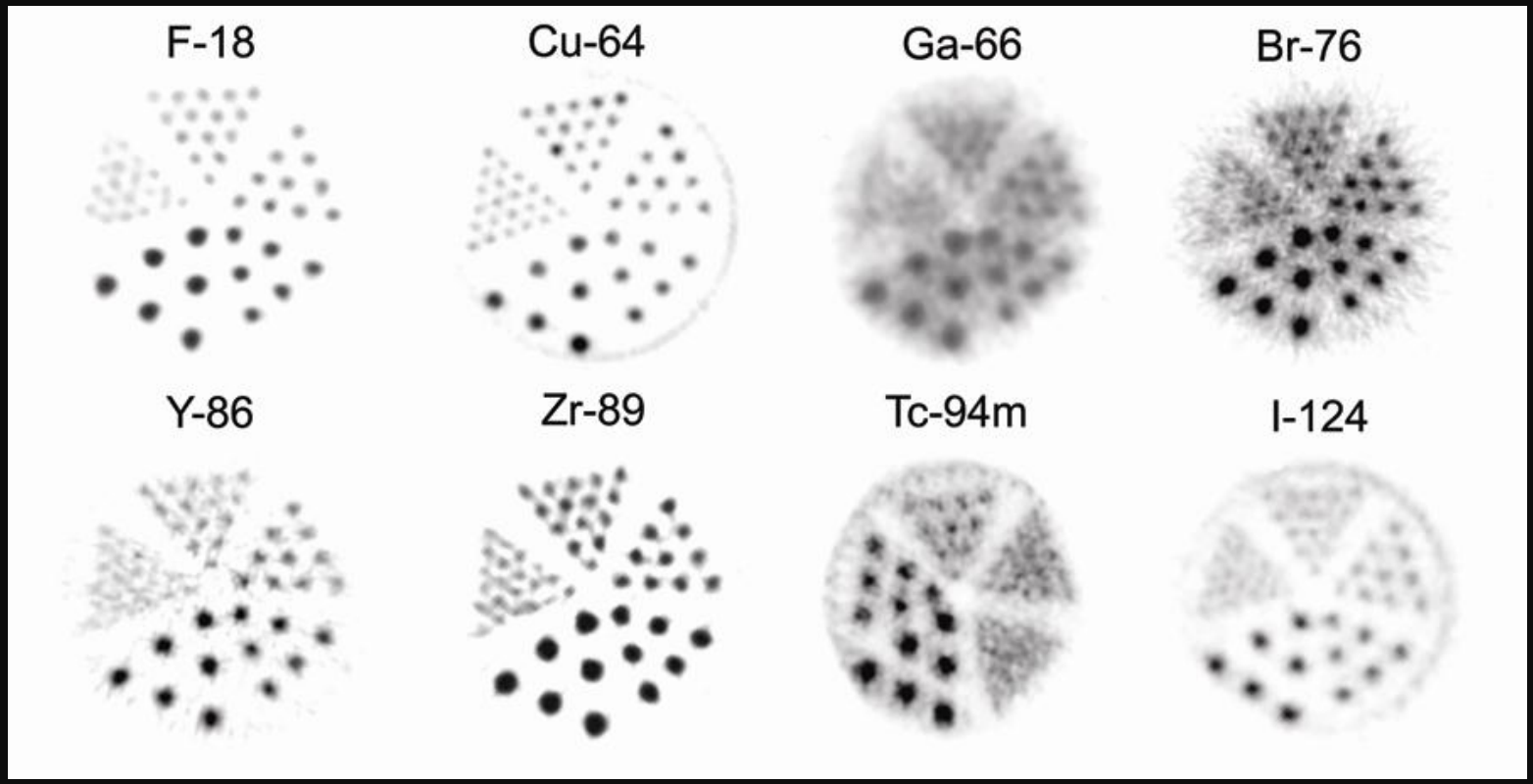
Metal radionuclides discussed

Radionuclides	Half-life	Decay	Production Route
Copper-64	12.7 h	EC/β^-/β^+	Cyclotron
Zirconium-89	3.27 d	EC/β^+	Cyclotron

Assessing Image quality: Derenzo Phantom



Assessing Image quality: Derenzo Phantom

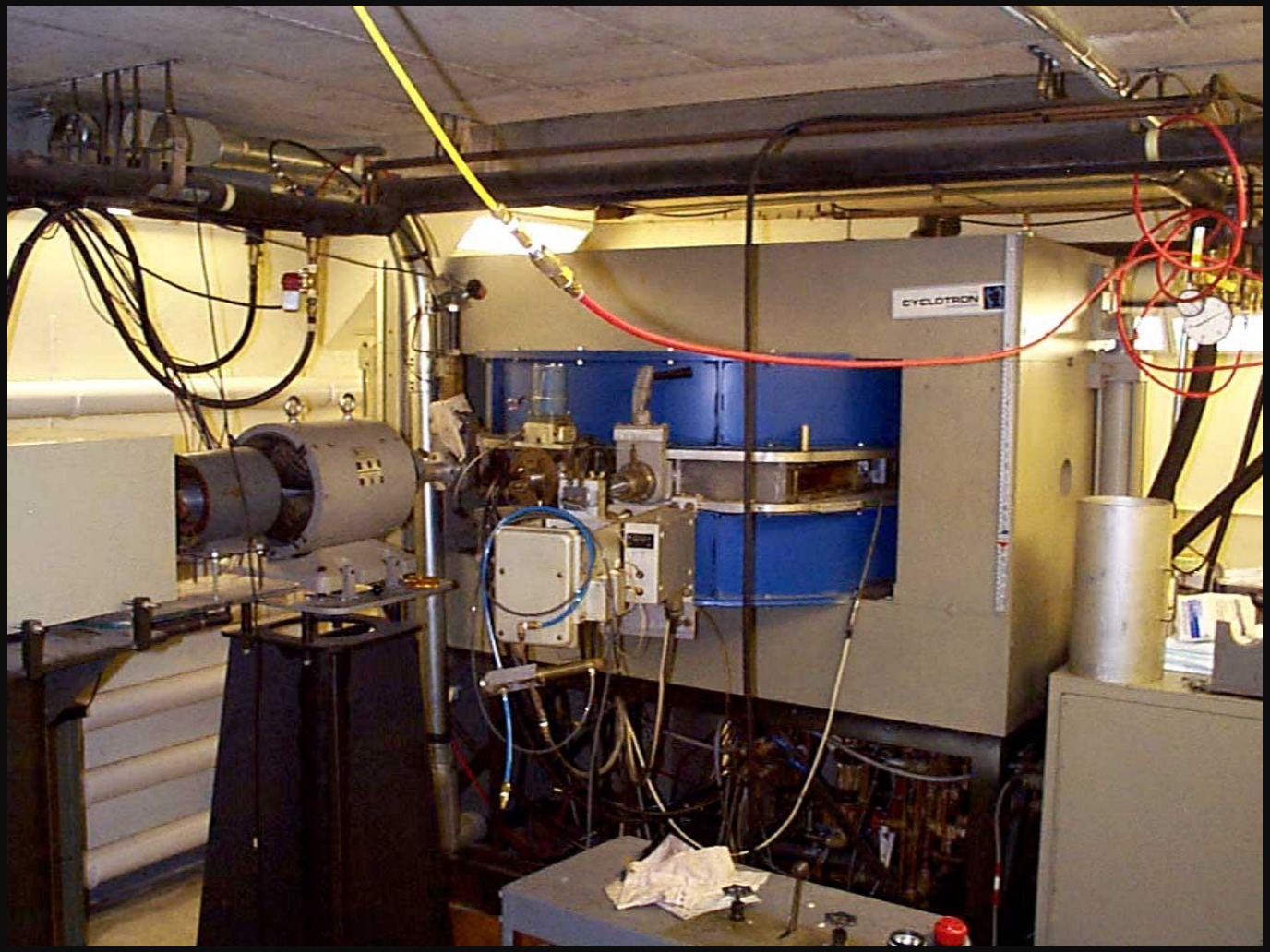


Cyclotron Production of Radionuclides

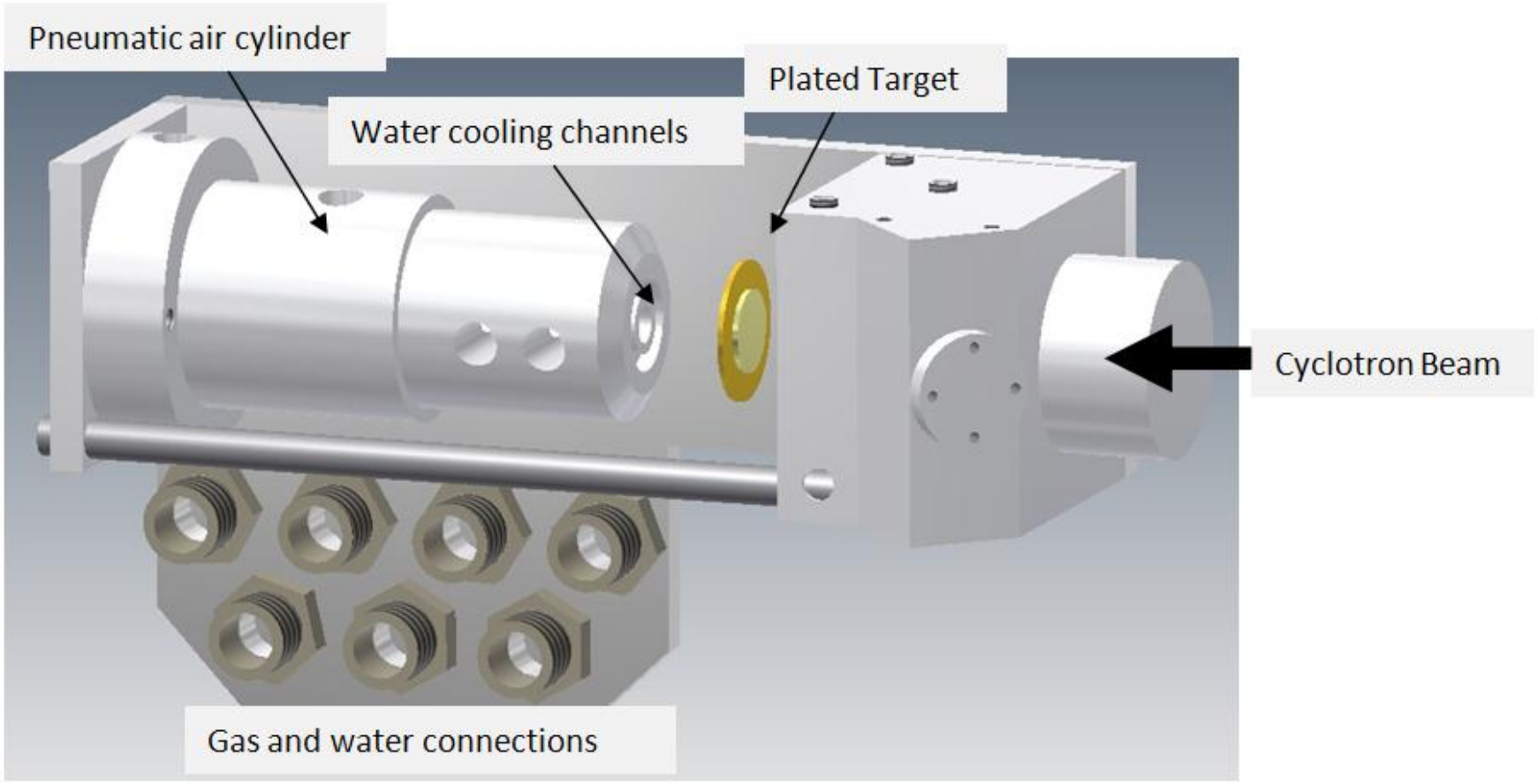
Production of PET isotopes

- β+ isotopes are proton rich
- For use in imaging we typically would like short lived isotopes (minutes to hours)
- Produced by proton induced reactions: (p,n), (p,α), (p,2n)……

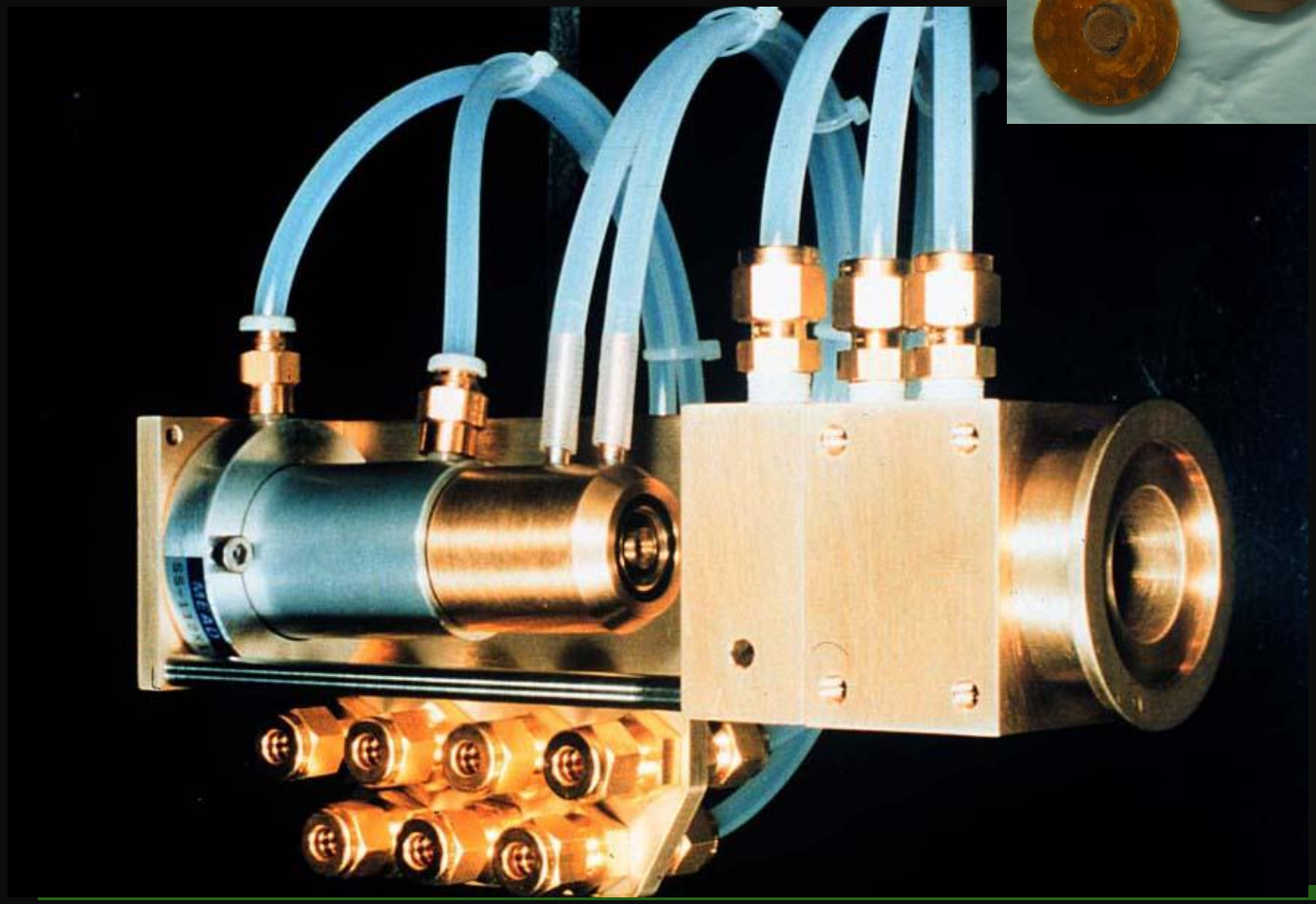
The CS-15



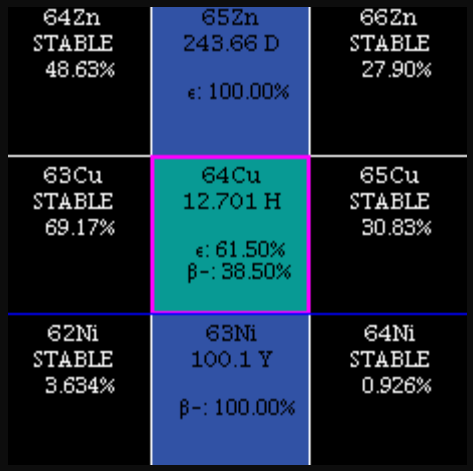
Targetry



Production

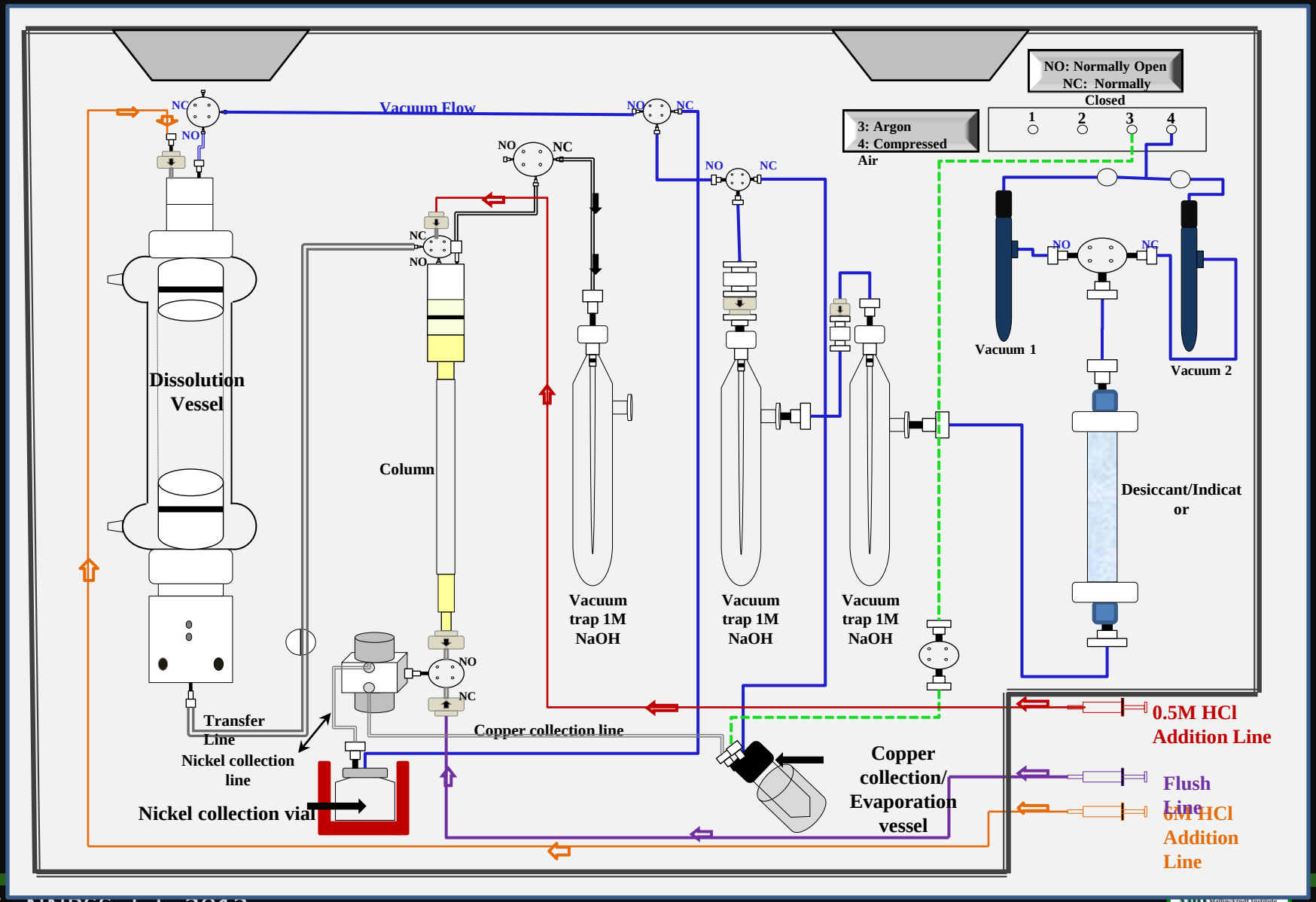


Copper-64



- $T_{1/2}$ 12.7 hours,
- β^+ (17.8%) β^- (38.4%)
- Used for imaging distribution of molecules with biological half-lives of hours-days
- Also potential for targeted radiotherapy
- Produced by ^{64}Ni(p,n) reaction with CS-15

Automated Separation



Zirconium-89

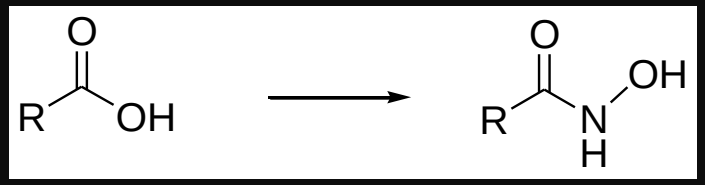
- Half-life of 3.17 d – well suited for study of pharmacokinetics of antibodies (achieve optimal biodistribution ~4-5 d)
- Immuno-PET - Scouting in preparation for radioimmunotherapy, confirming tumor targeting, and estimating dosimetry
- Generally inert to biological systems
- Decay properties
  - EC = 76.6%
  - β^+ = 22.3%
  - $R_{ave.}(\beta^+)$= 1.18 mm

Zr-89 production and purification

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

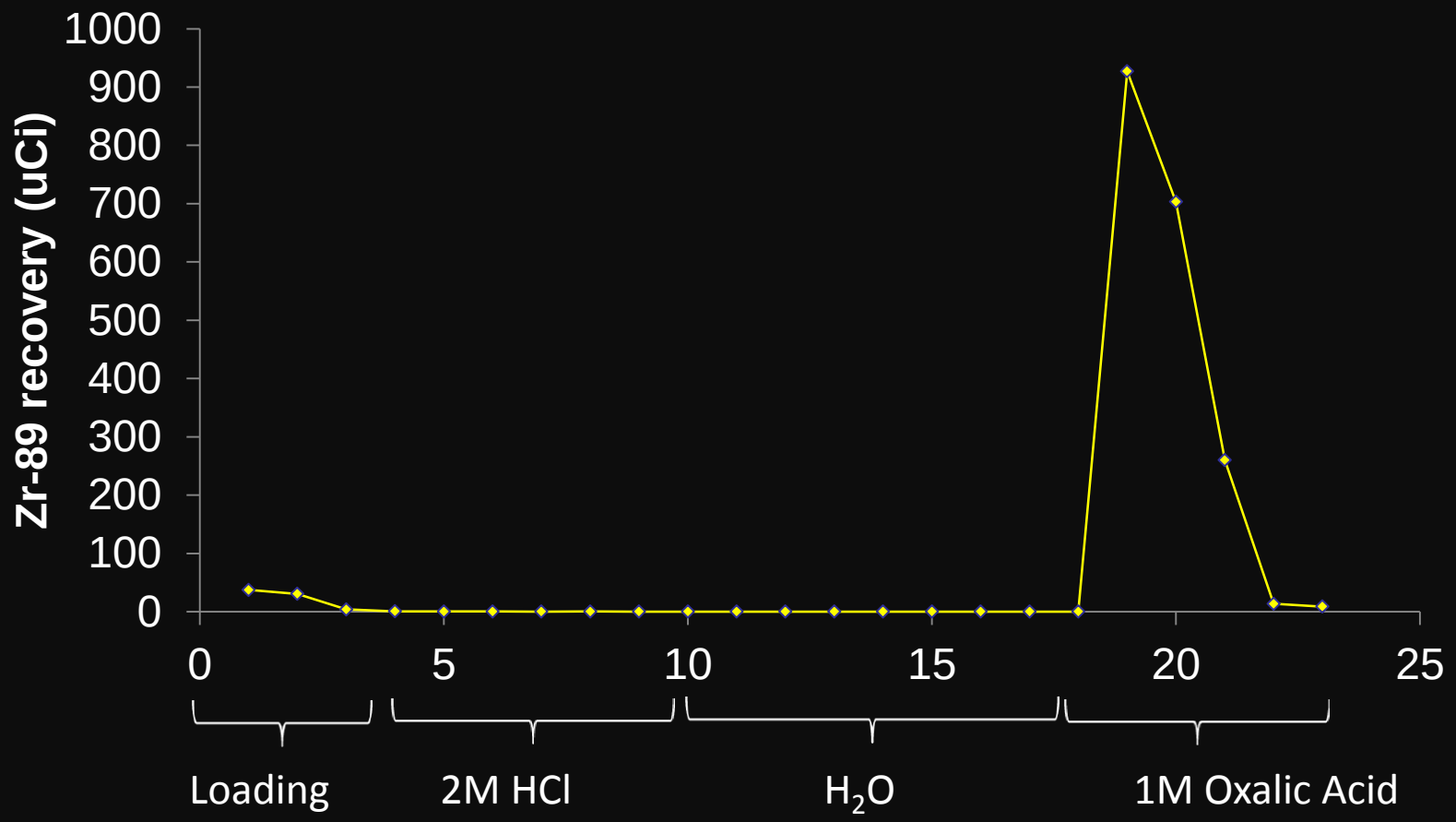
87Zr 1.68 H ε: 100.00%	88Zr 83.4 D ε: 100.00%	89Zr 78.41 H ε: 100.00%	90Zr STABLE 51.45%	91Zr STABLE 11.22%	92Zr STABLE 17.15%	93Zr 1.53E+6 Y β-: 100.00%
86Y 14.74 H ε: 100.00%	87Y 79.8 H ε: 100.00%	88Y 106.626 D ε: 100.00%	89Y STABLE 100%	90Y 64.053 H β-: 100.00%	91Y 58.51 D β-: 100.00%	92Y 3.54 H β-: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

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



Accell resin Hydroxamate resin

Zr-89 purification

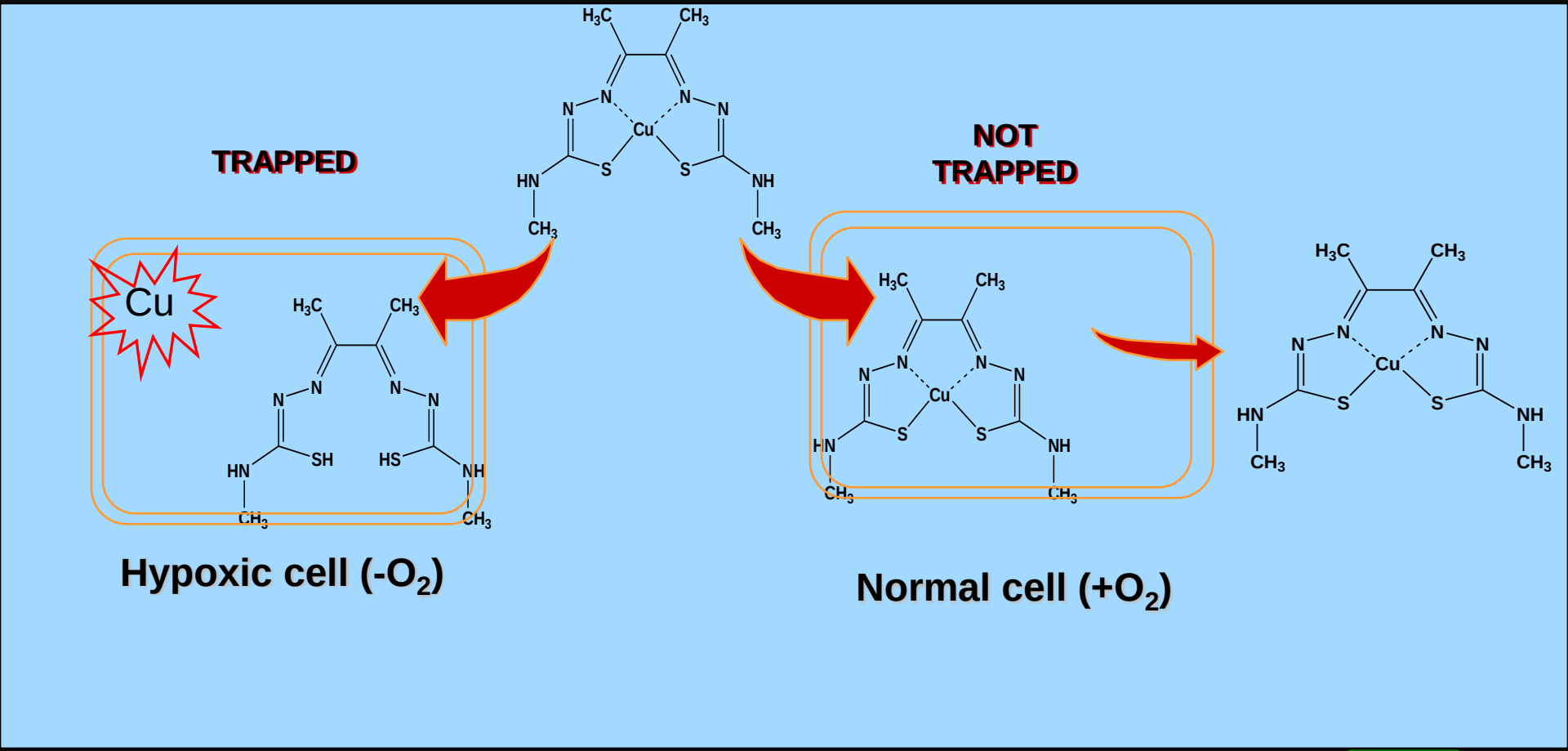


Copper-64 Imaging Agents

[^{64}Cu]ATSM: A Hypoxia Imaging Agent

- Hypoxia: lack of oxygen in tissue
- In cancer: Hypoxia influences response to treatment:
  - Radiotherapy - hypoxic cells are protected from lethal effects of conventional ionizing radiation therapy
  - Chemotherapy - effect of hypoxia on special genes and drug delivery
- Imaging of hypoxia is required in order to predict response to traditional therapies
- Imaging of hypoxia in the brain, heart and cancer have been explored

[^{64}Cu]ATSM: Proposed Mechanism



[^{64}Cu]ATSM: Clinical Studies

- Presence of tumor was confirmed in all patients on pretherapy CT and/or FDG-PET

- Treatment
  - Radiotherapy alone (11 NSCLC and 1 cervical cancer)
  - Radiation and chemotherapy (5 NSCLC and 13 cervical cancer)
  - Chemotherapy alone (3 NSCLC)

- Follow-up after therapy
  - Clinical evaluation at 4-6 weeks after completion of therapy and every 3 months thereafter for 2 years

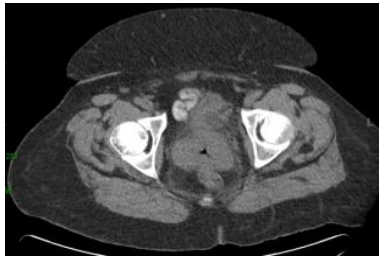
European Journal of Nuclear Medicine and Molecular Imaging Vol. 30, No. 6, June 2003

[^{64}Cu]ATSM: Cervical Cancer

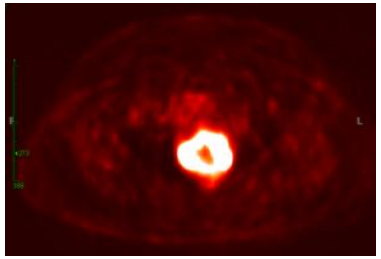
Responder

Non-Responder

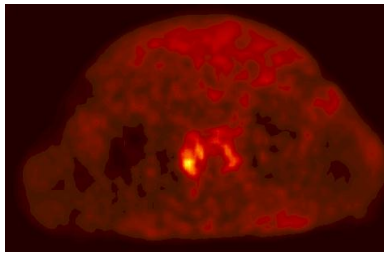
A



CT

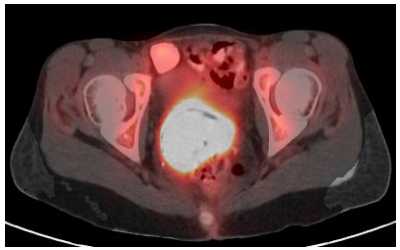


FDG-PET

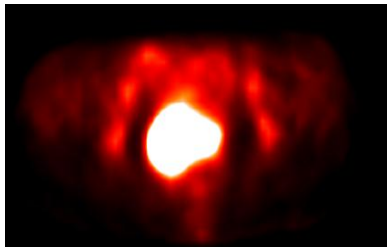


^{64}Cu-ATSM-PET
T/M = 4.4

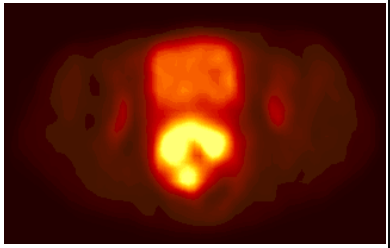
B



Fused PET/CT

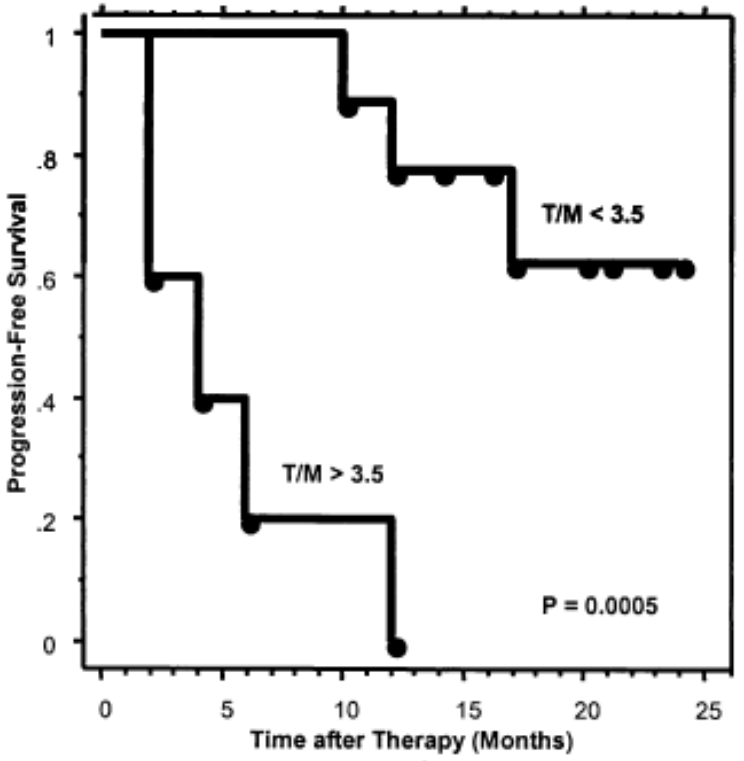


FDG-PET



^{64}Cu-ATSM-PET
T/M = 10.3

Clinical Prediction: Cervical Cancer



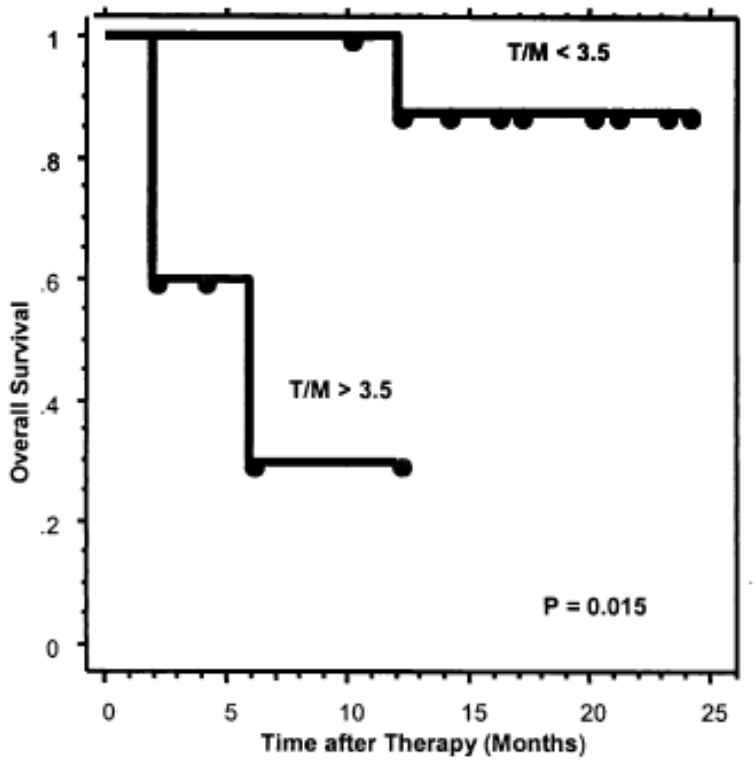


Fig. 2. Progression-free survival and overall survival based on ^{60}Cu-ATSM uptake using Kaplan-Meier method. Patient survival has an inverse relationship with tumor uptake of ^{60}Cu-ATSM assessed by tumor-to-muscle activity ratio (p = 0.0005 and p = 0.015, respectively).

- 5/14 pt's tumors were characterized as hypoxic
- All pts with hypoxic tumors developed recurrent disease
- 6/9 pts with normoxic tumors disease free at end of study

Int. J. Radiation Oncology Biol. Phys., Vol. 55, No. 5, pp. 1233–1238, 2003

Summary of [^{64}Cu]ATSM

- It is feasible to study human tumors with ^{64}Cu-ATSM-PET
- The T/M activity ratio is a simple reliable semiquantitative method for evaluation of tumor uptake of ^{64}Cu-ATSM
- Pre-therapy ^{64}Cu-ATSM-PET
  - Predictive of response to therapy
  - Predictive of disease-free survival
- ^{64}Cu-ATSM-PET may direct radiation therapy
- ^{64}Cu-ATSM-PET can be used to monitor the effect of therapeutic strategies known to overcome hypoxia

Zirconium-89 ImmunoPET

Antibody	Target	FDA-approved indication	Approval in Europe*	Mechanisms of action
Naked antibodies: solid malignancies				
Trastuzumab (Herceptin; Genentech): humanized IgG1	ERBB2	ERBB2-positive breast cancer, as a single agent or in combination with chemotherapy for adjuvant or palliative treatment	Similar	Inhibition of ERBB2 signalling and ADCC
		ERBB2-positive gastric or gastro-oesophageal junction carcinoma as first-line treatment in combination with cisplatin and capecitabine or 5-fluorouracil		
Bevacizumab (Avastin; Genentech/Roche): humanized IgG1	VEGF	For first-line and second-line treatment of metastatic colon cancer, in conjunction with 5-fluorouracil-based chemotherapy; for first-line treatment of advanced NSCLC, in combination with carboplatin and paclitaxel, in patients who have not yet received chemotherapy; as a single agent in adult patients with glioblastoma whose tumour has progressed after initial treatment; and in conjunction with IFNα to treat metastatic kidney cancer	Similar	Inhibition of VEGF signalling
Cetuximab (Erbitux; Bristol-Myers Squibb)‡: chimeric human–murine IgG1	EGFR	In combination with radiation therapy for the initial treatment of locally or regionally advanced SCCHN; as a single agent for patients with SCCHN for whom prior platinum-based therapy has failed; and palliative treatment of pretreated metastatic EGFR-positive colorectal cancer	Similar	Inhibition of EGFR signalling and ADCC
Panitumumab (Vectibix; Amgen)‡: human IgG2	EGFR	As a single agent for the treatment of pretreated EGFR-expressing, metastatic colorectal carcinoma	Similar	Inhibition of EGFR signalling
Ipilimumab (Yervoy; Bristol-Myers Squibb): IgG1	CTLA4	For the treatment of unresectable or metastatic melanoma	Similar	Inhibition of CTLA4 signalling
Naked antibodies: haematological malignancies				
Rituximab (Mabthera; Roche): chimeric human–murine IgG1	CD20	For the treatment of CD20-positive B cell NHL and CLL, and for maintenance therapy for untreated follicular CD20-positive NHL	Similar	ADCC, direct induction of apoptosis and CDC
Alemtuzumab (Campath; Genzyme): humanized IgG1	CD52	As a single agent for the treatment of B cell chronic lymphocytic leukaemia	Similar	Direct induction of apoptosis and CDC
Ofatumumab (Arzerra; Genmab): human IgG1	CD20	Treatment of patients with CLL refractory to fludarabine and alemtuzumab	Similar	ADCC and CDC
Conjugated antibodies: haematological malignancies				
Gemtuzumab ozogamicin (Mylotarg; Wyeth): humanized IgG4	CD33	For the treatment of patients with CD33-positive acute myeloid leukaemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy; withdrawn from use in June 2010	Not approved in the European Union	Delivery of toxic payload, calicheamicin toxin
Brentuximab vedotin (Adcetris; Seattle Genetics): chimeric IgG1	CD30	For the treatment of relapsed or refractory Hodgkin's lymphoma and systemic anaplastic lymphoma	Not approved in the European Union	Delivery of toxic payload, auristatin toxin
^{90}Y-labelled ibritumomab tiuxetan (Zevalin; IDEC Pharmaceuticals): murine IgG1	CD20	Treatment of relapsed or refractory, low-grade or follicular B cell NHL	Similar	Delivery of the radioisotope ^{90}Y
		Previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy		
^{131}I-labelled tositumomab (Bexxar; GlaxoSmithKline): murine IgG2	CD20	Treatment of patients with CD20 antigen-expressing relapsed or refractory, low-grade, follicular or transformed NHL	Granted orphan status drug in 2003 in the European Union	Delivery of the radioisotope ^{131}I, ADCC and direct induction of apoptosis

ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; CLL, chronic lymphocytic leukaemia; CTLA4, cytotoxic T lymphocyte-associated antigen 4; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; IgG, immunoglobulin G; INFα; interferon-α; NHL, non-Hodgkin's lymphoma; NSCLC, non-small-cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck; VEGF, vascular endothelial growth factor. *Based on information from the European Medicines Agency. ‡Not recommended for patients with colorectal cancer whose tumours express mutated KRAS.

Andrew M. Scott, Jedd D. Wolchok & Lloyd J. Old
Nature Reviews Cancer 12, 278-287 (April 2012)

^{89}Zr: Herceptin

- Well characterized antibody

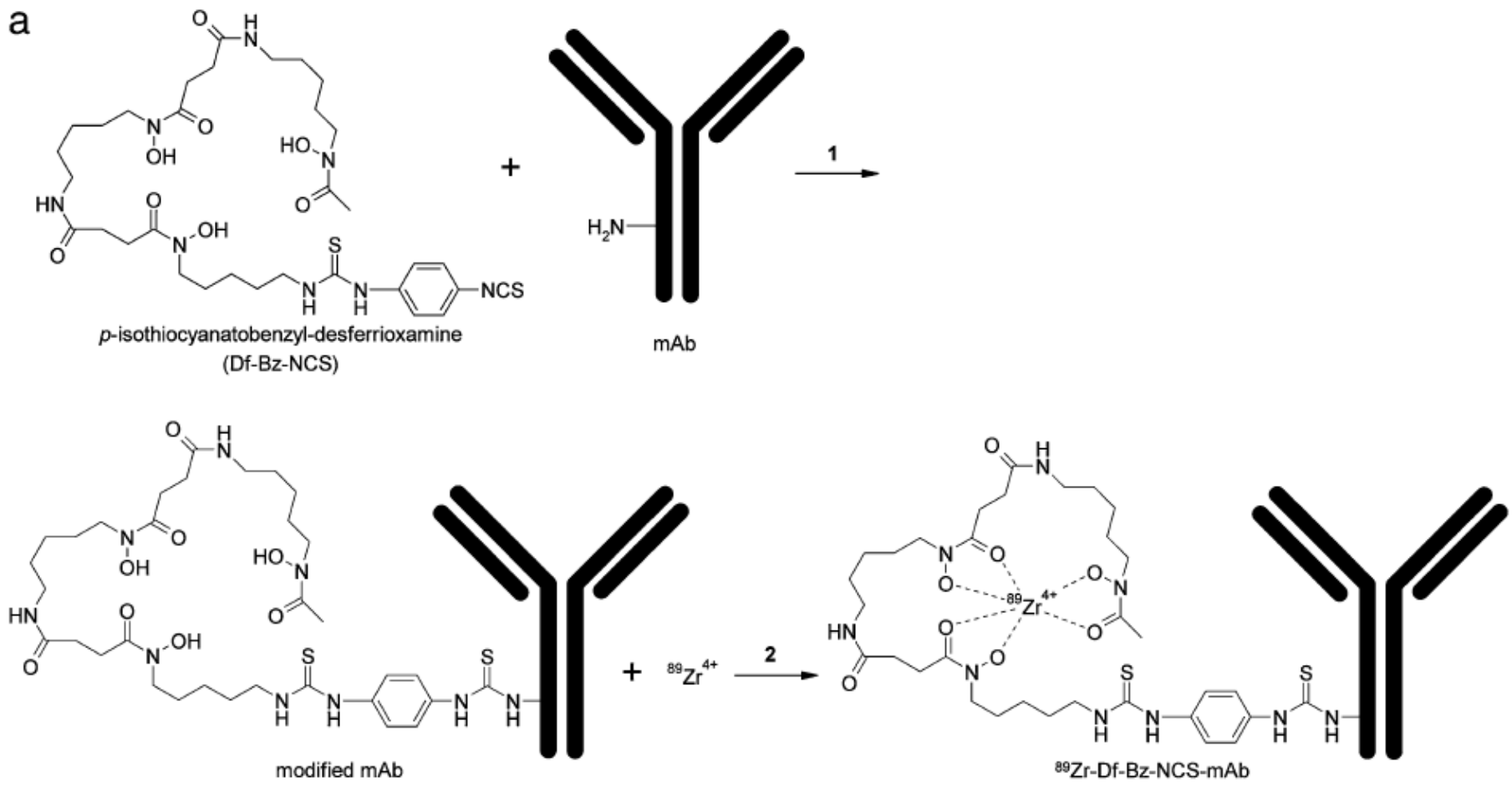
INDICATIONS AND USAGE

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).

- Herceptin imaging agent may be useful for predicting response
- Conjugation with DFO-Bz-NCS
  - Vosjan *et al. Nature protocols* 5(4):739-43; 2010

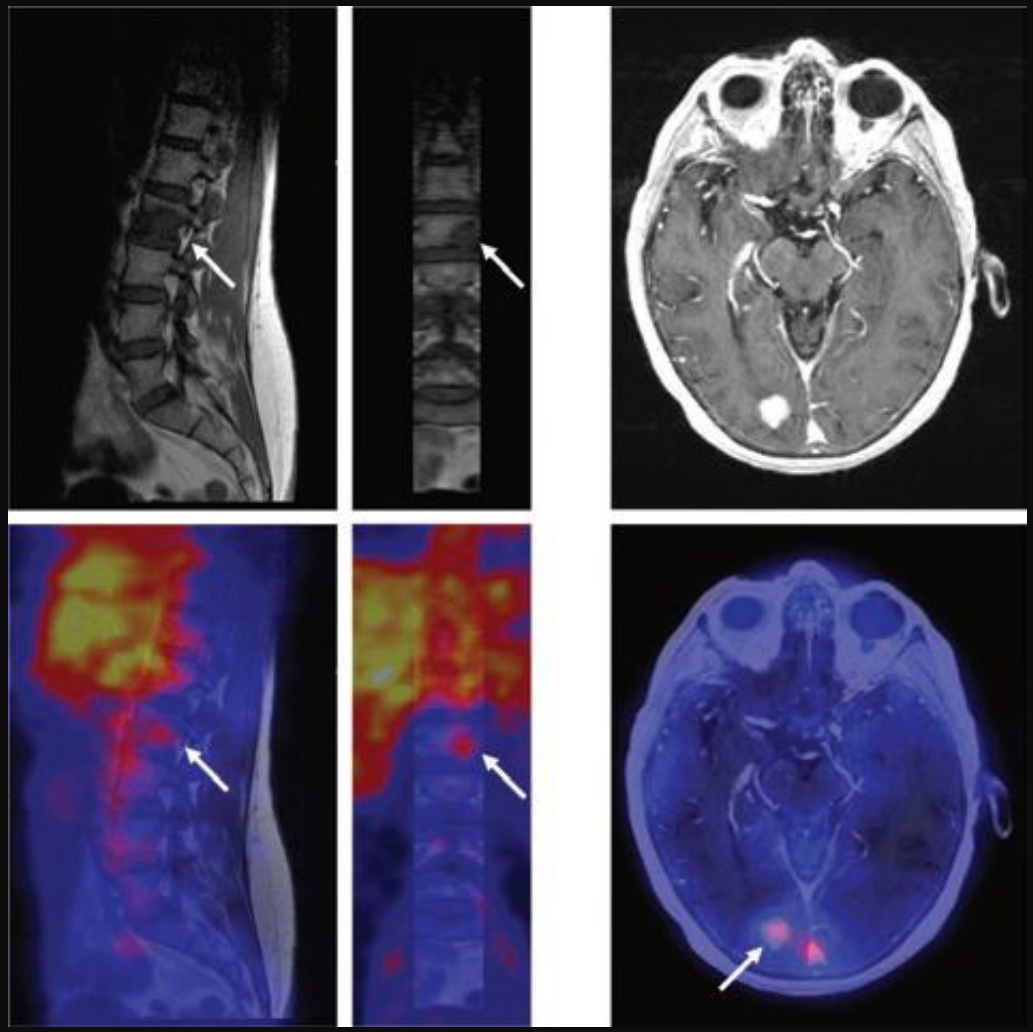
^{89}Zr: Conjugation and Labeling

Eur J Nucl Med Mol Imaging (2010) 37:250–259



^{89}Zr-trastuzumab

Examples of fusion images from HER2 PET and MRI scans. (a) In a vertebral metastasis seen on MRI but unapproachable for biopsy, HER2 status was revealed by 89Zr-trastuzumab uptake on PET imaging. (**b) Example** of HER2-positive brain lesion undetected by conventional scans, revealed by 89Zr-trastuzumab PET imaging, and subsequently confirmed by MRI.

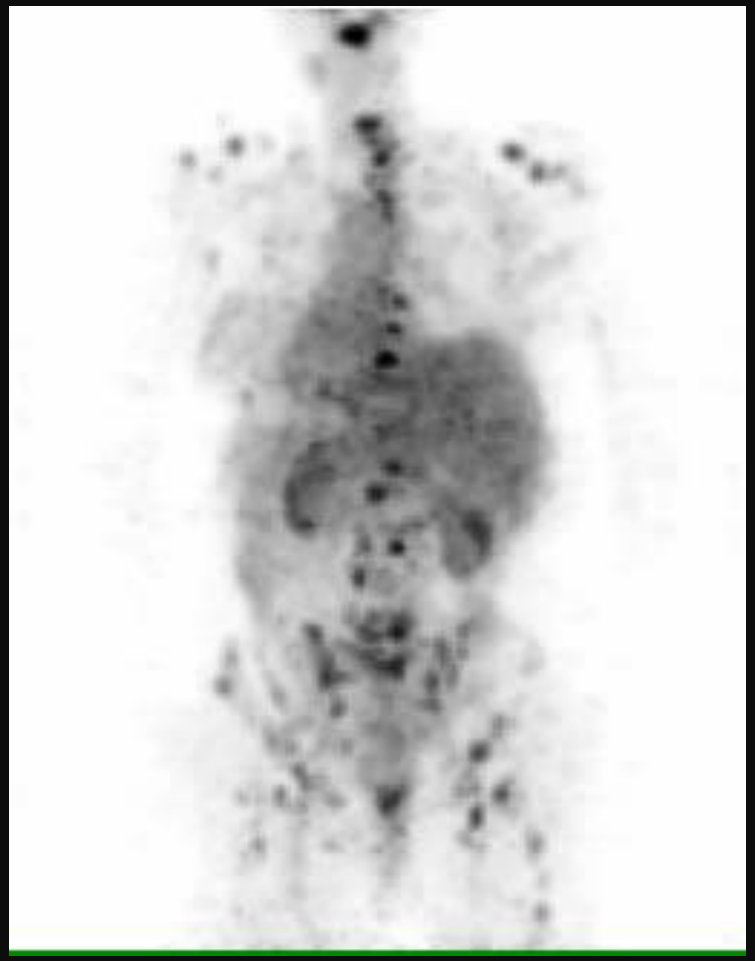


Dijkers et al *Clinical Pharm and Therapeutics* May 2010

^{89}Zr-trastuzumab

In this study, ^{89}Zr-trastuzumab allowed the researchers
to distinguish between lesions with HER2 overexpression and
those without.

The PET images produced with ^{89}Zr-trastuzumab showed high spatial resolution and good signal- to-noise ratio, resulting in an image quality unapproachable by our previous ^{111}In-trastuzumab SPECT scans.

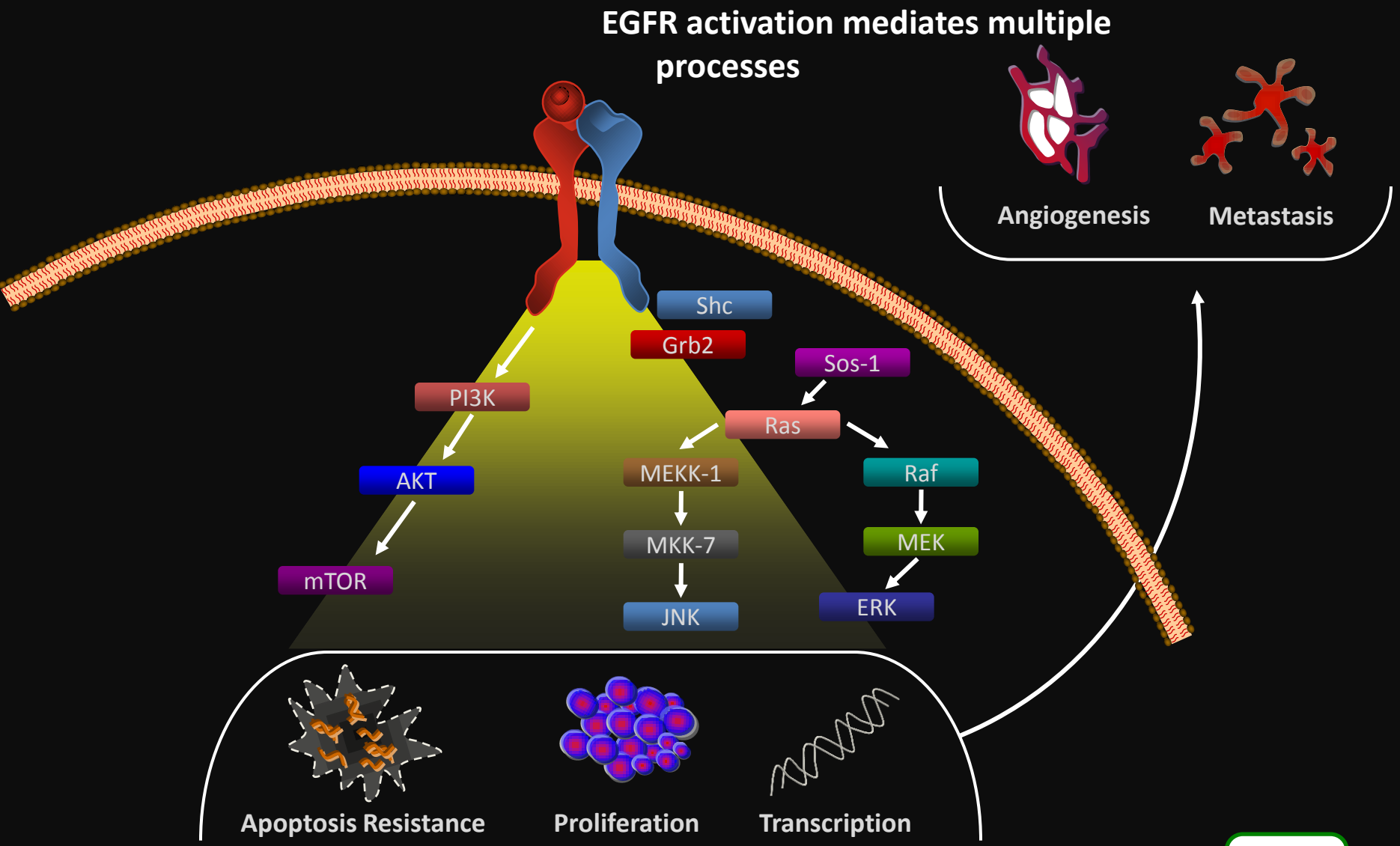


Dijkers et al *Clinical Pharm and Therapeutics* May 2010

^{89}Zr-Panitumumab for ImmunoPET Imaging of the Epidermal Growth Factor Receptor

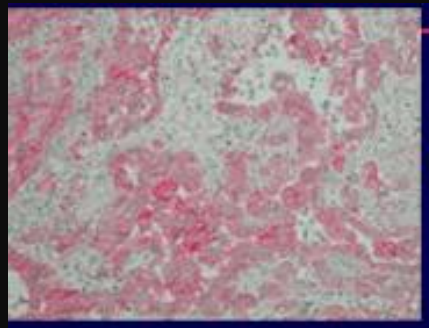
Washington University in St. Louis
School of Medicine
MIR Mallinckrodt Institute of Radiology

EGFR in Human Carcinogenesis

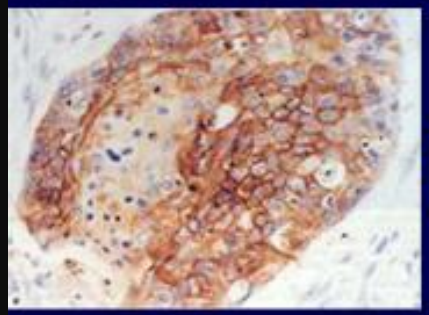


Adapted from: Ciardiello F, et al. N Engl J Med. 2008;358:1160-1174.

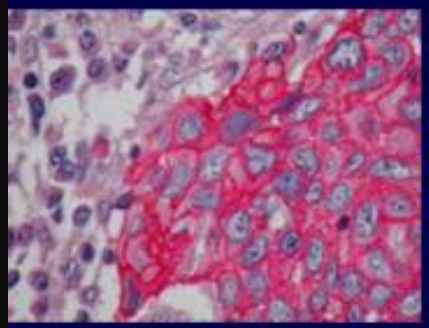
EGFR Expression in Solid Tumors



Colorectal



Lung (NSCLC)



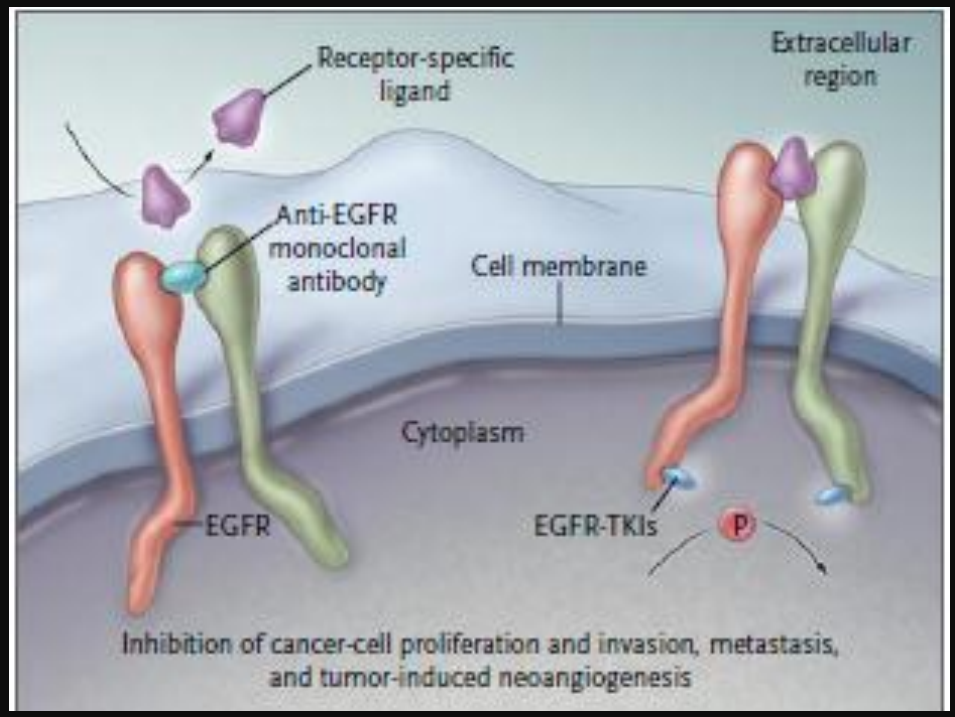
Head & Neck (SCCHN)

EGFR is expressed in a variety of solid tumors

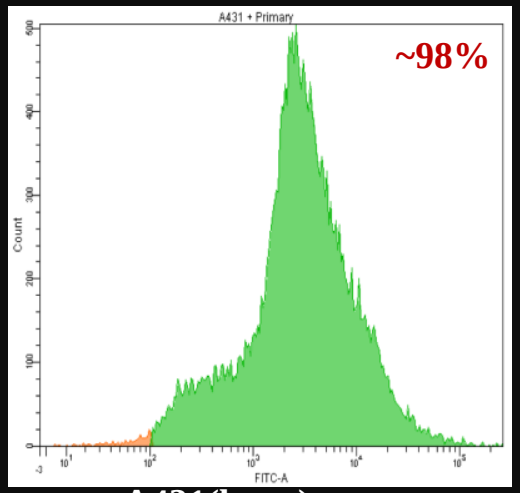
Colorectal cancer	72-82%
Head & neck cancer	95-100%
Lung cancer (NSCLC)	40-80%
Breast cancer	14-91%
Ovarian cancer	35-70%
Renal cell cancer	50-90%

EGFR-Targeted Monoclonal Antibodies

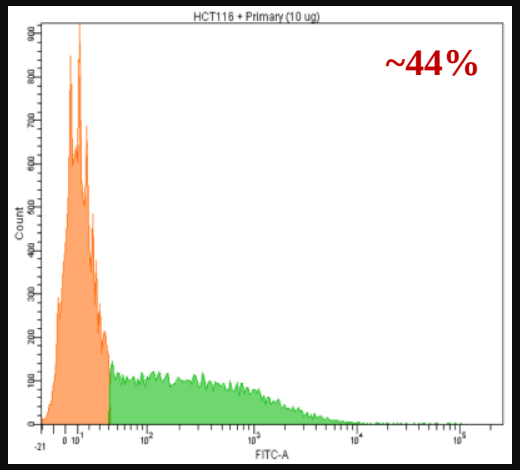
- **Cetuximab**
  - Human-mouse chimeric IgG_1 mAb
  - For advance colon cancer
- **Panitumumab**
  - Fully humanized IgG_2 mAb
  - advance colon cancer, non-small cell lung cancer, esophageal cancer, and pancreatic cancer



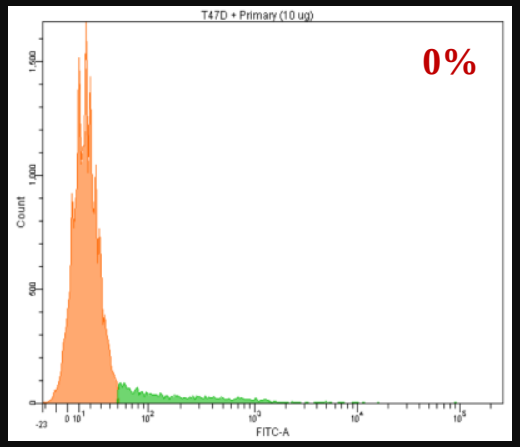
EGFR Expression on Different Cancer Cell Lines : Flow Cytometry Data



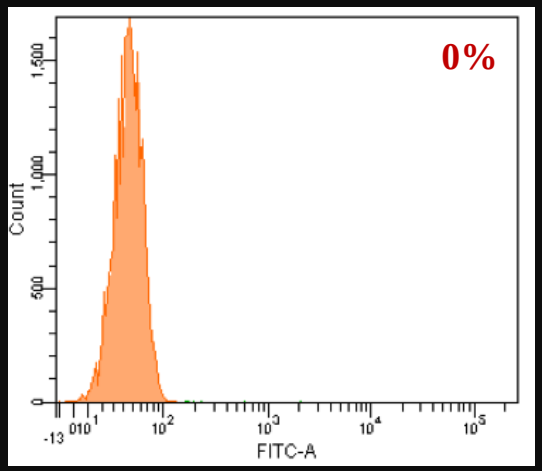
A431(lung)



HCT116 (colorectal)



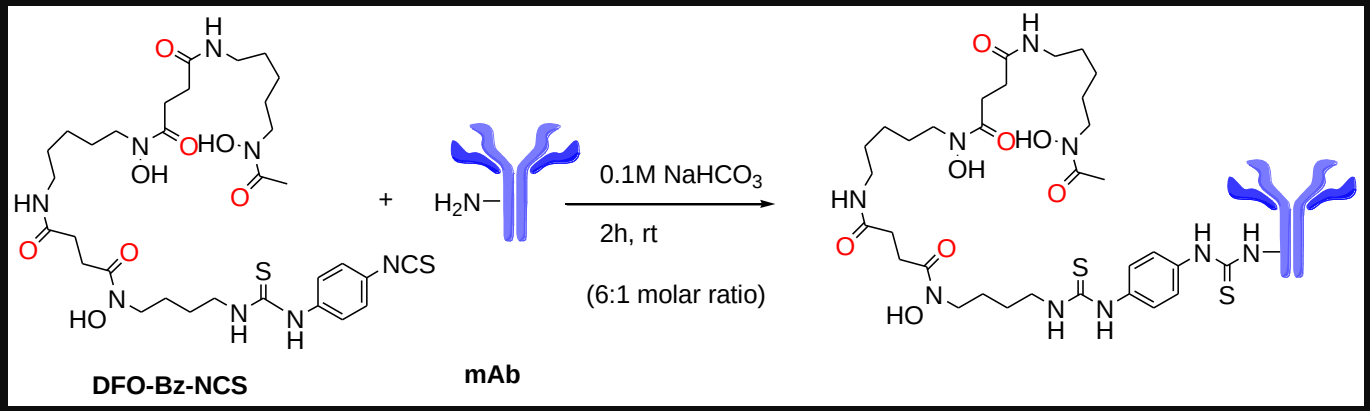
T47D (breast)



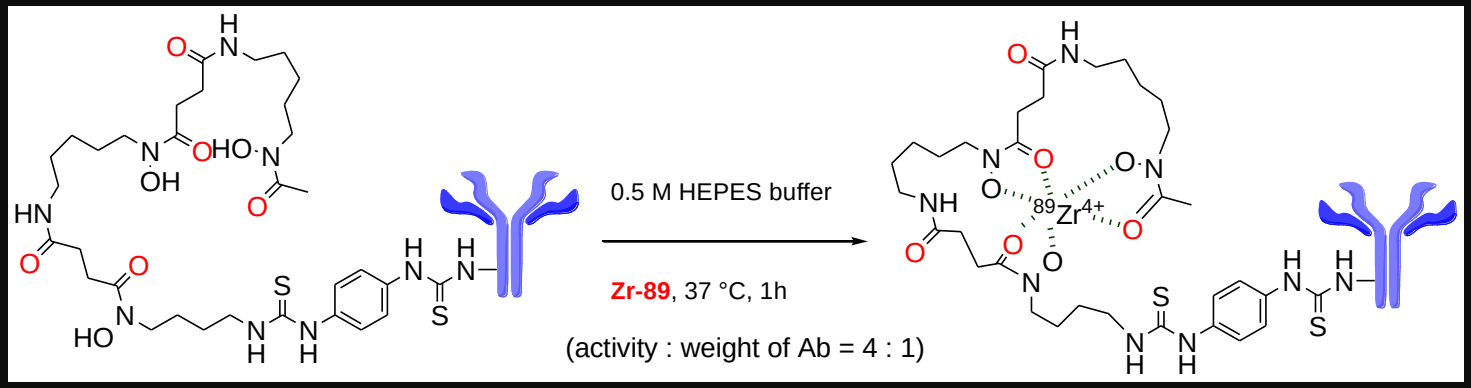
MDA-MB-435(breast)

Labeling of Panitumumab with ^{89}Zr

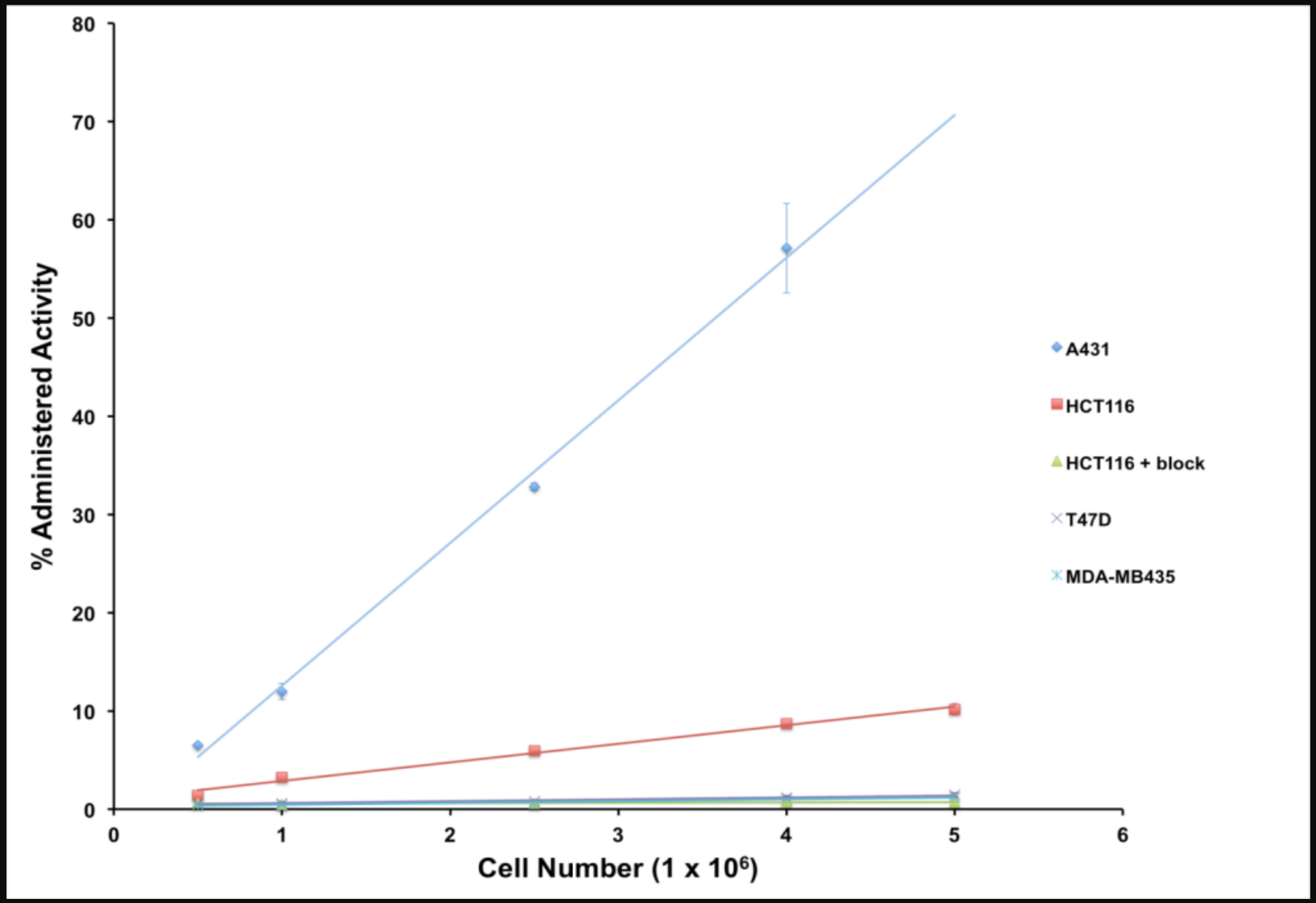
(a) mAb conjugation to DFO-Bz-NCS



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



Cell Uptake Studies



microPET and BioD studies

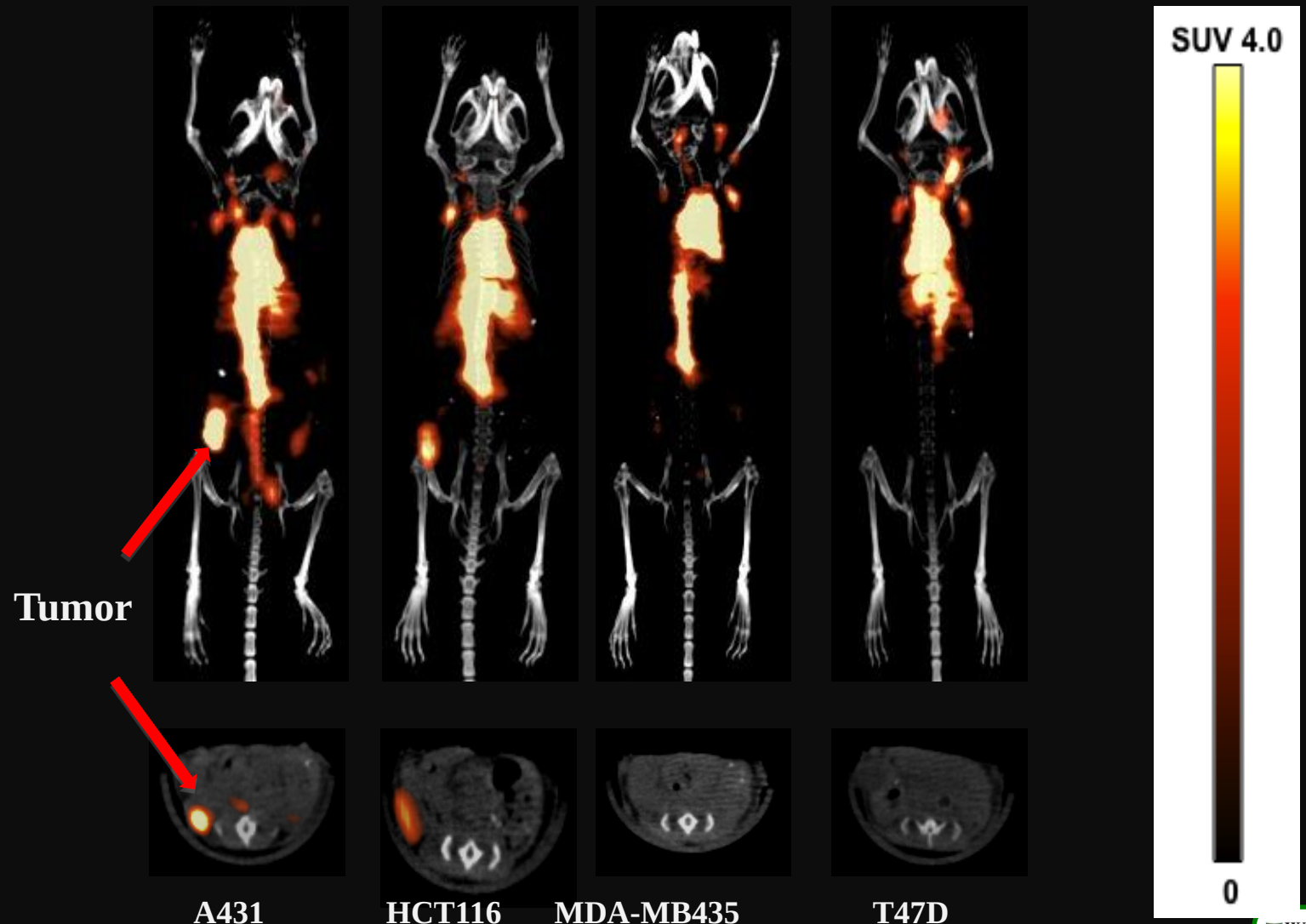
- Athymic nude mice, 6-8 weeks of age
- 4 x 10^6 cells injected into right flank
- Tumor size ~ 200 mm^3
- ~15 µCi for BioD and ~ 85 µCi for microPET

- Blocking Studies

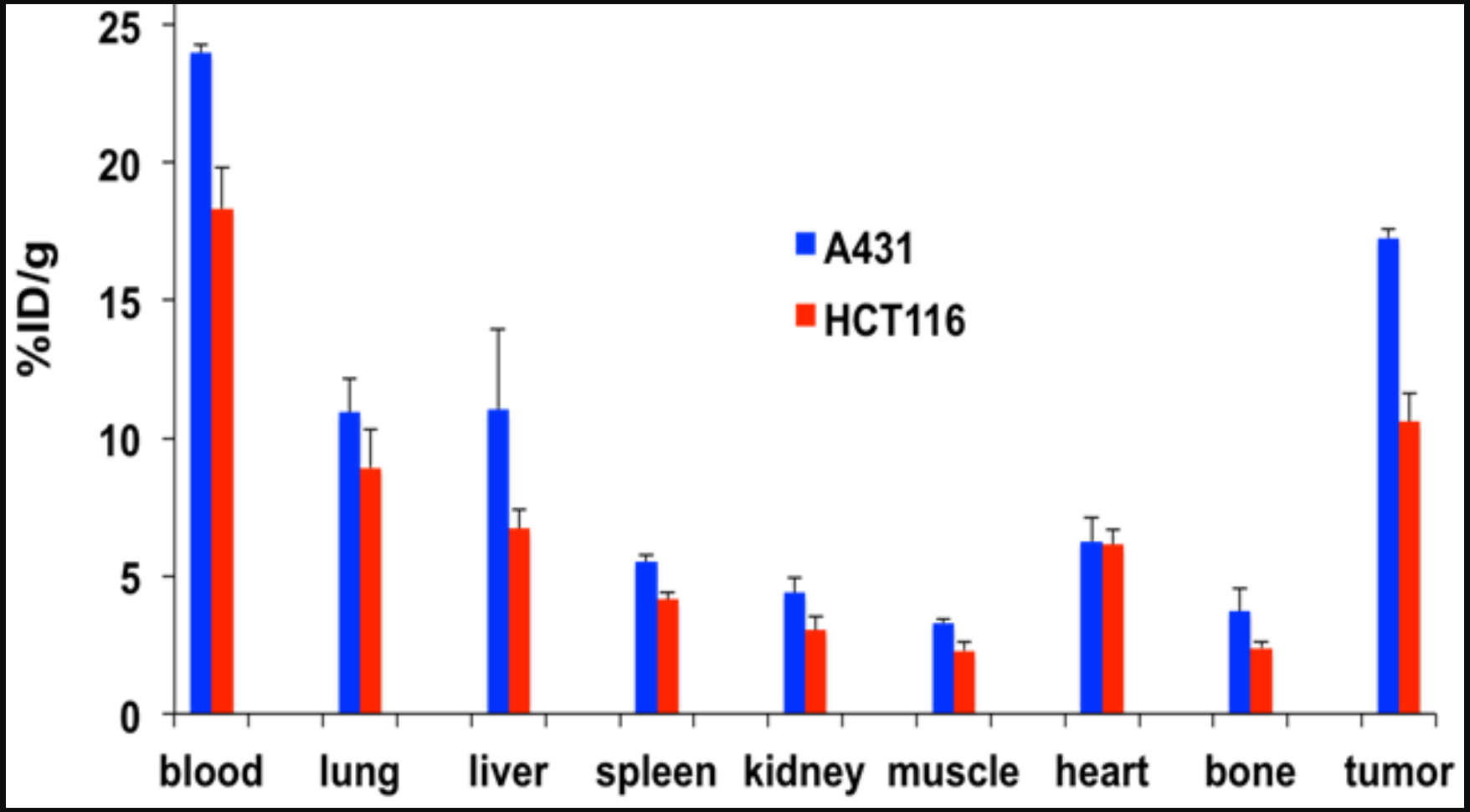
HCT116 tumor cell line with moderate EGFR expression

1 mg of unlabeled panitumumab was injected 2h before injection of activity

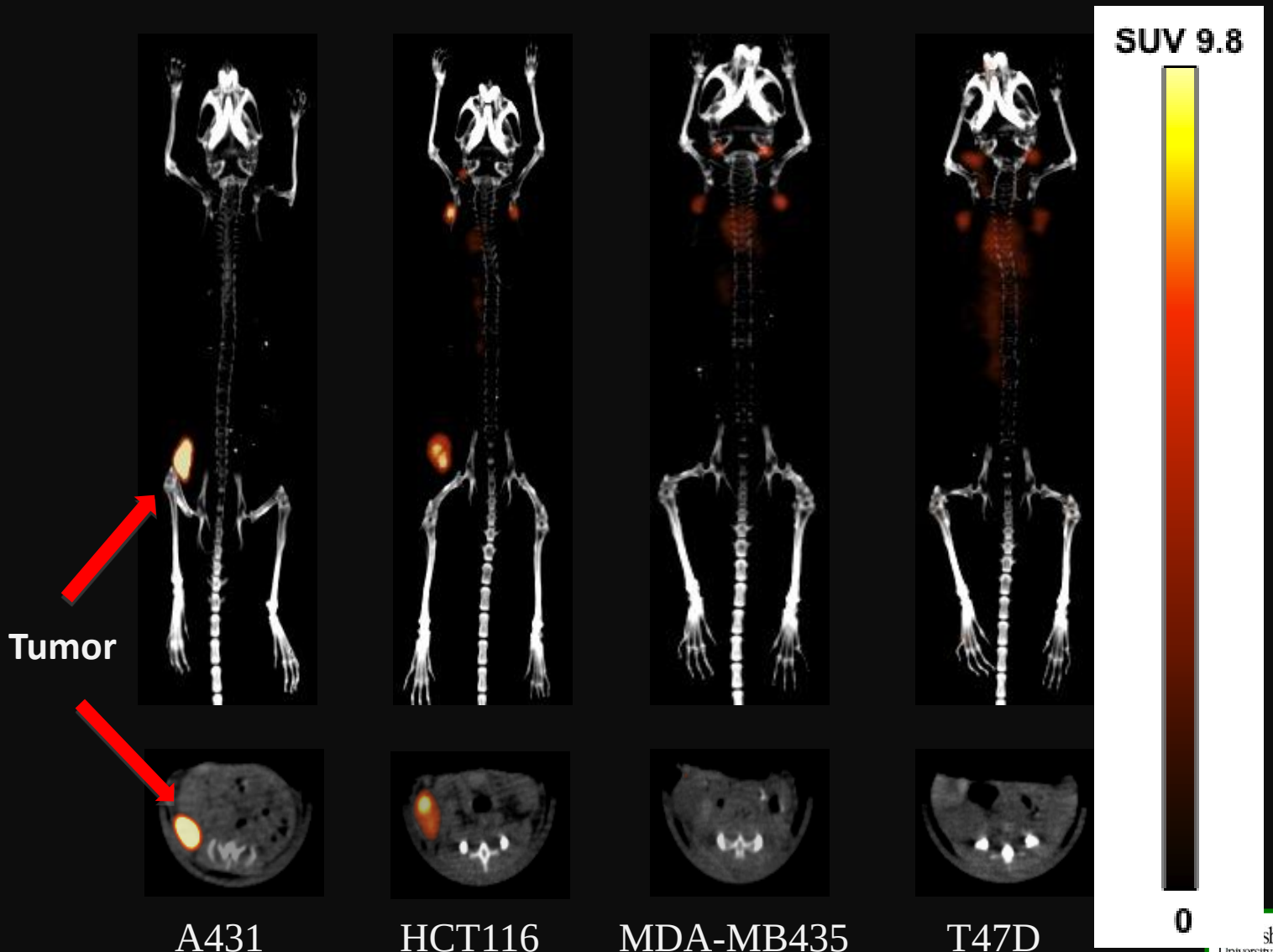
Imaging EGFR Expression with [^{89}Zr]DFO-Bn-NCS-Panitumumab at 24 h Post Injection



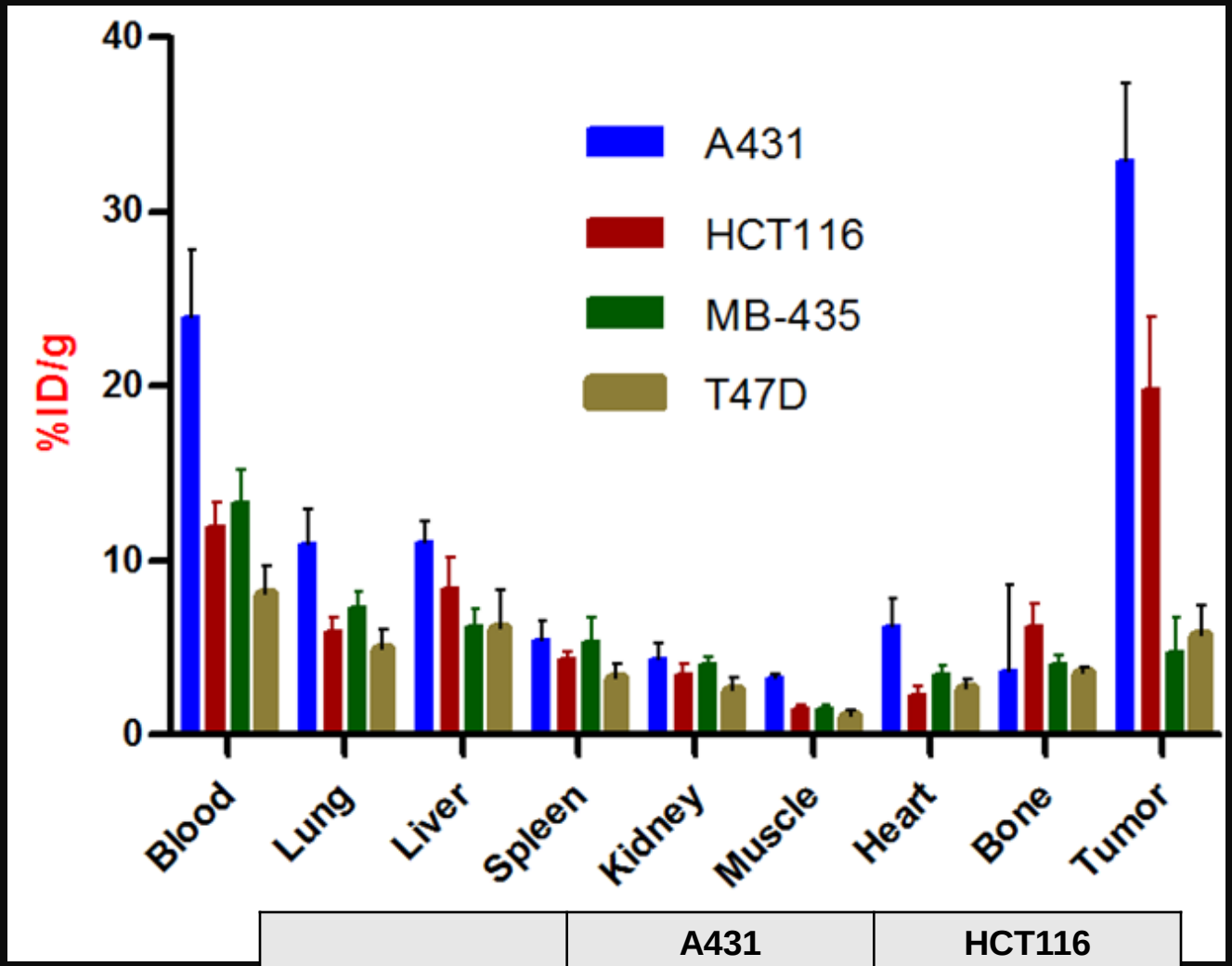
Biodistribution Studies at 24 h Post Injection



Imaging EGFR Expression with [^{89}Zr]DFO-Bn-NCS-Panitumumab at 120 h Post Injection



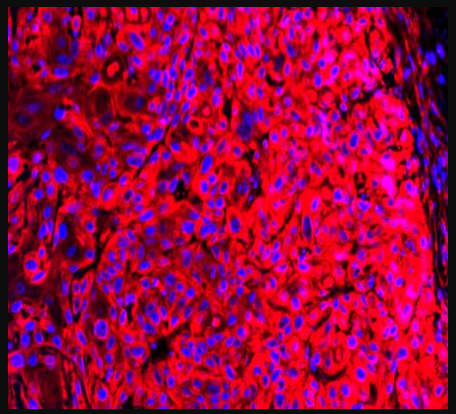
Biodistribution Studies at 120 h Post Injection



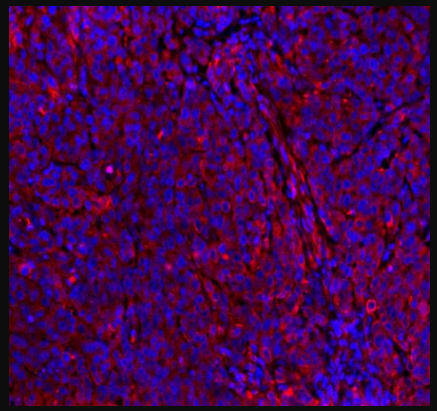
Tumor/Muscle ratio

	A431	HCT116
24 h post	5.2	4.6
120 h post	16.4	12.8

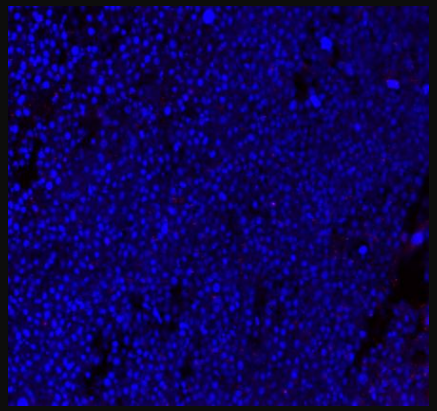
Immunofluorescent Staining of Tumors



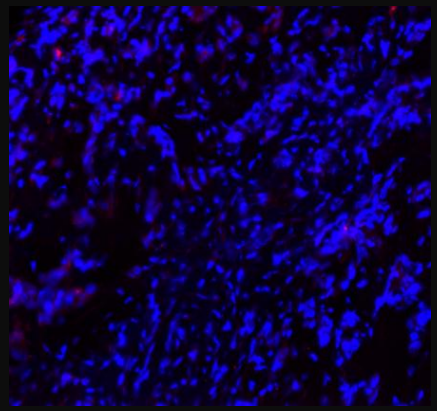
A431



HCT116



MDA-MB435

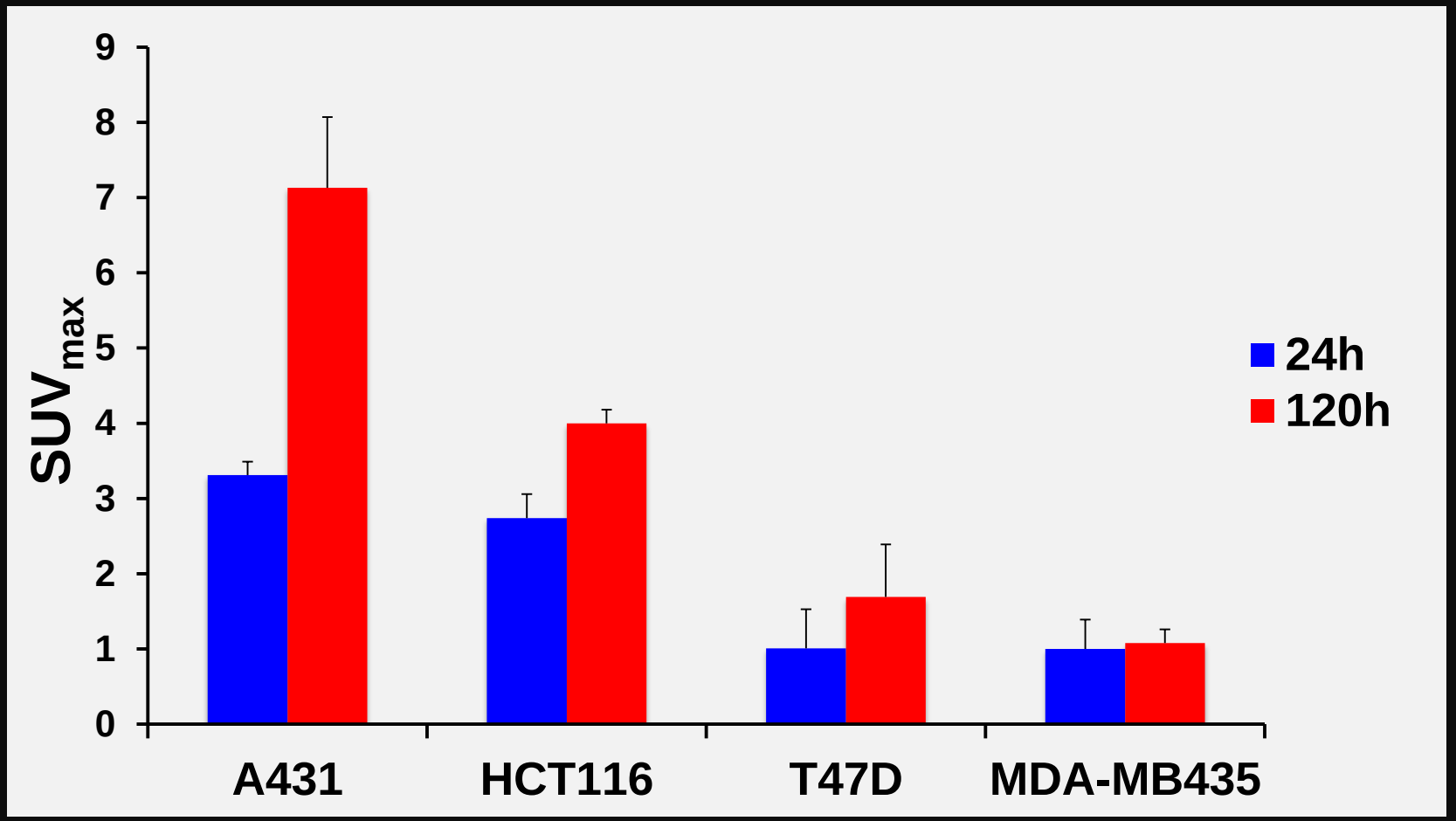


T47D

DAPI (nucleus)

Anti-EGFR

SUV_{max} of Tumors



Outlook

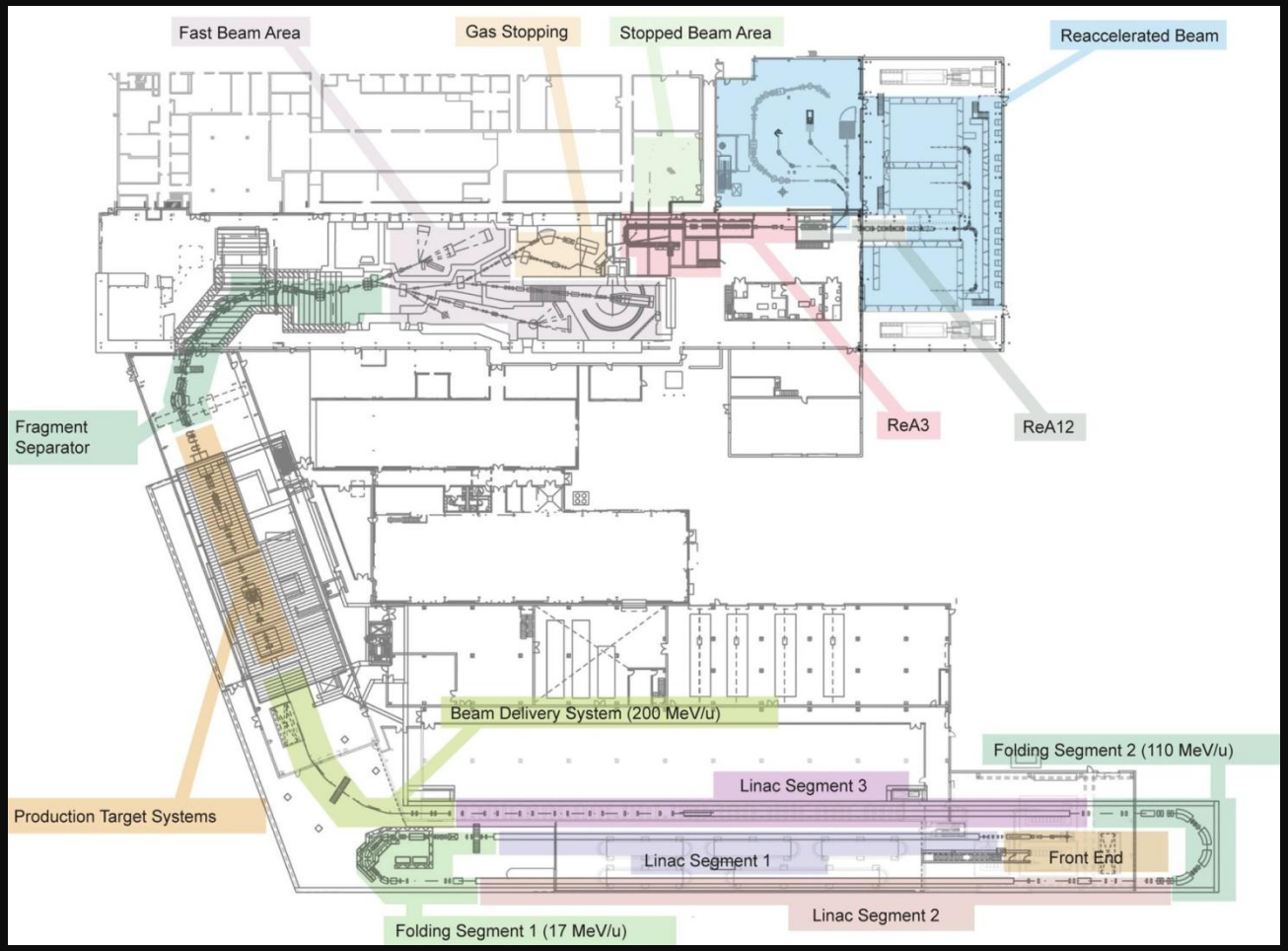
-Nuclear medicine offers very sensitive techniques to non-invasively investigate biological phenomena

-New isotopes and new imaging agents can aid in the future of "personalized medicine"

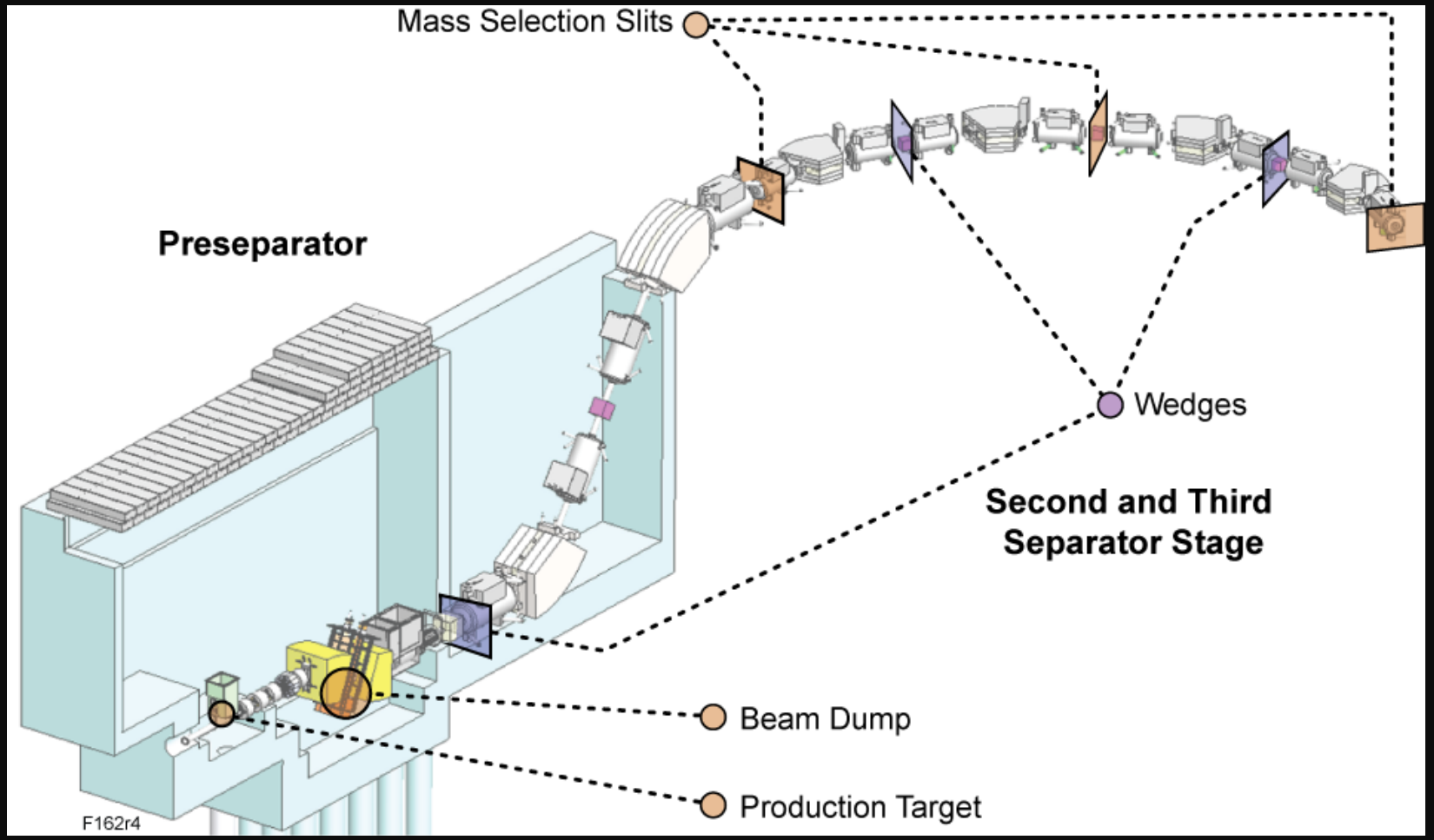
Isotope Harvesting?

- FRIB (facility for rare isotope beams)
  - Broadens the energy range and types of rare isotope beams currently available.
  - Rare isotope beams come from primary beams of different types that are fragmented. In the process of fragmentation lots of other isotopes will be simultaneously created and available for harvest in the beam dump.
  - Some of these "orphan" isotopes are relevant for many scientific applications.
    - Medicine, Nuclear Power, Homeland Security, Stockpile Stewardship, Industrial and Environmental Tracers

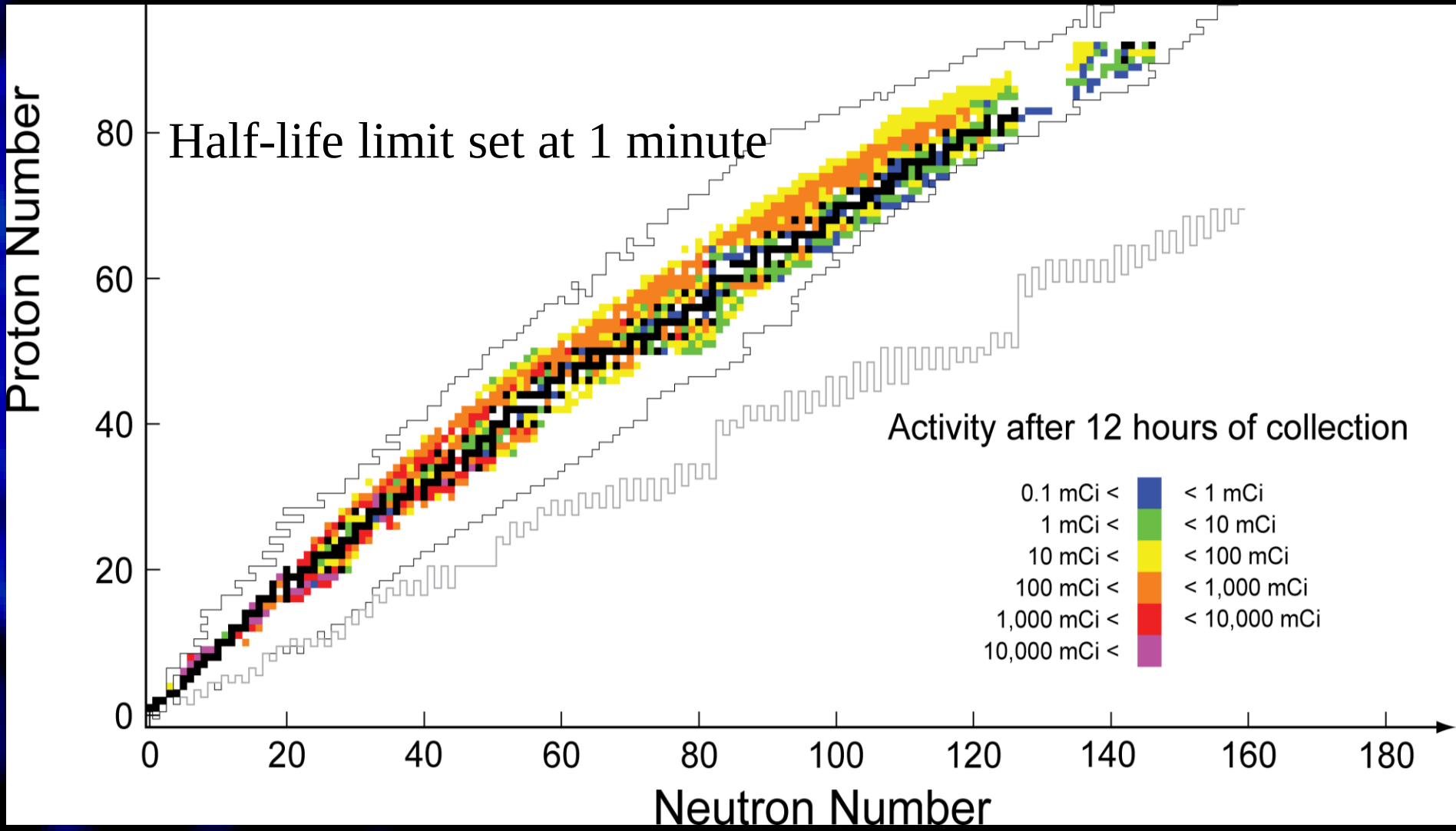
Schematic of FRIB



Schematic of Proposed Secondary Beam Separator at FRIB



Separated Isotopes from FRIB



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