Production of PET Radiometals: ^{64}Cu and ^{89}Zr

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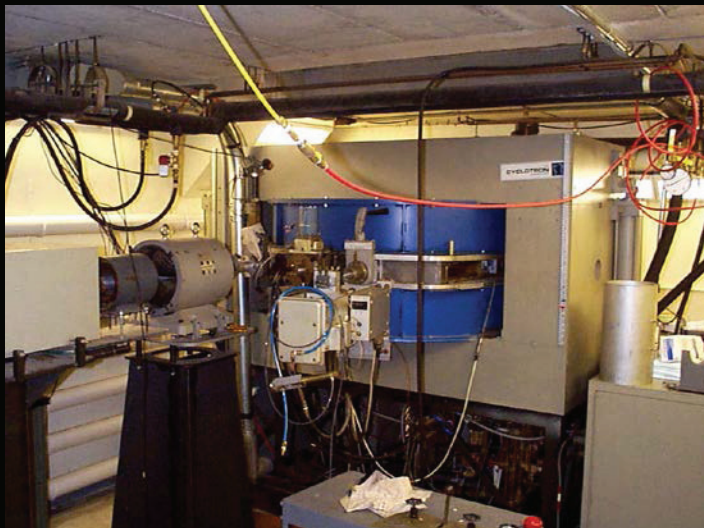
Principles of Positron Emission Tomography (PET)

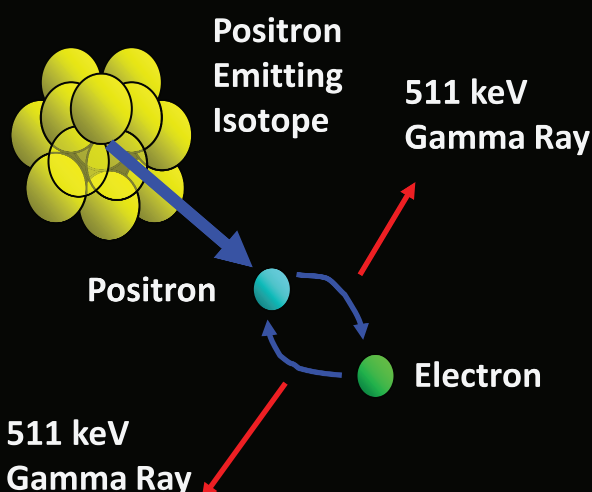
- Based on tracer principle
- Tracer labeled with positron emitting radioisotope
- Positron decay
- Coincidence detection of annihilation radiation

Principles of PET Imaging



Positron-emitting isotopes produced on cyclotrons or generators

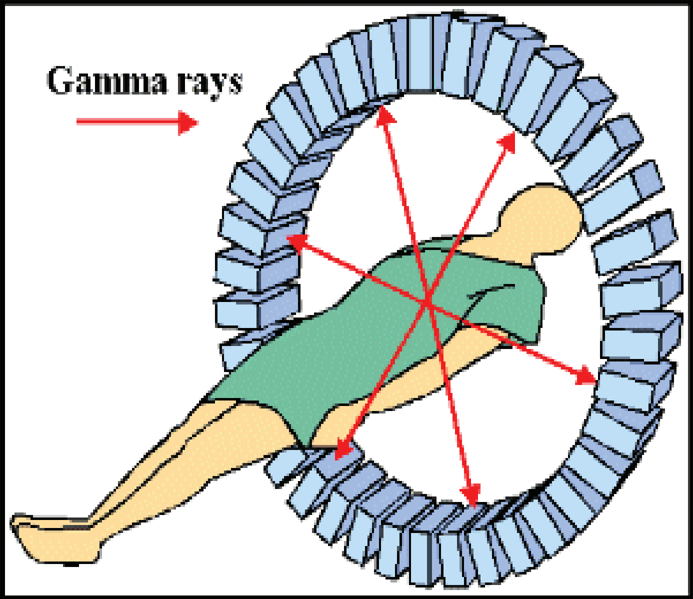
Injection of a tracer compound labeled with a positron-emitting radionuclide



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



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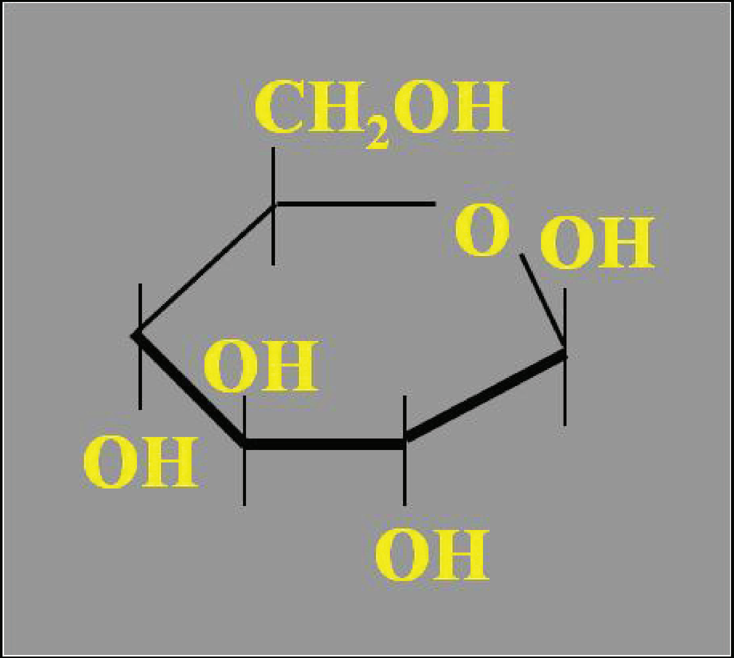
Why Use PET Imaging?

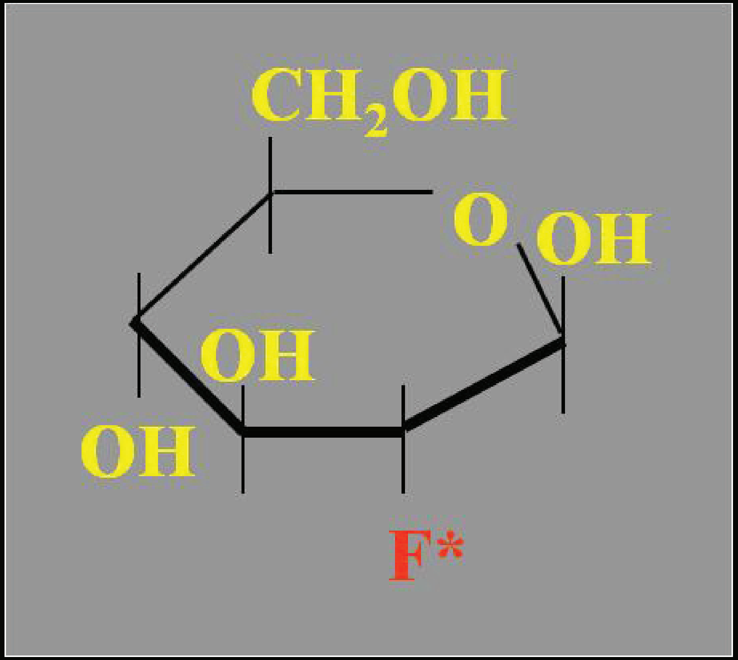
- PET imaging is a very sensitive tool capable of providing quantitative information about biochemical and physiological processes in a non-invasive manner.

PET Radiopharmaceutical: FDG

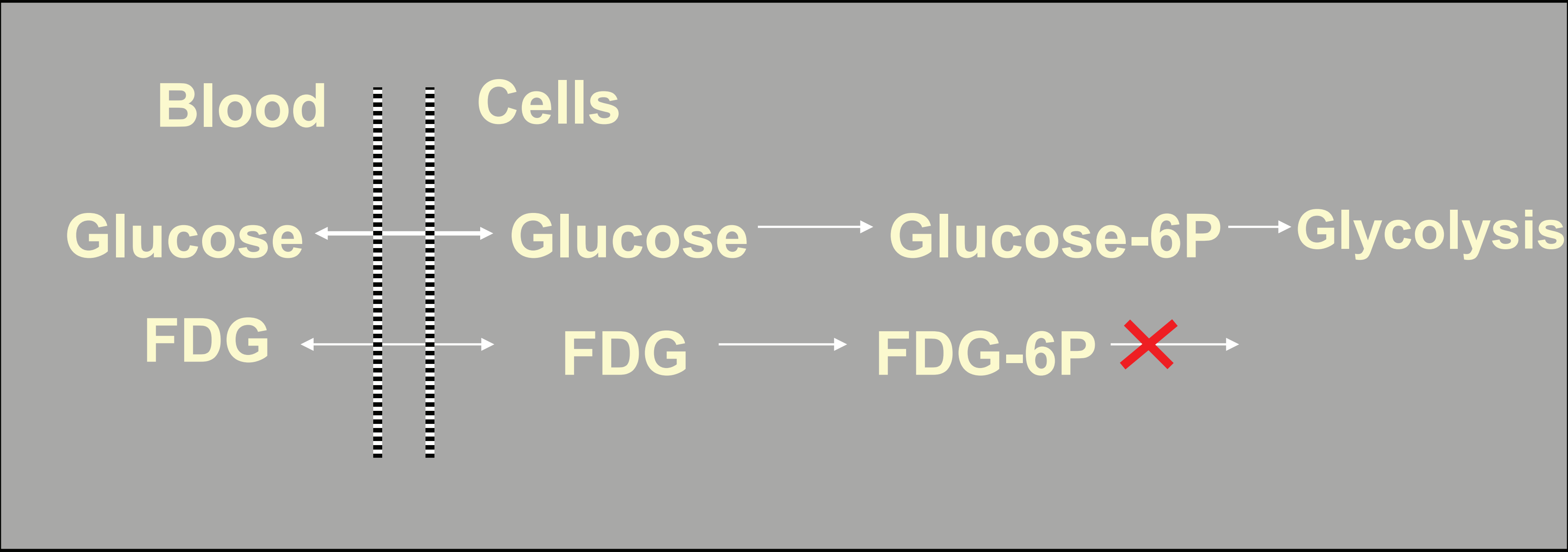
Glucose



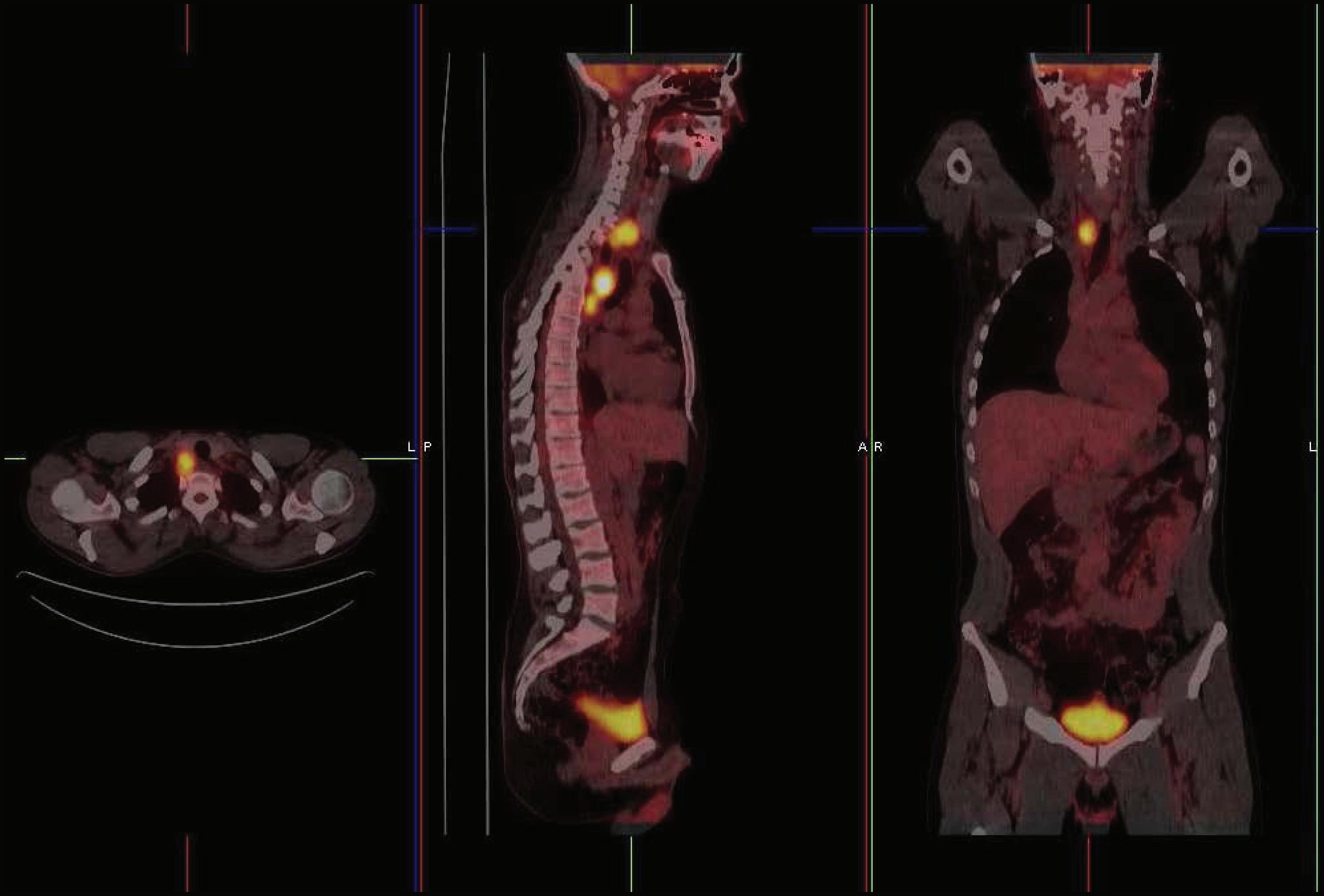
Fluorodeoxyglucose (FDG)



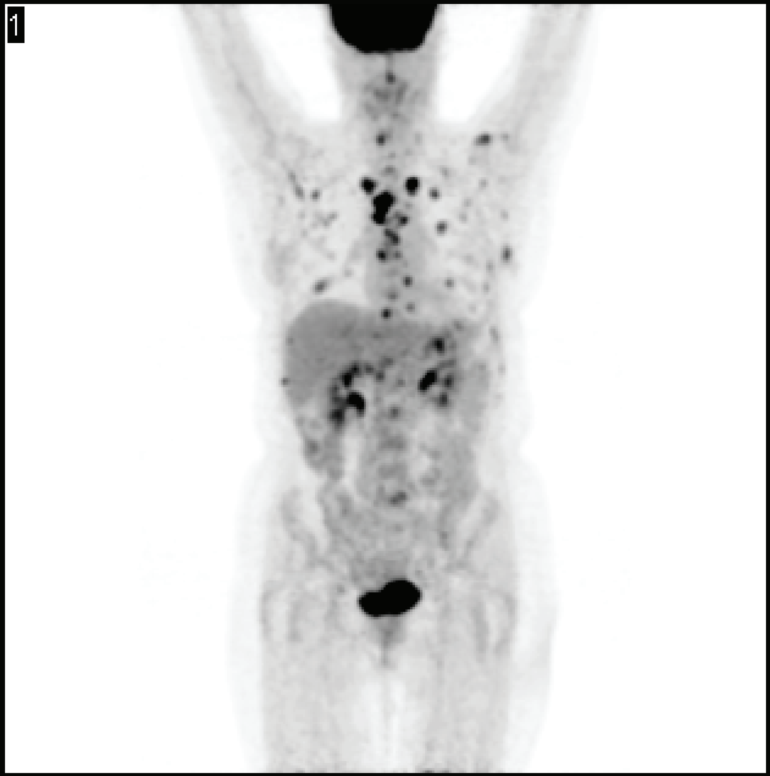
FDG Uptake and Retention



Diagnostic Medicine: Present



59 year old woman with T-cell lymphoma



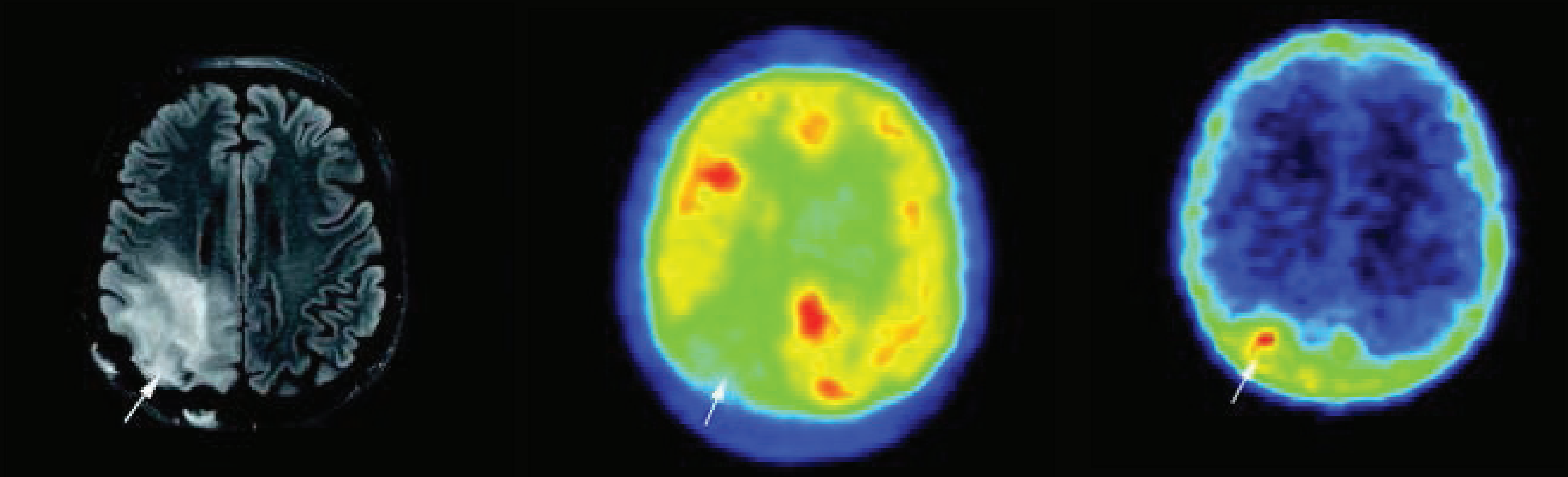
Initial study

4 months later,
after chemotherapy

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



FDG

^{68}Ga-BBN

Clinical Nuclear Medicine. 36(2):101-108, February 2011.

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)

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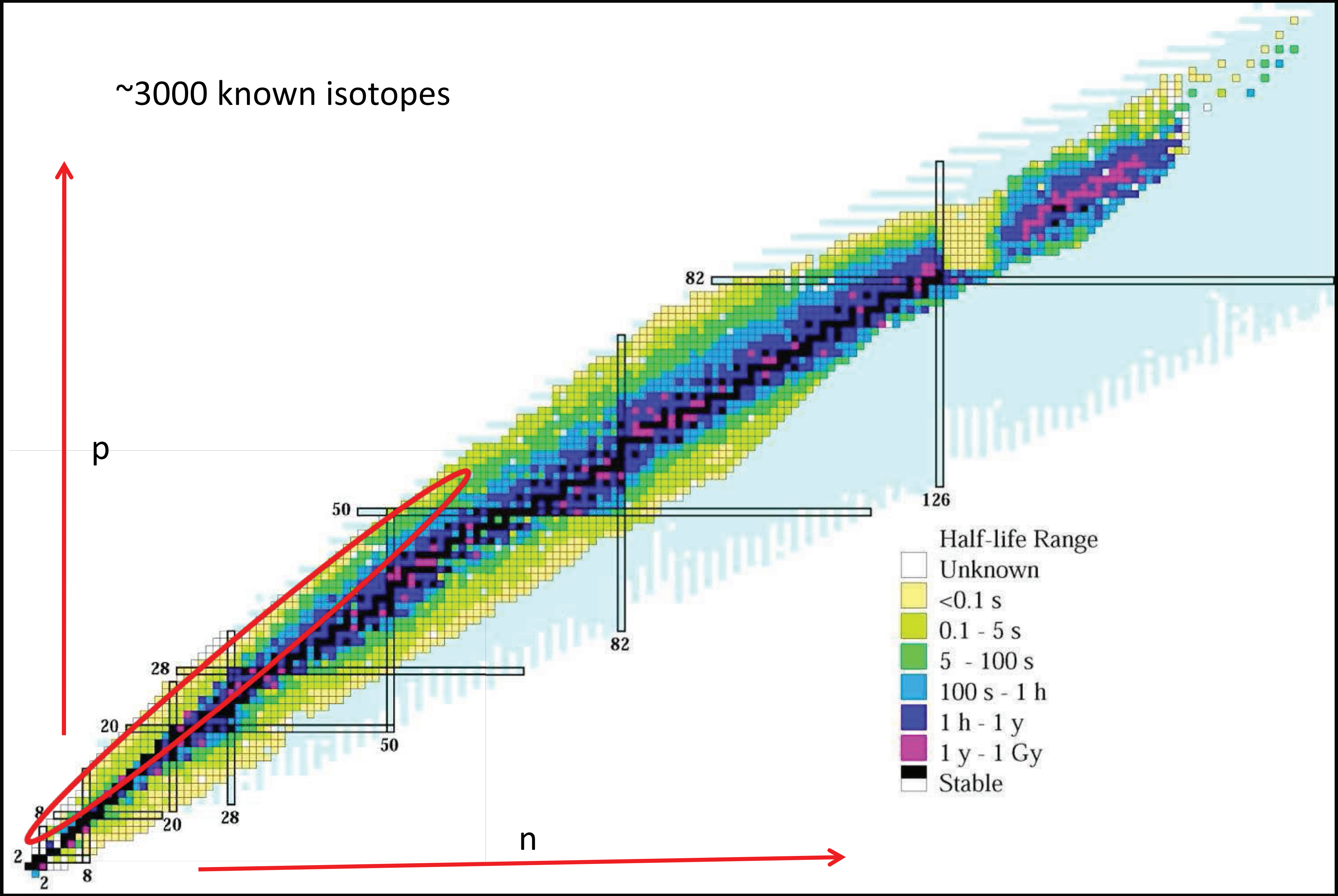
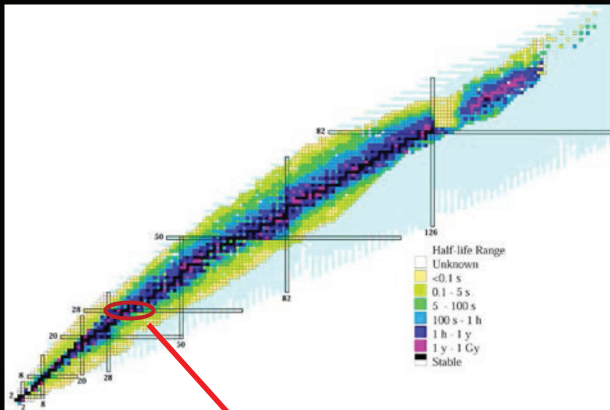
Common PET isotopes

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

The Toolbox



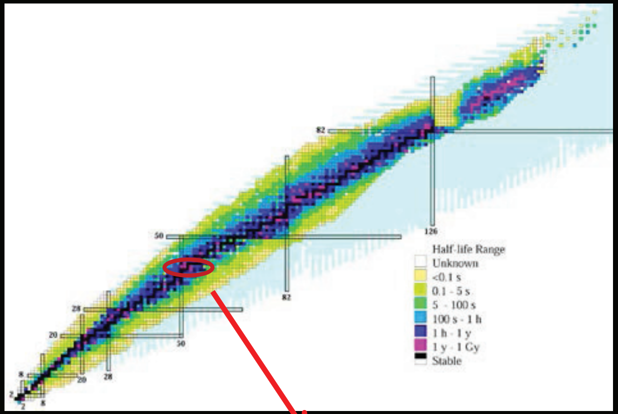
~3000 known isotopes
p
n
2
2
8
8
20
20
28
28
50
50
82
82
126
Half-life Range
Unknown
<0.1 s
0.1 - 5 s
5 - 100 s
100 s - 1 h
1 h - 1 y
1 y - 1 Gy
Stable



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:

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%
	45	46	47	48	49	50	51

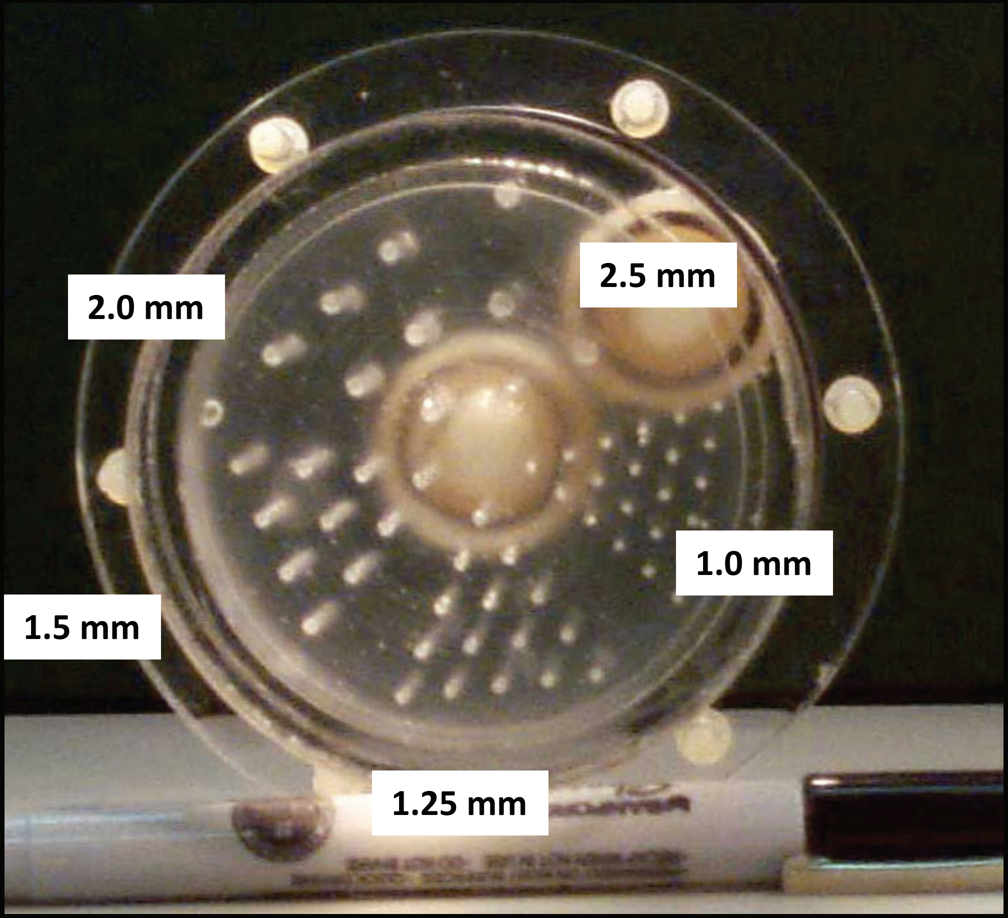
Radiometals

- 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.

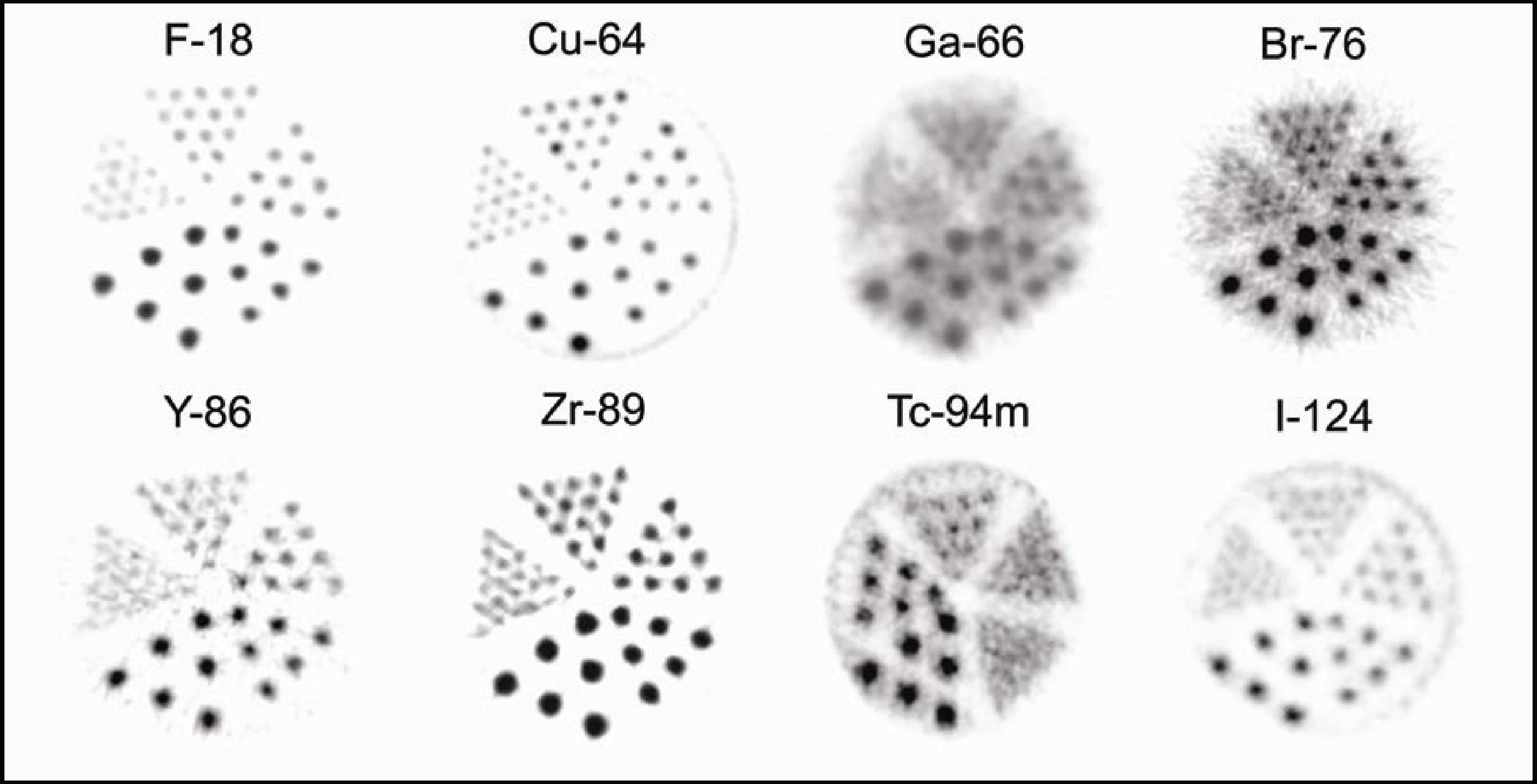
Metal radionuclides discussed

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

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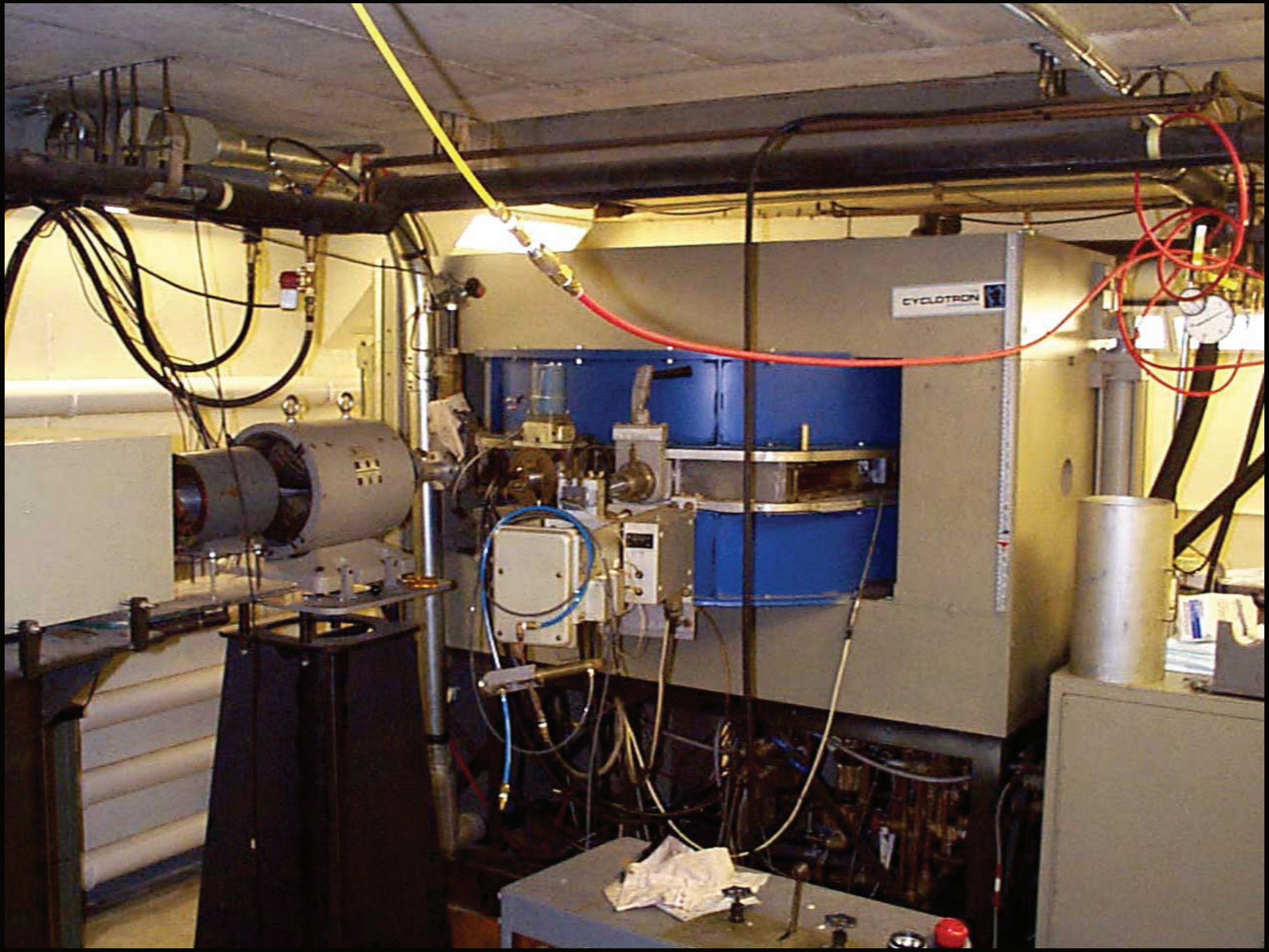
The CS-15



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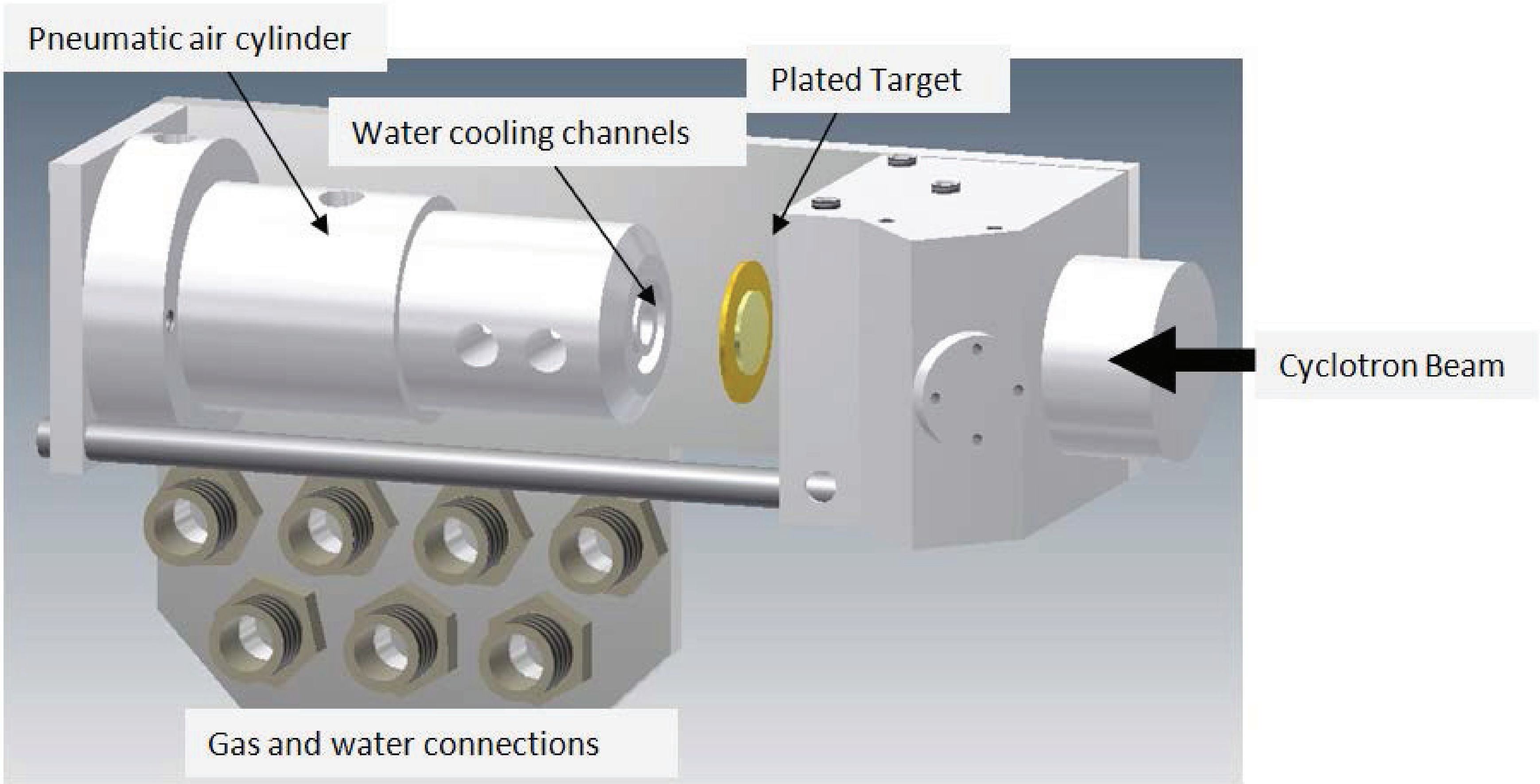
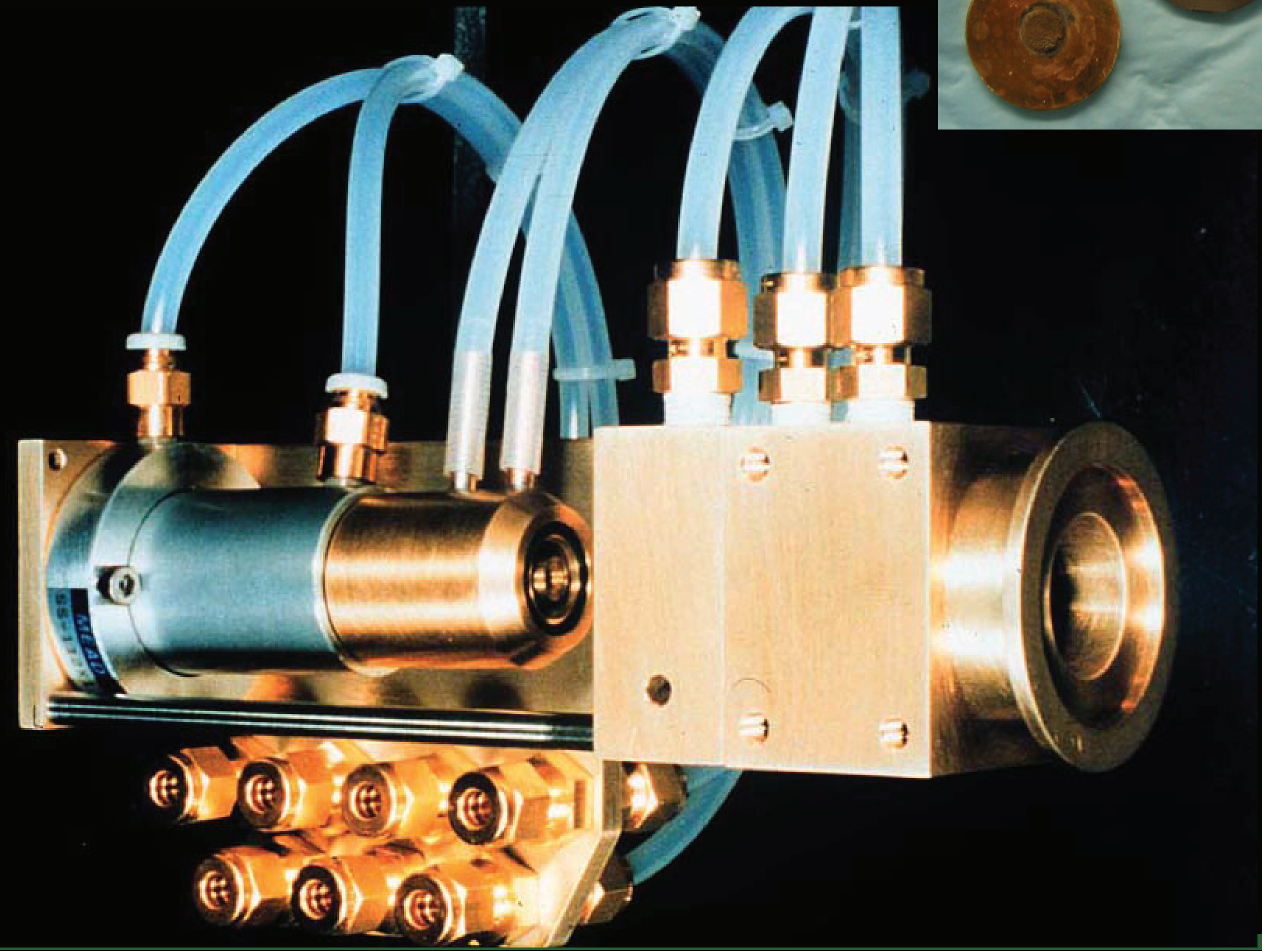
Targetry



Pneumatic air cylinder
Plated Target
Water cooling channels
Cyclotron Beam
Gas and water connections

Production

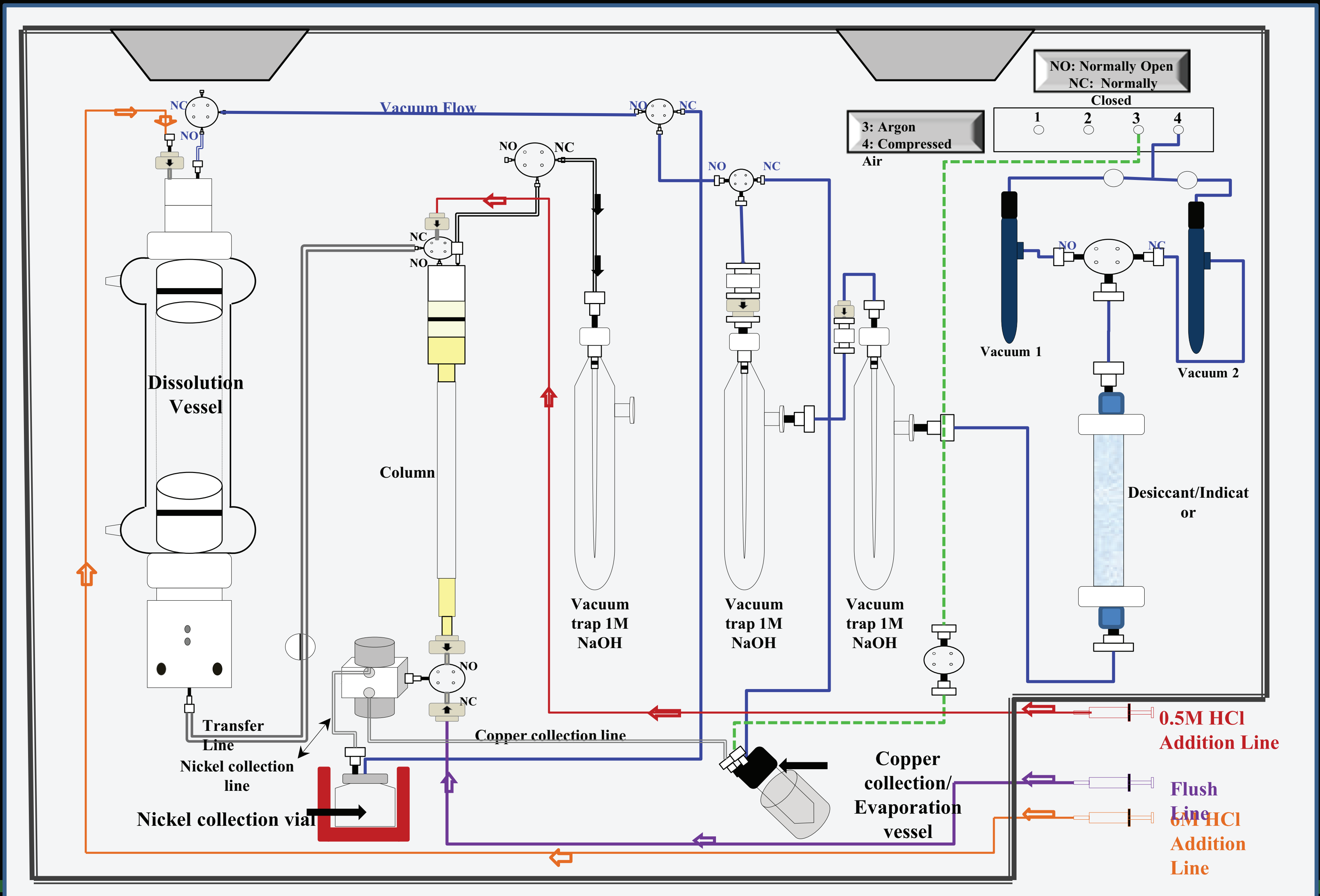


Copper-64

64Zn STABLE 48.63%	65Zn 243.66 D ϵ: 100.00%	66Zn STABLE 27.90%
63Cu STABLE 69.17%	64Cu 12.701 H ϵ: 61.50% β-: 38.50%	65Cu STABLE 30.83%
62Ni STABLE 3.634%	63Ni 100.1 Y β-: 100.00%	64Ni STABLE 0.926%

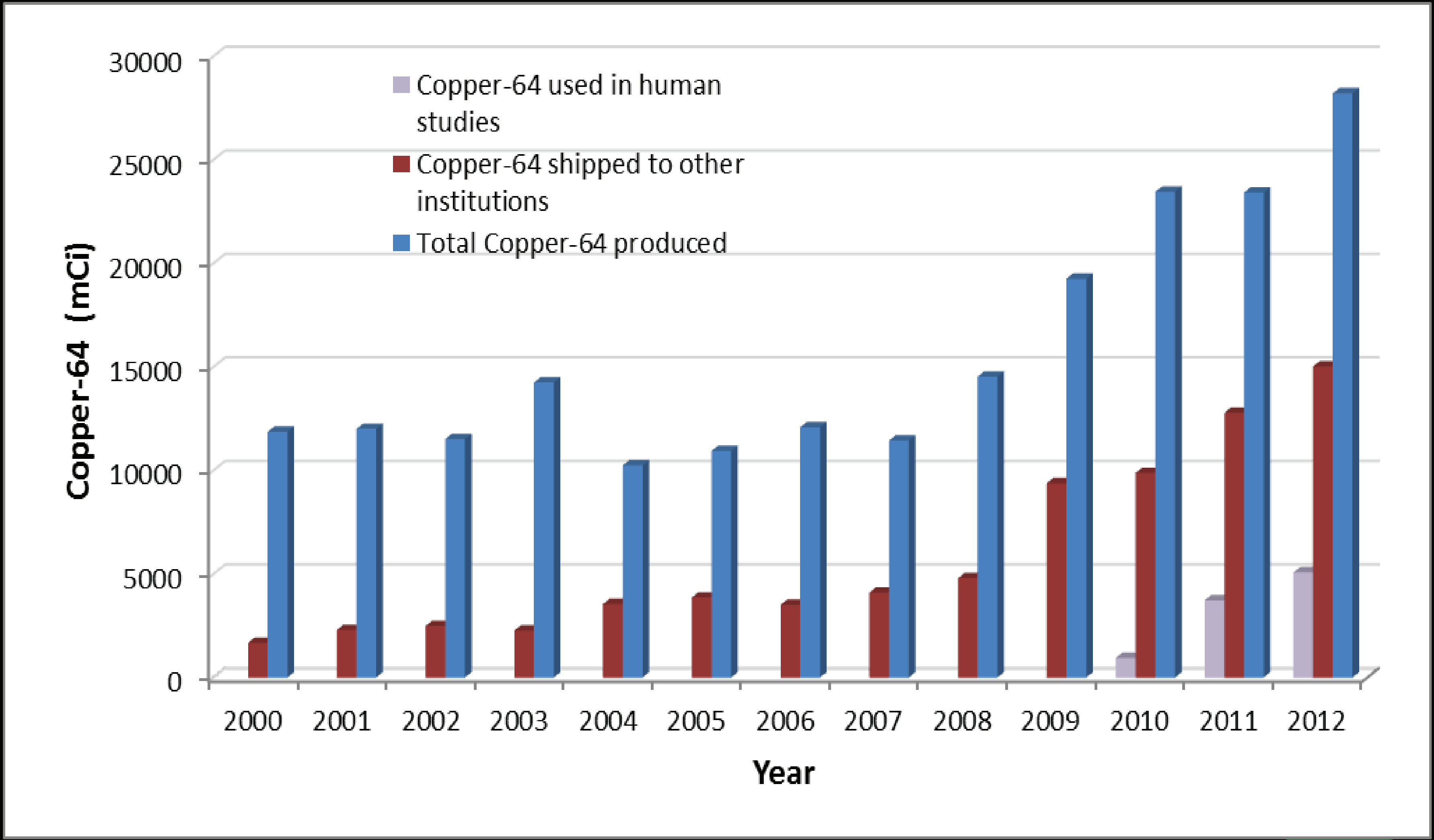
- $T_{1/2}$ 12.7 hours,
- β^+ (17.8%) β^- (38.4%)
- Used for imaging distribution of molecules with biological half-lives of hours-days
- Also potential for targeted radiotherapy
- Produced by ^{64}Ni(p,n) reaction with CS-15

Automated Separation



Automated Separation

Copper-64



30000
25000
20000
15000
10000
5000
0
Copper-64 (mCi)
Copper-64 used in human studies
Copper-64 shipped to other institutions
Total Copper-64 produced
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Year

Zirconium-89

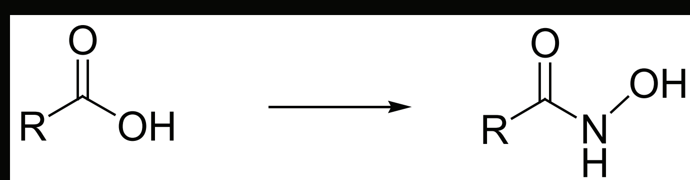
- Half-life of 3.27 d – well suited for study of pharmacokinetics of antibodies (achieve optimal biodistribution ~4-5 d)
- Immuno-PET - Scouting in preparation for radioimmunotherapy, confirming tumor targeting, and estimating dosimetry
- Generally inert to biological systems
- Decay properties
  - EC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

Zr-89 production and purification

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

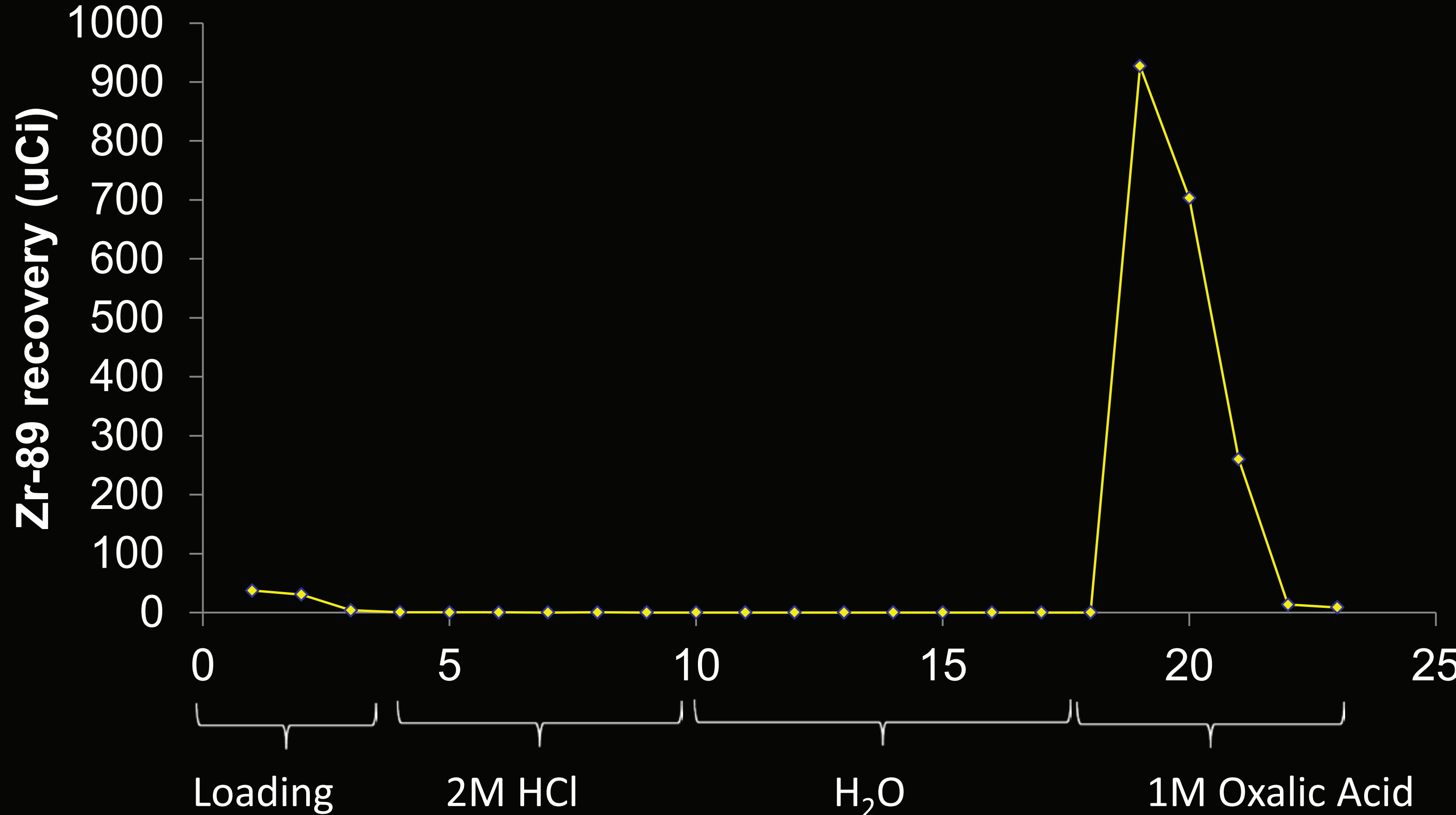
87Zr 1.68 H ϵ: 100.00%	88Zr 83.4 D ϵ: 100.00%	89Zr 78.41 H ϵ: 100.00%	90Zr STABLE 51.45%	91Zr STABLE 11.22%	92Zr STABLE 17.15%	93Zr 1.53E+6 Y β-: 100.00%
86Y 14.74 H ϵ: 100.00%	87Y 79.8 H ϵ: 100.00%	88Y 106.626 D ϵ: 100.00%	89Y STABLE 100%	90Y 64.053 H β-: 100.00%	91Y 58.51 D β-: 100.00%	92Y 3.54 H β-: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

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



Accell resin Hydroxamate resin

Zr-89 purification



Scale up

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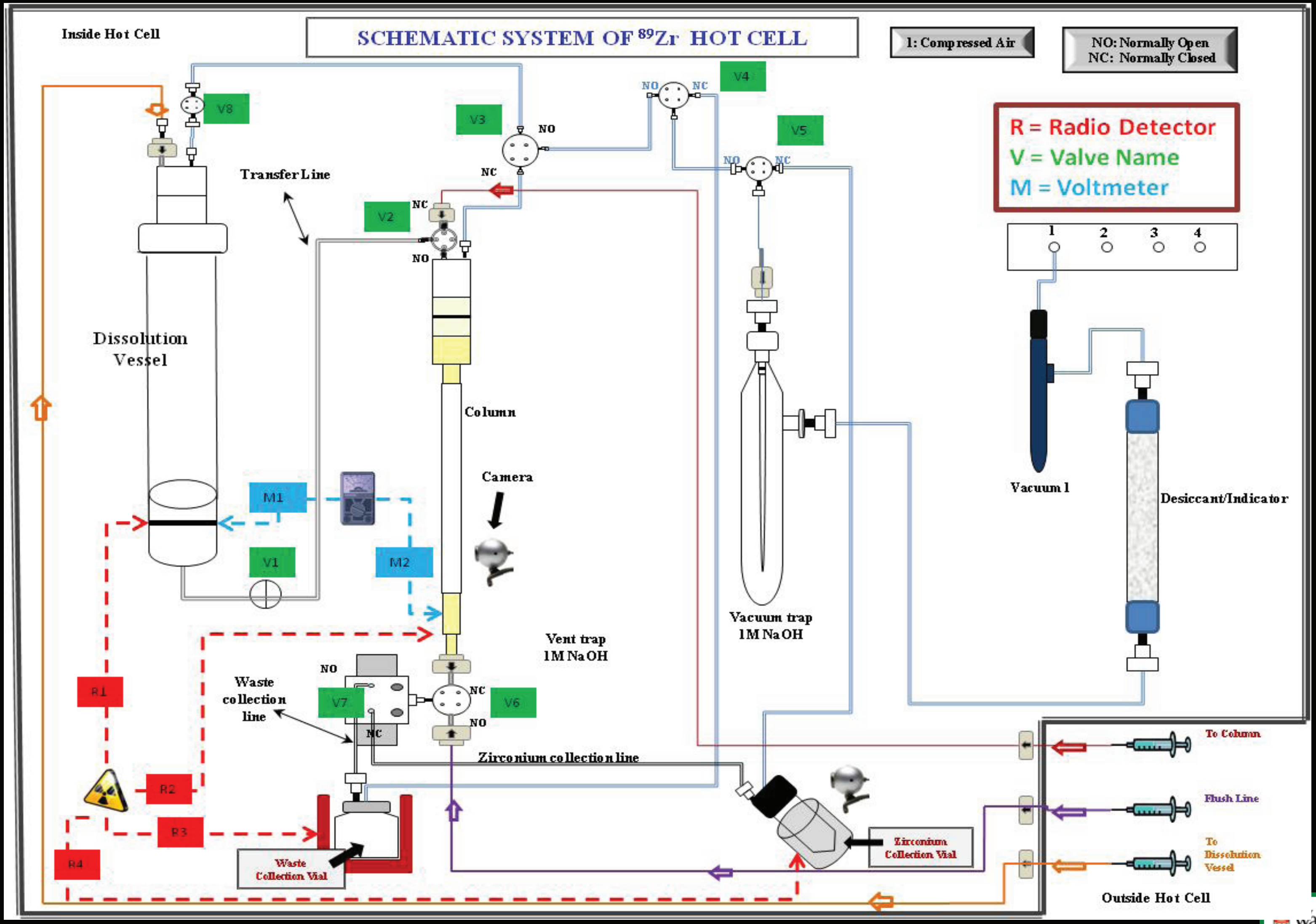
Automated Separation



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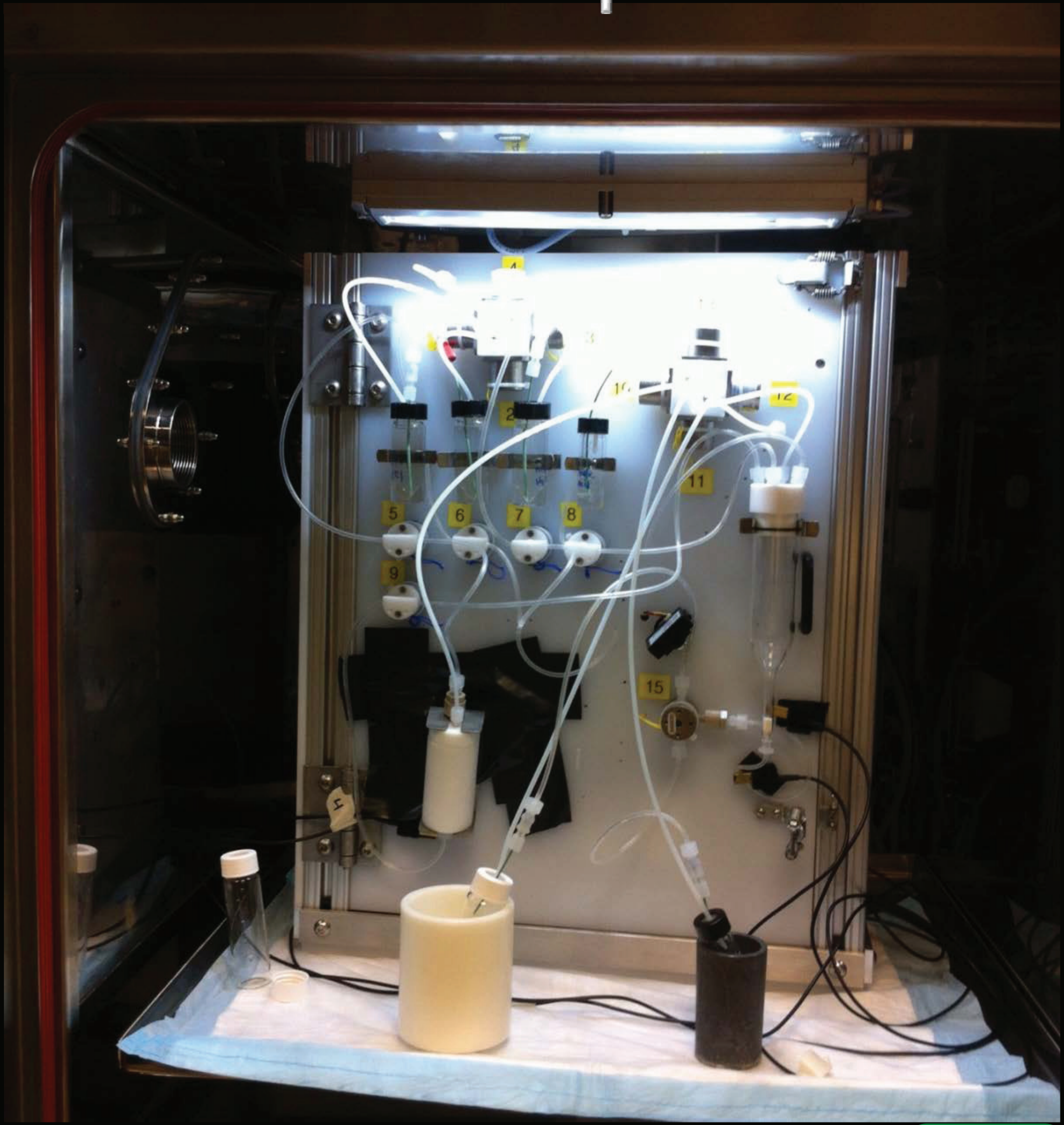
Scale Up and Automated Separation



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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)

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

NA PAC, Oct 3rd 2013

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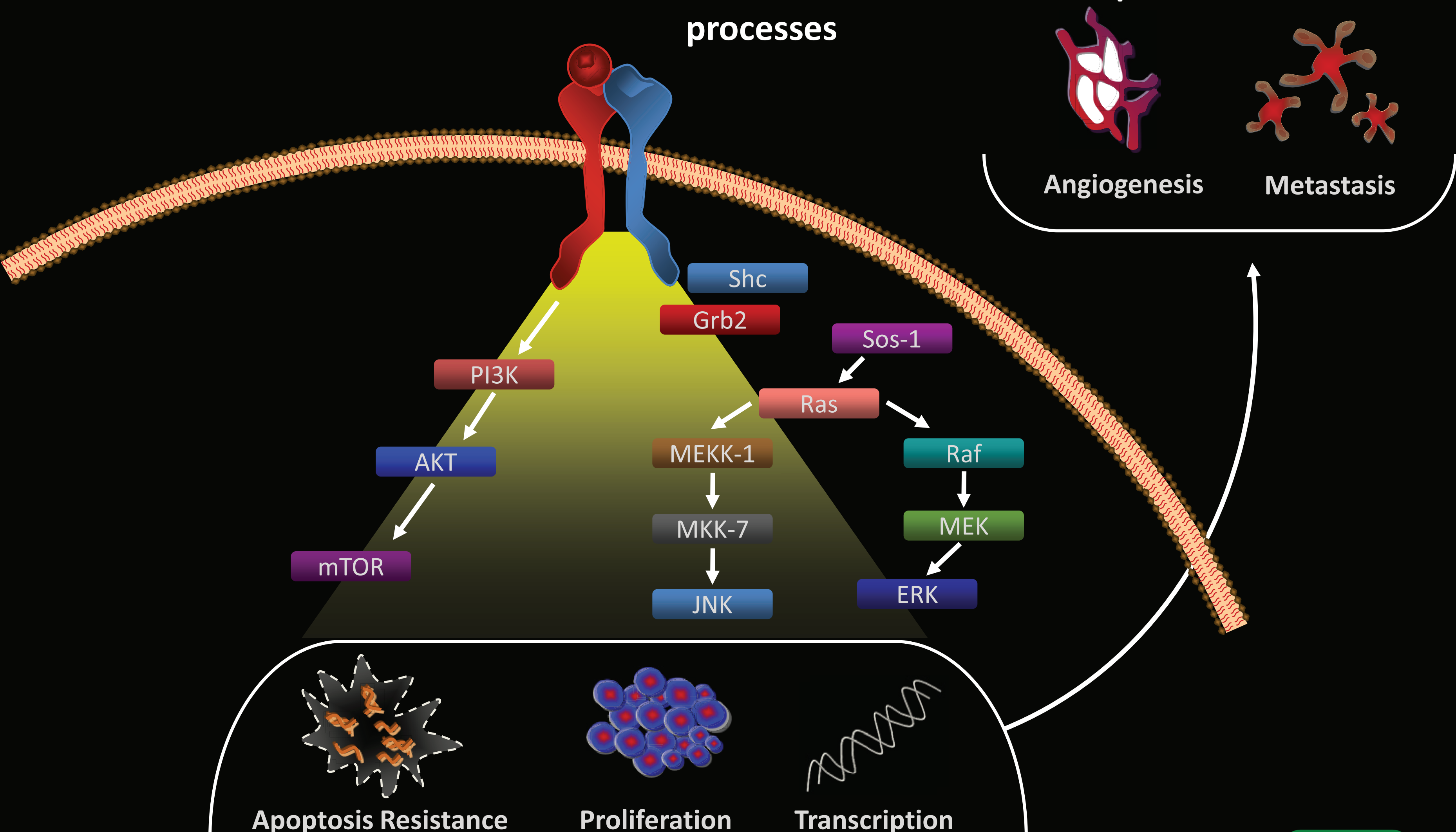
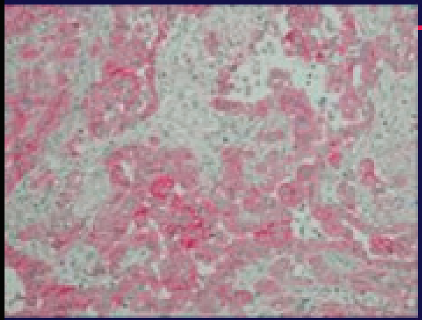
EGFR in Human Carcinogenesis

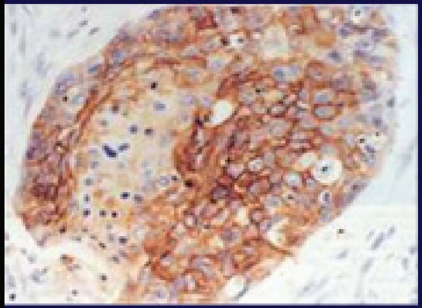
EGFR activation mediates multiple processes

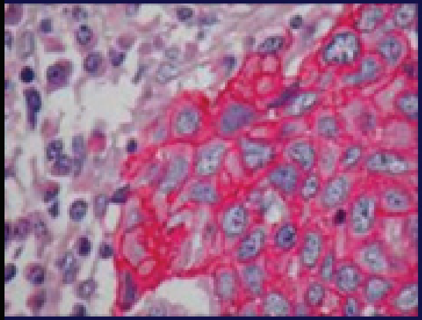


Adapted from: Ciardiello F, et al. N Engl J Med. 2008;358:1160-1174.

EGFR Expression in Solid Tumors


Colorectal


Lung (NSCLC)


Head & Neck (SCCHN)

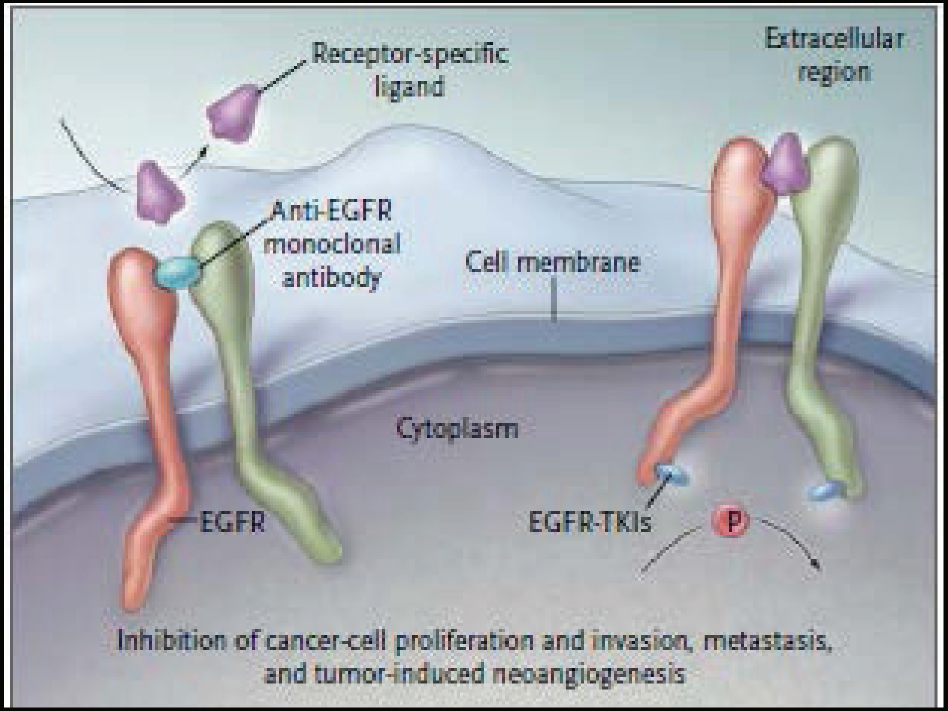
EGFR is expressed in a variety of solid tumors

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

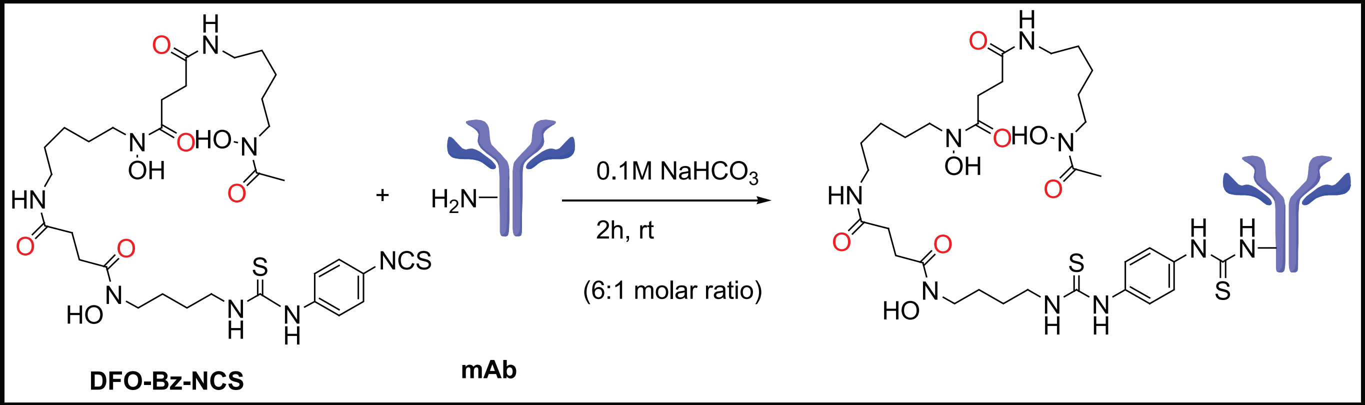
- Cetuximab
  - Human-mouse chimeric IgG_1 mAb
  - For advanced colon cancer

- Panitumumab
  - Fully humanized IgG_2 mAb
  - advance colon cancer, non-small cell lung cancer, esophageal cancer, and pancreatic cancer

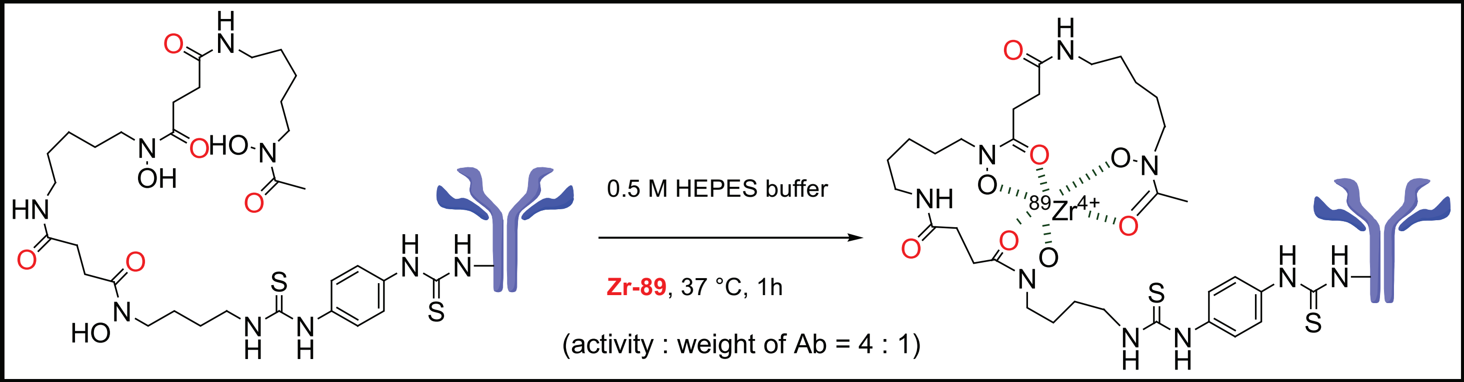


Labeling of Panitumumab with ^{89}Zr

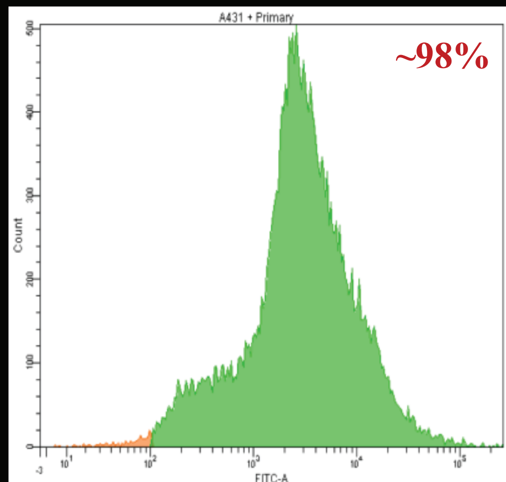
(a) mAb conjugation to DFO-Bz-NCS



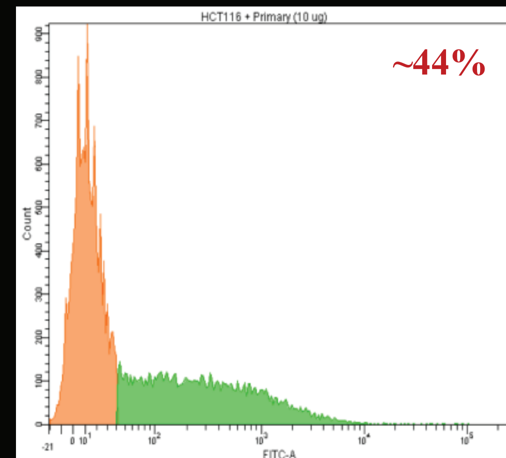
(b) Radiolabeling of DFO-Bz-NCS-Panitumumab



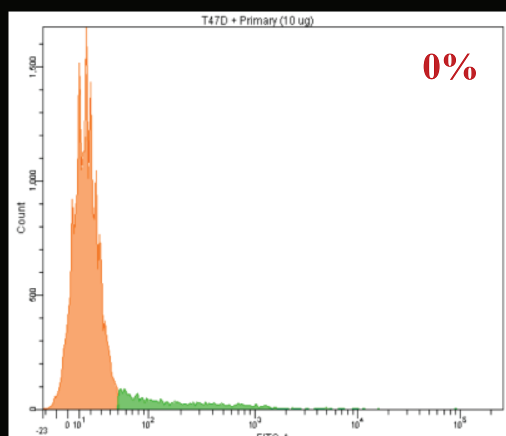
EGFR Expression on Different Cancer Cell Lines : Flow Cytometry Data



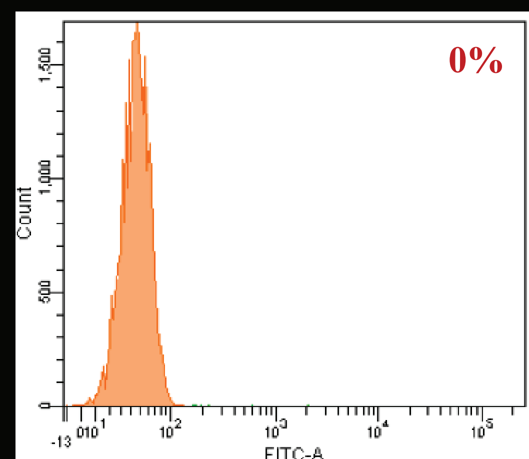
A431(lung)



HCT116 (colorectal)

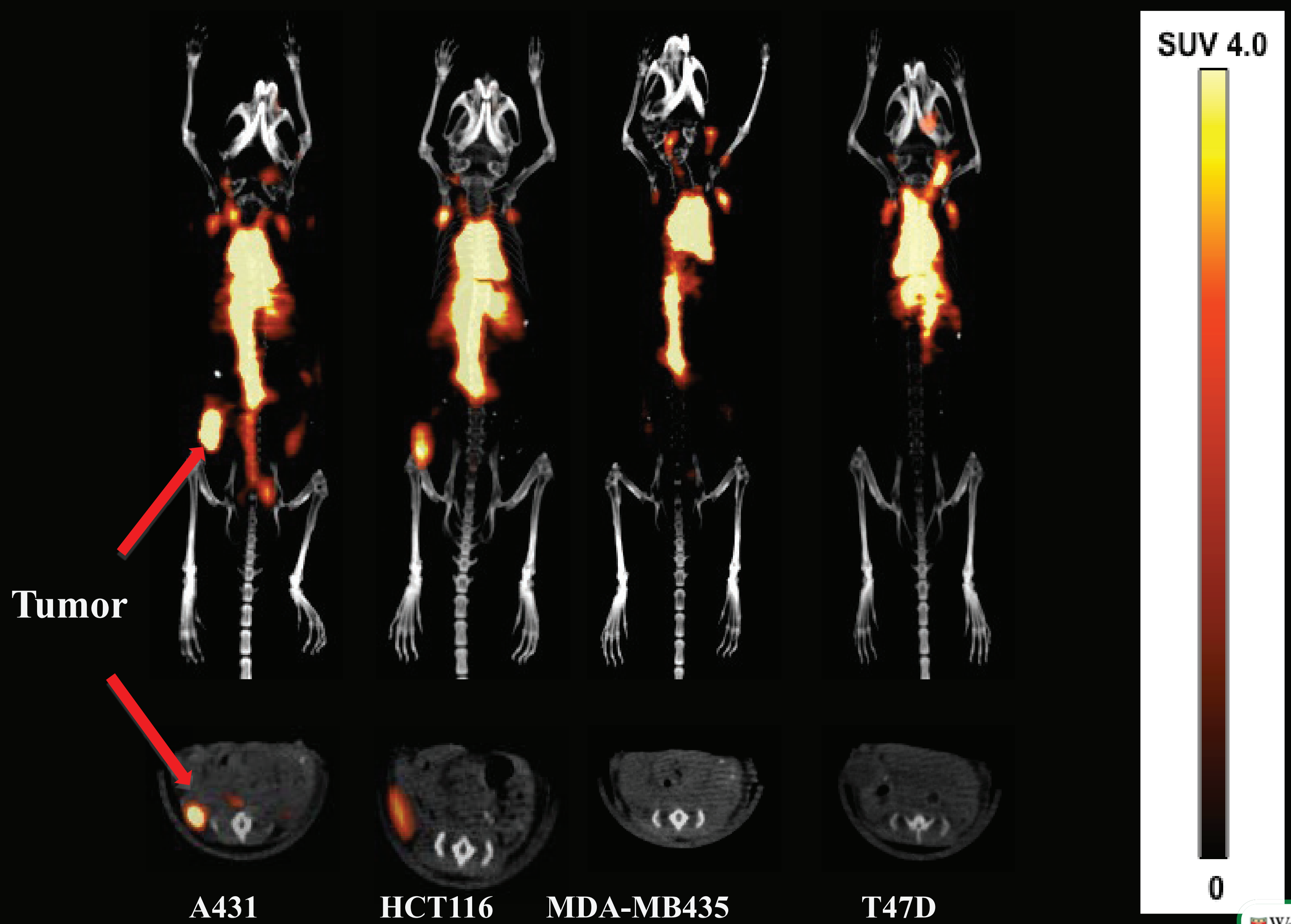


T47D (breast)



MDA-MB-435(breast)

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



Cheng et al Mol. Imaging 2013

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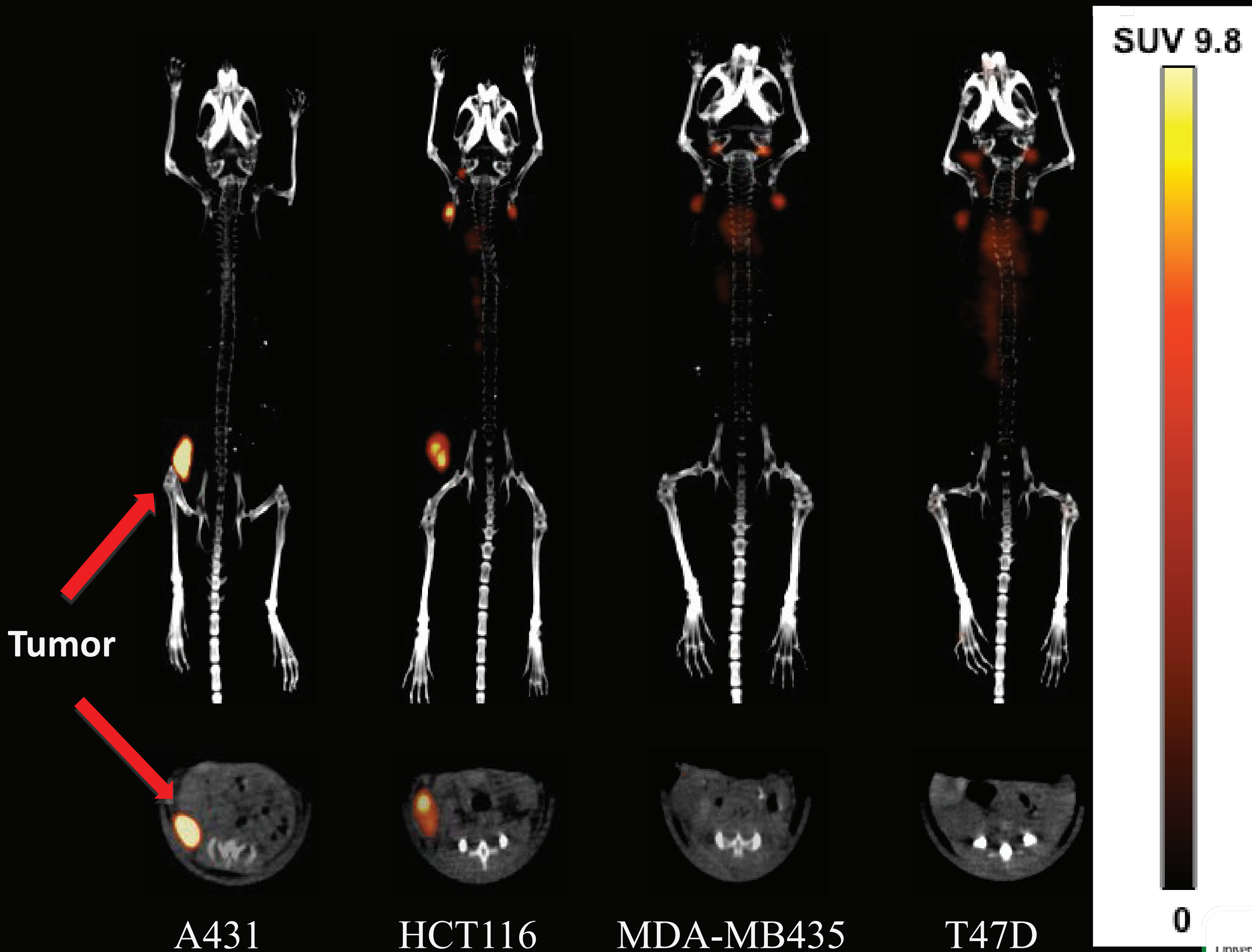
Imaging EGFR Expression with [^{89}Zr]DFO-Bn-NCS-Panitumumab at 120 h Post Injection



Cheng et al Mol. Imaging 2013

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”

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